Organosilicon Compounds as Water Scavengers in Reactions of Carbonyl Compounds

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Abstract: The literature data on the application of organosilicon compounds as water scavengers in reactions of carbonyl compounds is surveyed. The reactions leading to both carbon–carbon (in particular, aldol-type condensations) and carbon–nitrogen bond formation, the synthesis of iminium salts by elimination reactions and heterocyclizations are considered.

1   Introduction

The chemistry of carbonyl compounds has always attracted the attention of organic chemists because of their great synthetic potential that has not yet been exhausted despite the overwhelming amount of research performed in this area. Most of the reactions of these compounds (e.g., aldol-type condensations, imine synthesis, heterocyclizations) result in water formation. Therefore, the successful outcome of these reactions relies on the use of appropriate reagents that can act not only as catalysts but also as water scavengers. The early examples of the reagents of that type included concentrated inorganic acids (H_2SO_4, H_3PO_4, etc.) and alkalis [e.g., NaOH, KOH, $Ba(OH)_2$].[1] Despite the high catalytic and dehydrating activities of these systems, they lack efficiency as most of the substrates are unstable under the reaction conditions. One way to solve this problem is to use milder reagents such as

organic acids (e.g., acetic, formic or *p*-toluenesulfonic) or amines (triethylamine, piperidine, pyridine, etc.).[2] However, the latter lack sufficient dehydrating activity, therefore they can be used only if the reaction equilibrium is shifted towards the products. Otherwise, additional tools should be applied to make the equilibrium state more favorable, such as azeotropic distillation of water and use of ceolytes or anhydrous inorganic salts.

The methods mentioned above still find application; nevertheless, they cannot satisfy the growing demands of organic and medicinal chemistry. Therefore it is not surprising that water scavengers have evolved drastically since the 19th century (Figure 1). Some examples of these regents include Al_2O_3, MgO, $TiCl_4$, cation-exchanged zeolites, SiO_2, calcite, fluorite, modified Mg-Al hydrotalcite, and Lewis acidic ionic liquids.[3–7] Several criteria for reagents that can be expected to be efficient as water scavengers are formulated from both the literature data and our own experience (the most critical are italicized):

– stability to air exposure and long-term storage;
– commercial availability and low cost;
– *wide applicability*;
– solubility in common organic solvents;
– high activity under normal conditions and the possibility of use at elevated temperatures;
– *simple and efficient synthetic protocols*;
– high selectivity, conversion and yields in the reactions;
– *simple procedures for the separation of the products formed from the scavenger*.

Organosilicon compounds satisfy most of the requirements cited above. The chemical behavior of these compounds is determined primarily by the tendency of the silicon atom to expand its valence shell, giving rise to five- and six-coordinate intermediates, therefore, they can be considered as Lewis acids. Unlike many traditional metal-centered activators, silicon Lewis acids are compatible with most synthetically valuable nucleophiles and are not prone to aggregation, thus substantially simplifying the analysis of the reaction mechanisms.[8]

Most of the organosilicon compounds discussed in this review are halogenosilanes (in particular, chlorotrimethylsilane). Apart from increasing the Lewis acidity of silicon atom, the intrinsic role of the halogeno substituent is related to the high acceptability of Si–X bond towards hydrolysis which is explained by the strong preference of silicon
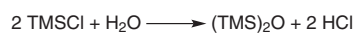
to form silicon–oxygen bonds. In addition, an easily removable hydrogen halide is formed upon hydrolysis of halogenosilanes (Scheme 1), which increases the catalytic activity of the system further. The advantages that halogenosilanes have as water scavengers in reactions of carbonyl compounds are summarized in Figure 2.

$$2 \text{ TMSCl} + H_2O \longrightarrow (TMS)_2O + 2 \text{ HCl}$$

Scheme 1 Hydrolysis of chlorotrimethylsilane

The main goal of this review is to survey the literature data on the application of organosilicon compounds as water scavengers in the reactions of carbonyl compounds. The reactions leading to carbon–carbon and carbon–nitrogen bond formations, formation of iminium salts by elimination reactions, and heterocyclizations are all considered. In some cases, related transformations resulting in elimination of small molecules other than water are also discussed. It should be noted that the use of polyphosphoric acid trimethylsilyl ester (PPSE) and related compounds is beyond the scope of this review, as the properties of this water scavenger are defined by the P–O–P fragment and are not related to the silicon atom.[9]

Biographical Sketches

Dmitriy M. Volochnyuk was born in 1980 in Irpen, Kiev region, Ukraine. He graduated from Kiev State University, Chemical Department in 2002 and was awarded an MS in chemistry. He recieved his PhD in chemistry in 2005 from Institute of Organic Chemistry, National Academy of Sciences of Ukraine under the supervision of Dr. A. Kostyuk with research concentration in the chemistry of enamines. At present, he divides his time between the Institute of Organic Chemisty, as deputy head of the Organophosphorus Department, senior scientific worker, and Enamine Ltd (Kiev, Ukraine), as Director of Chemistry. His main interests are fluoroorganic, organophosphorus, heterocyclic and combinatorial chemisiry. He is co-author of 61 papers.

Sergey V. Ryabukhin was born in Kirovograd in 1979. He received his MS in chemistry (2001) and PhD in organic chemistry (2007) from Kyiv National Taras Shevchenko University under the supervision of Prof. Dr. Sci. Andrey A. Tolmachev. At present, he works in Enamine Ltd. (Kyiv, Ukraine) as a director of the Combinatorial Chemistry Department and lectures about combinatorial chemistry in Kyiv National Taras Shevchenko University. His scientific interests include combinatorial chemistry, molecular design, drug discovery, modern methods in organic synthesis, chemistry of heterocyclic compounds, bioorganic and medicinal chemistry. He is co-author of 30 papers.

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Oleksandr O. Grygorenko was born in Brody in 1982. He received his MS in chemistry (2004) and PhD in organic chemistry (2007) from Kyiv National Taras Shevchenko University under the supervision of Prof. Dr. Sci. Igov V. Komarov. At present, he divides his time between Kyiv National Taras Shevchenko University as Assistant Professor, and Enamine Ltd. (Kiev, Ukraine) as researcher in the Custom Synthesis Department. His scientific interests include modern methods in organic synthesis, molecular rigidity concept, chemistry of amino acids and related compounds, bioorganic and medicinal chemistry. He is co-author of 8 papers.
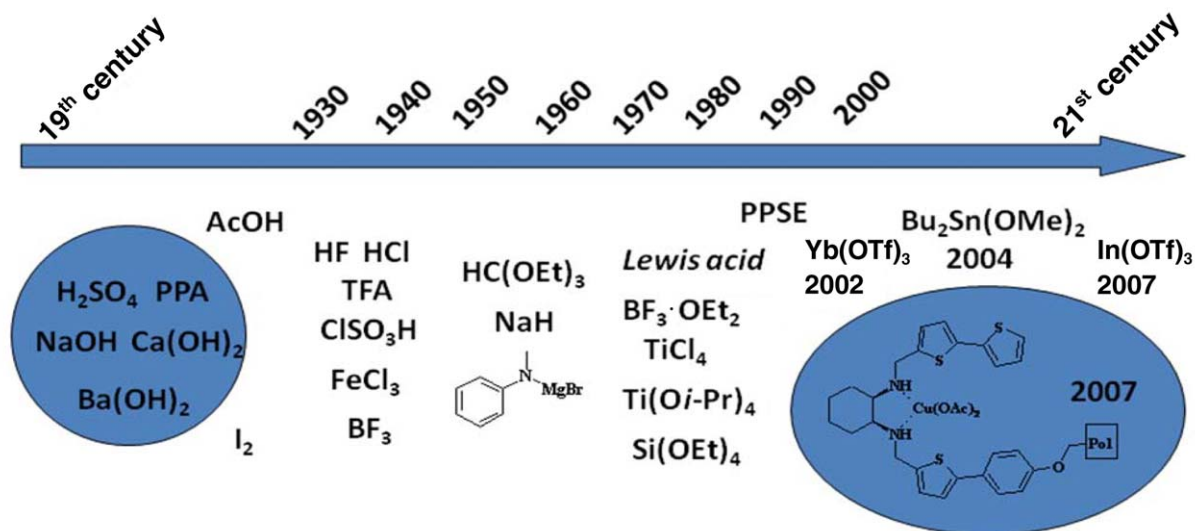
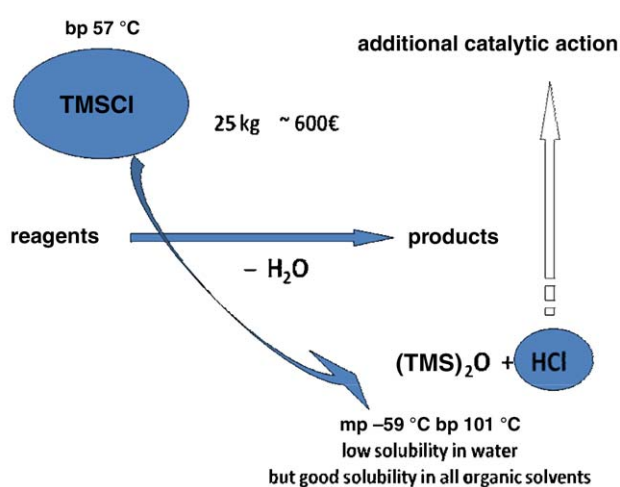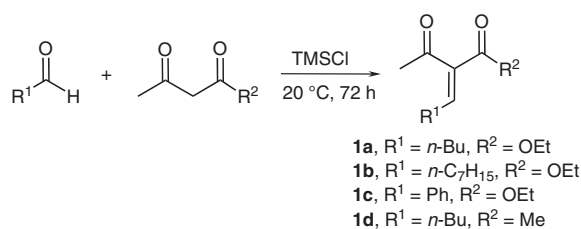**Figure 1** Evolution of water scavengers

Figure 2 Advantages of chlorotrimethylsilane as water scavenger

2 Reactions Leading to Carbon–Carbon Bond Formation

In this section, silicon-promoted reactions of aldehydes and ketones with carbon nucleophiles such as carbonyl compounds, activated alkenes and aromatic compounds are considered. Most of the reactions discussed include the use of chlorotrimethylsilane itself, or as a reagent component, as water scavengers.

2.1 Aldol-Type Condensations

One of the first literature examples of chlorotrimethylsilane-mediated aldol-type condensation was reported by Zav'yalov and co-workers.[10a] Aliphatic and aromatic aldehydes reacted with ethyl acetoacetate under mild conditions to give Knoevenagel adducts **1** in 70–75% yields (Scheme 2).

1a, R^1 = *n*-Bu, R^2 = OEt
1b, R^1 = *n*-C$_7$H$_{15}$, R^2 = OEt
1c, R^1 = Ph, R^2 = OEt
1d, R^1 = *n*-Bu, R^2 = Me

Scheme 2

The method was extended to some other carbonyl compounds.[10b] In particular, Knoevenagel adduct **1d** was obtained in condensation of butyraldehyde and acetylacetone. Reaction of benzaldehyde with diethyl malonate or *p*-bromoacetophenone in the presence of chlorotrimethylsilane required the use of zinc chloride as cocatalyst; compounds **2a**,**b** were obtained from these reactions in 60–70% yields. Reaction of benzaldehyde with acetylacetone, acetophenone and α-bromoacetophenone afforded the β-chloro ketones **3**, **4a** and **4b**, respectively (Scheme 3).

A chlorotrimethylsilane–*N*,*N*-dimethylformamide system was applied to the synthesis of 5-(arylmethylene)hexahydropyrimidine-2,4,6-triones **5** (from barbituric acid and the corresponding aromatic aldehydes) possessing immunosuppressive, fungicidal and anti-inflammatory activities (Scheme 4).[11]
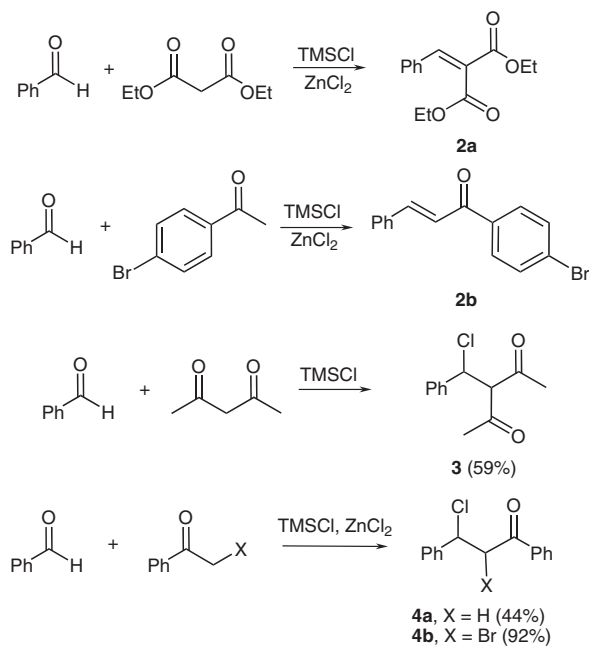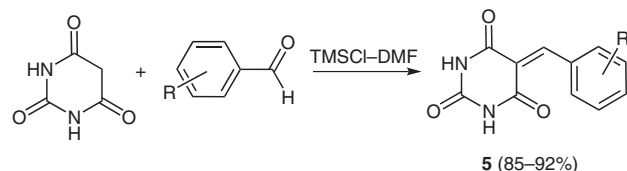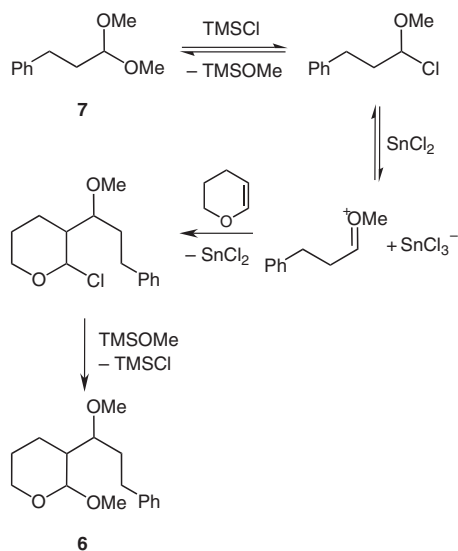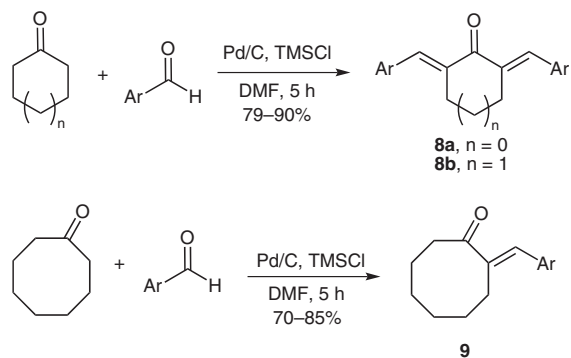
Combinations of chlorotrimethylsilane with other Lewis acids (e.g., SnCl$_2$,[12–14] BF$_3$·OEt$_2$,[13] TiCl$_4$[15] or InCl$_3$[16]) were found to be efficient as promoters for the addition reactions of aldehydes, acetals and α,β-unsaturated ketones with π-donor alkenes (enol silyl ethers, dihydropyrans, styrenes) as well as for Knoevenagel-type condensations under very mild conditions.[8] For example, adduct **6** was obtained in 64% yield by the reaction of 3-phenyl-1,1-dimethoxypropane (**7**) and 3,4-dihydropyran in the presence of chlorotrimethylsilane and tin(II) chloride at 0 °C (Scheme 5).[12]

Scheme 3
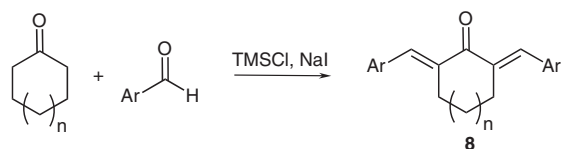

Scheme 4

Scheme 5

Scheme 6

8 in high yields. In the case of cyclooctanone, the 1:1 adducts **9** were obtained exclusively (Scheme 6).

Reaction of acetophenones and aromatic aldehydes under the conditions described above allowed for the substituted alkylideneacetophenones **10** to be obtained, whereas the analogous transformation in the case of cycloalkanones and aliphatic aldehydes led to the 2-alkylidenecyclo-alkanones **11** (Scheme 7). These products were also obtained when a chlorotrimethylsilane–ytterbium(III) tri-flate system was used as reaction promoter.[18]
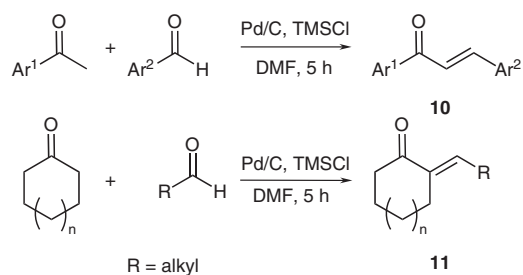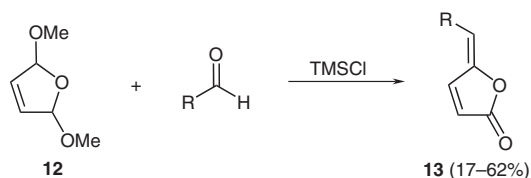

Scheme 7

α,α′-Bis(benzylidene)cycloalkanones **8** were also obtained, in 70–95% yields, by the reaction of alicyclic ketones and aromatic aldehydes in the presence of iodotrimethylsilane, generated in situ from chlorotrimethylsilane and sodium iodide in acetonitrile (Scheme 8).[19]
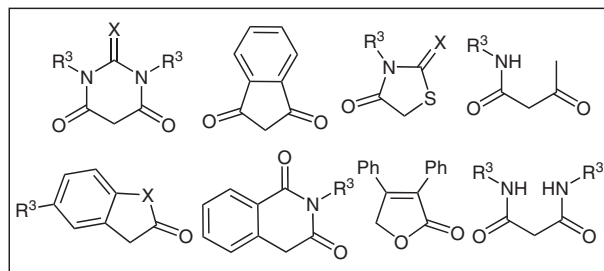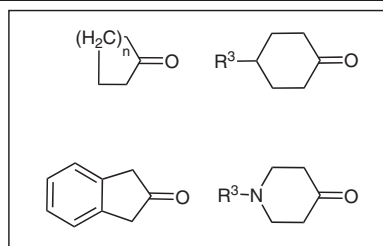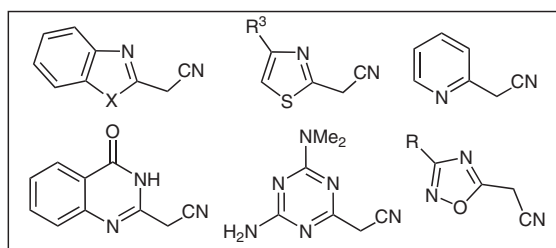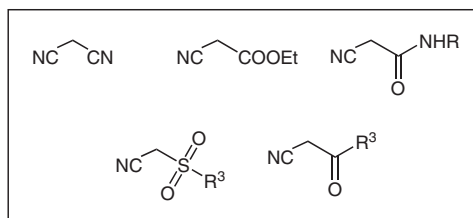

Scheme 8

The chlorotrimethylsilane-induced condensation of 2,5-dihydro-2,5-dimethoxyfuran (**12**) and aromatic or heteroaromatic aldehydes led to the formation of the corresponding γ-arylidene-α,β-butenolides **13** in 17–62% yields (Scheme 9).[20,21]

All of the procedures described above for Knoevenagel-type condensations are limited in scope due to the volatil-

Recently, a system of chlorotrimethylsilane, *N,N*-dimeth-ylformamide and palladium-on-carbon was shown to be an efficient catalyst in the aldol condensation of aldehydes with cycloalkanones and acetophenones.[17] In particular, the reaction of cyclopentanone and cyclohexanone with aromatic aldehydes led to the formation of the 2:1 adducts
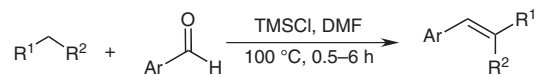
Scheme 9

Scheme 10 Selected examples of methylene active compounds R^{1}CH$_2$R^2 are given

ity of chlorotrimethylsilane (bp 57 °C). In the case of the substrates possessing low reactivity, a modification of the water scavenger is needed; for example, introducing a second Lewis acid as a co-reagent. An alternative approach[22] includes performing the reactions in sealed reactors, which allows heating of the reaction mixture to the desired temperature without loss of chlorotrimethylsilane or hydrogen chloride from the reaction mixture. The optimized reaction conditions [TMSCl (3 equiv), DMF, 100 °C, 0.5–6 h] allowed for the execution of Knoevenagel-type condensations of aromatic aldehydes with cyanoace-

tic acid derivatives, hetaryl acetonitriles, cycloalkanones [in this case, α,α′-bis(arylidene)cycloalkanones **8** were obtained] and cyclic methylene active compounds (Scheme 10).

The proposed mechanistic scheme for the reaction postulates a double function for chlorotrimethylsilane as activator for both the aldehyde and the methylene reaction components, owing to the formation of the silyl derivatives **14a–c** and **15a–c** (Scheme 11). The latter react to form intermediates **16a–c**. In the next step, extrusion of hexamethyldisiloxane (HMDS) and elimination of hydrogen chloride occur from **16a–c**, giving the final products **17a–c**.[22]

The condensation proceeds in a stereoselective manner affording exclusively alkenes that possess a *trans* disposition of the aryl substituent and the possible silylation site (circled in Scheme 11) even if such a product is not the most thermodynamically stable of the two possibilities (as in the case of compound **18a**).[22]

The method discussed above was successfully applied to less reactive substrates such as aryl methyl ketones and methyl derivatives of π-acceptor heterocycles (Scheme 12).[22]

Other methylene active compounds were also used as substrates in chlorotrimethylsilane-mediated Knoevenagel-type condensations, including hydroxymethyl, chloromethyl and tosyloxymethyl derivatives of heterocycles (Scheme 13 and Scheme 14).[23] The latter transformations allowed for the preparation of chlorovinyl derivatives **19** that are difficult to obtain by other methods.

When *o*-dialkylamino aldehydes were used as carbonyl components in chlorotrimethylsilane-mediated Knoevenagel-type condensations, the reactions were accomplished by way of ring fusion; this is referred to as the *T*-amino effect (Scheme 15).[24,25] A set of methylene active compounds was successfully applied to this transformation under optimized reaction conditions [TMSCl (4 equiv), DMF, 100 °C, 12 h]. In the case of pyridine as a solvent, benzylidene derivatives were obtained as a result of the usual Knoevenagel reaction. Thus, free hydrogen chloride, which is formed in *N,N*-dimethylformamide and not in pyridine as a solvent, is essential for the *T*-amino effect.

When aldehydes processing cyclic dialkylamino moieties were applied to these conditions, tricyclic fused heterocycles **20** were obtained.

When Meldrum's acid (**21**) was used as a substrate in the reaction described above, fused nipecotic acid derivatives **22** were obtained in a one-pot procedure (Scheme 16).[26] In the latter reaction, moderate diastereoselectivity was observed (de ~60%).

A system comprising chlorotrimethylsilane, sodium iodide, and acetonitrile–dichloromethane was successfully applied to promote a reductive Knoevenagel-type condensation.[27,28] The reaction results in C-arylmethylation of the corresponding methylene active compound (e.g.,
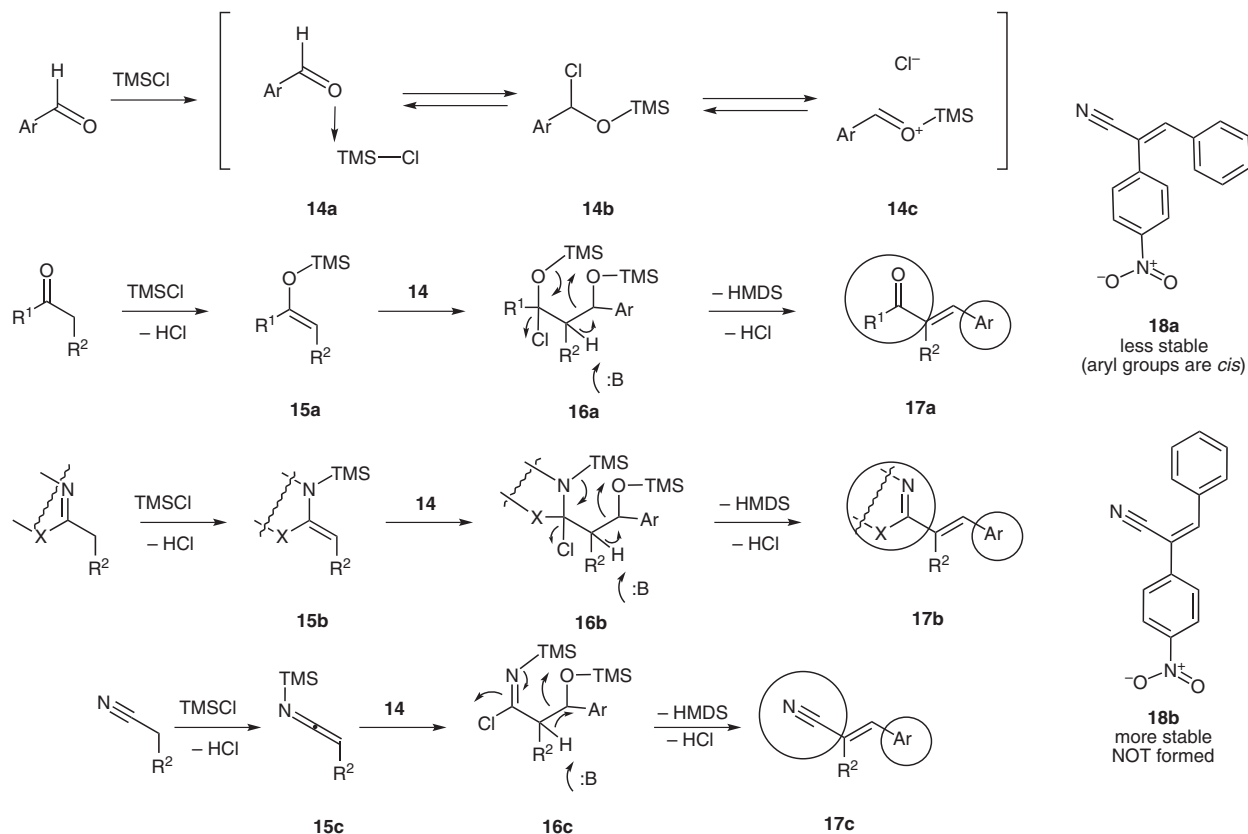
**Scheme 11**   Mechanistic scheme for the chlorotrimethylsilane-promoted Knoevenagel-type condensation
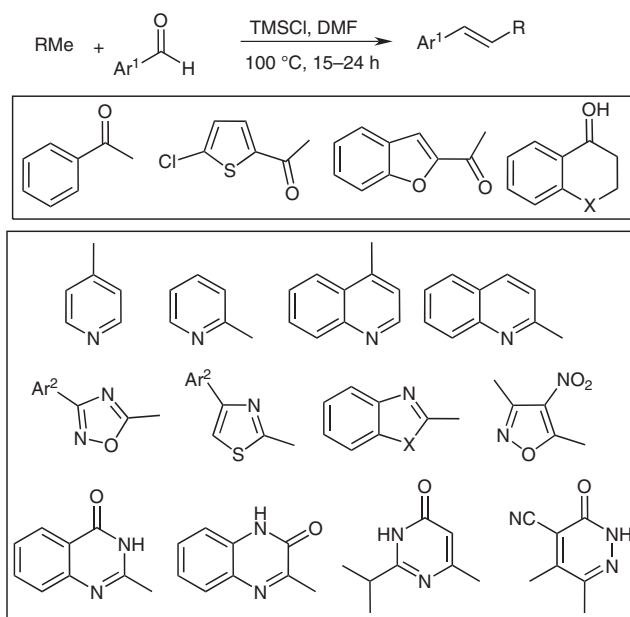
Scheme 12   Selected examples of compounds RMe are given; X = O, S, NR[1]

Scheme 13

acetylacetone or ethyl acetoacetate) thus leading to the products **23**. The proposed mechanism for this reaction is shown in Scheme 17. The postulate is supported by the isolation of intermediate **24a** (68%) in the case where diethyl ether was used as the solvent.[27]
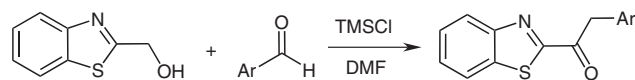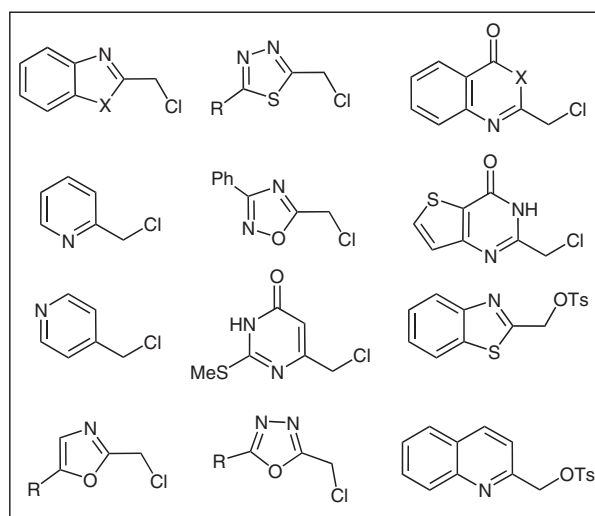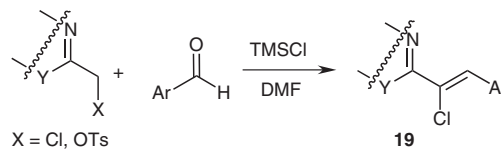
Scheme 14   Selected examples of heterocyclic derivatives are given

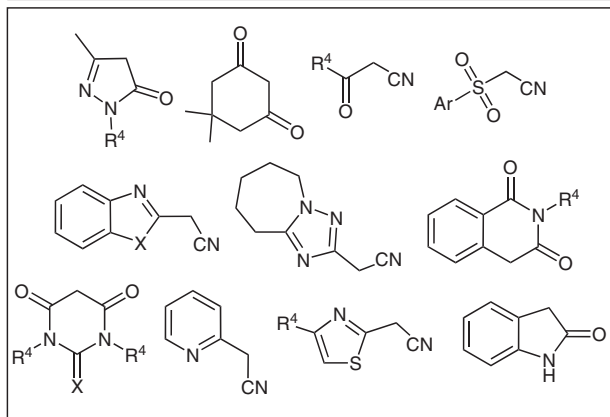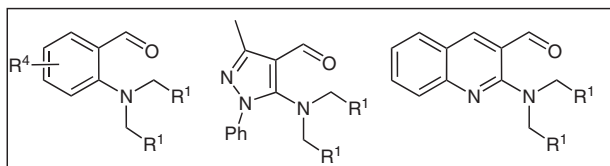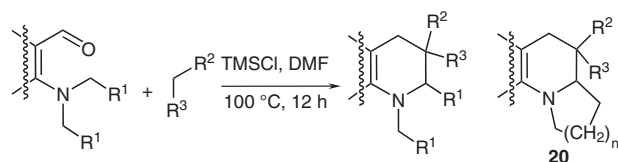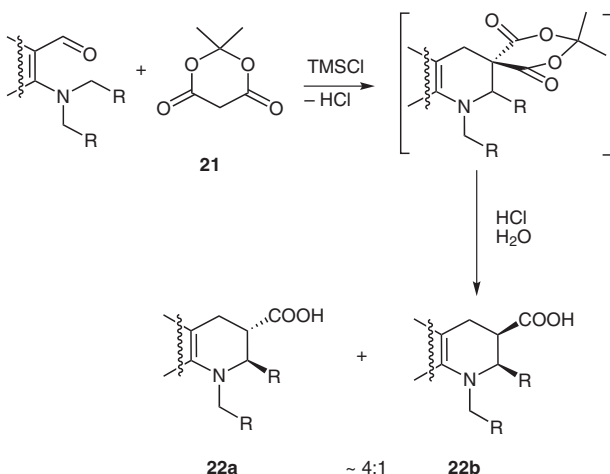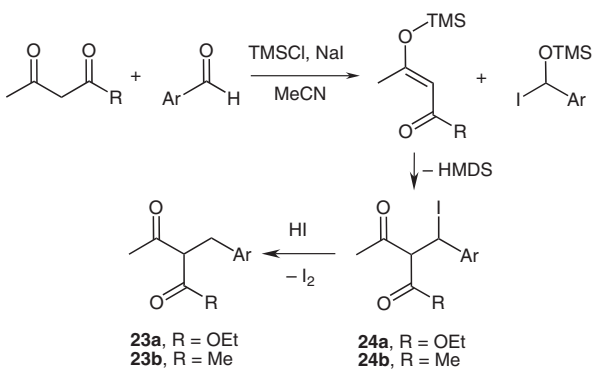**Scheme 15** Selected examples of aromatic aldehydes and methylene active compounds are given
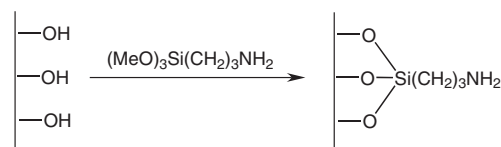

Scheme 16

Scheme 17

An example of a heterogeneous catalyst used in Knoevenagel-type condensations is represented by silica gel functionalized with amino groups; this catalyst was prepared by the treatment of silica gel with (3-aminopropyl)trimethoxysilane (Scheme 18).[29]

Scheme 18

In some cases, the Knoevenagel reactions discussed above were accomplished by self-condensation of the starting aldehydes.[13,17,30,31] Analogous halogenosilane-promoted self-condensations of preparative significance were also reported in the literature. Thus, acetone and cyclohexanone underwent self-condensation smoothly, in the presence of a chlorotrimethylsilane–sodium bromide system, to give the corresponding β-bromo ketones (Scheme 19).[30]
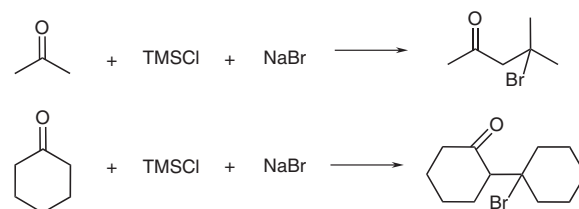
Scheme 19

Aldehydes of the formula RCH_2CHO formed self-condensation products **26** in 78–89% yields in the presence of iodotrimethylsilane. A mechanistic scheme of the reaction was suggested. The key step of the transformation was postulated to be the reaction between trimethylsilyl-iodohydrine **27** (formed by TMSI addition to the starting aldehyde) and trimethylsilyl enolate **28** (formed from **27** by HI elimination) (Scheme 20).[13]
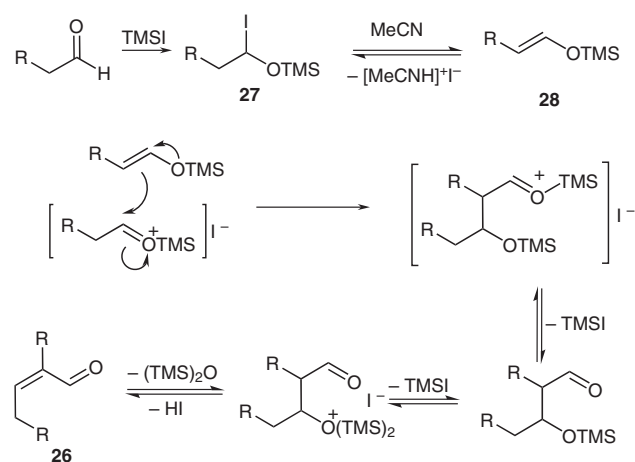
Scheme 20

Complexes of chlorotrimethylsilane with Lewis acids appeared to be more efficient as promoters of aldehyde self-condensations than iodotrimethylsilane. That can be explained by lower nucleophilicity of complex anion [LA·Cl]⁻ (where LA is Lewis acid) comparing to iodide ion. Trimethylsilyl triflate (TMSOTf) appeared to be the most efficient among the reagents used for this reaction.[13]

2.2   Other Reactions

Apart from the aldol-type condensations discussed above, the transformations considered in this section include reactions of C-electrophiles with activated alkenes and aromatic compounds.

The reaction of aliphatic aldehydes with 1,1-diarylethylenes led to the formation of complex mixtures that include 1,1-bis(2,2-diarylethylenyl)alkanes **29** and cyclic ketals **30** as the main products.[13] In contrast, chlorides **31** were the only products formed, in 80% yield, in the reaction of acetals and styrene in the presence of chlorotrimethylsilane–tin(II) chloride (Scheme 21).[12]
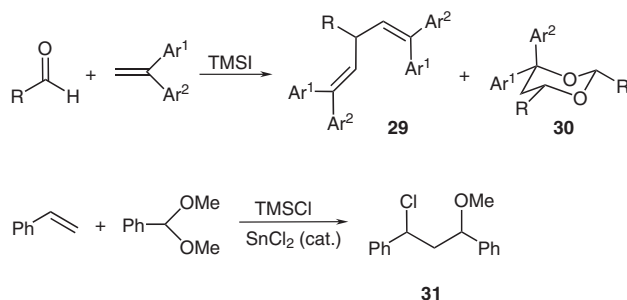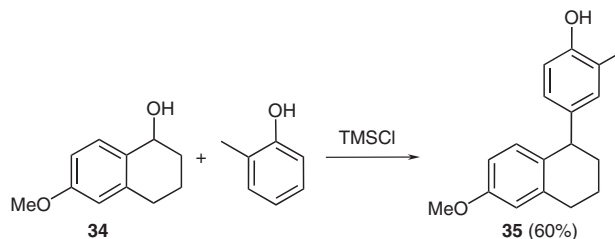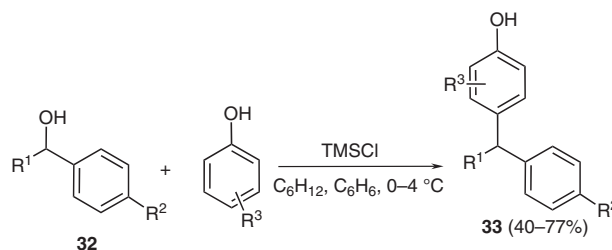

Scheme 21

Chlorotrimethylsilane is a convenient catalyst in Friedel–Crafts reactions.[32,33] In particular, it was applied successfully in the condensation of alcohols **32** and substituted phenols that led to diarylmethanes **33**. In an analogous reaction of o-cresol and secondary alcohol **34**, compound **35** was obtained in 60% yield (Scheme 22).[32]

A chlorotrimethylsilane-promoted reaction of salicylic aldehyde and 1-methylfuran allowed (2-hydroxyphenyl)difurylmethane (**36**) to be obtained in 90% yield (Scheme 23).[33]

3   Reactions Leading to Carbon–Nitrogen Bond Formation

3.1   Two-Component Condensations

In this section, two-component condensations of aldehydes and ketones with various nitrogen-containing compounds (e.g., primary amines, amides, ureas, and hydrazines) leading to the formation of imines or derivatives thereof are under consideration. Analogous conden-

Scheme 22
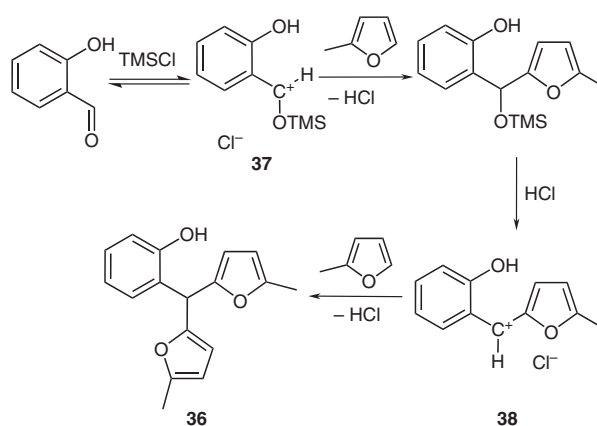
Scheme 23

sations with secondary amines affording iminium salts are also discussed.

A chlorotrimethylsilane–N,N-dimethylformamide system was successfully applied in the reaction of cyclic β-diketones (cyclohexane-1,3-dione, dimedone) and aromatic amines to give N-arylenamino ketones **39**, which are intermediates in the syntheses of some analgesics (Scheme 24).[34]
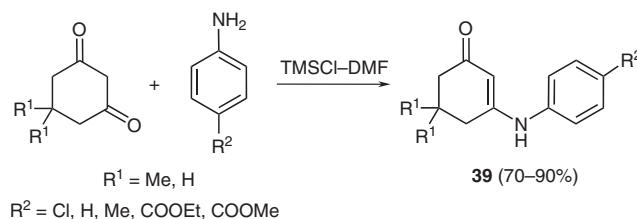
Scheme 24

Use of chlorotrimethylsilane as the reaction promoter allowed Schiff bases to be obtained, even from weakly basic amines. An example of this is shown in Scheme 25.[35]
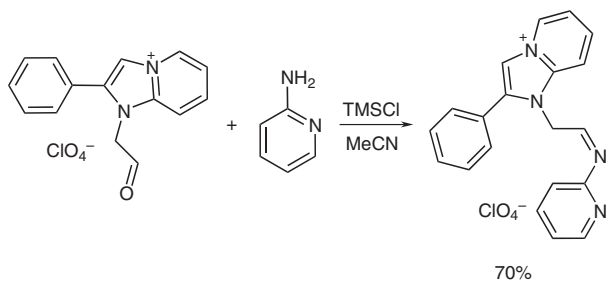
Scheme 25

The condensation of aromatic/heteroaromatic amines with 1-methylparabanic acid was studied extensively. In particular, reaction of 1-methylparabanic acid and preclathridin A (**40**) in the presence of chlorotrimethylsilane, triethylamine, imidazole and DMAP afforded alkaloid clathridin A (**41**) regioselectively in 73% yield (Scheme 26).[36]
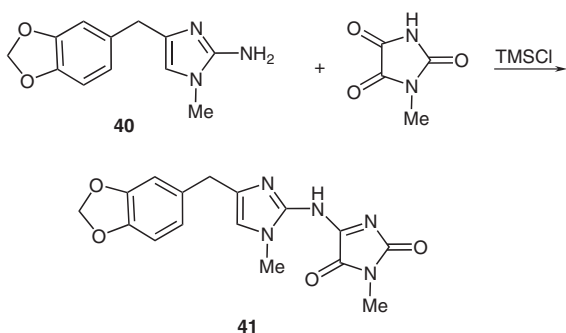
Scheme 26

Tetraethylorthosilicate [Si(OEt)$_4$] was proven to be an efficient reagent in the synthesis of sterically hindered ketimines **42** and **43** (Scheme 27).[37] This water scavenger does not form acidic products upon hydrolysis; thus, an excess of the amine is not needed in the reaction.

Scheme 27

Reactions of *o*-(dialkylamino)anilines and aromatic aldehydes performed in sealed reactors at 100 °C resulted in the *T*-amino effect, thus leading to the formation of dihydrobenzimidazoles **44**. To avoid the acid-catalyzed dis-

mutation of the final products, pyridine was used as solvent. This transformation was extended to include the use of acetophenones, cyclic ketones and heterocyclic aldehydes as the carbonyl components in the reaction (Scheme 28). The 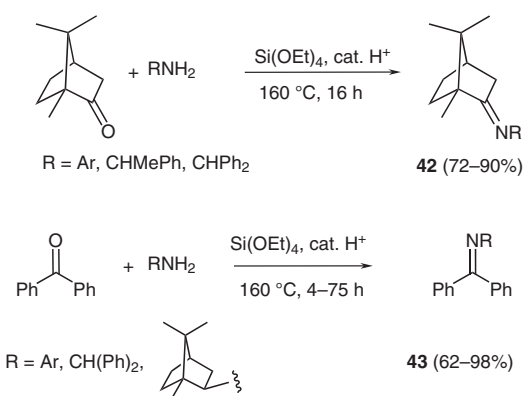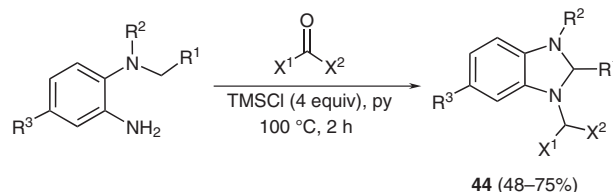reaction scope showed its limitations in the case of electron-rich aldehydes; in this case, dismutation products were isolated from the reaction mixture. The *T*-amino effect was also not observed in the case of *o*-piperidinylanilines as amine components; usual imine formation was observed instead.[38]

Scheme 28

The proposed mechanistic scheme suggests silylated aminal **45** as a key reaction intermediate. A [1,6]-hydride shift in **45** accompanied by silicon–oxygen bond formation affords iminium salt **46**, which undergoes fast cyclization into the final product (Scheme 29).[38]
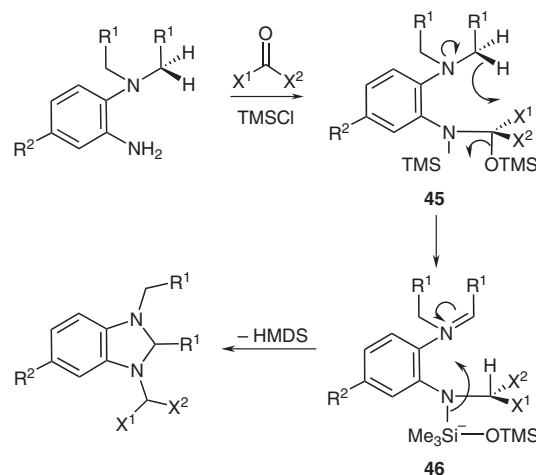
Scheme 29

Carbonyl compounds and amides or ureas were found to react with chlorotrimethylsilane–*N*,*N*-dimethylformamide at room temperature to afford the corresponding condensation products in good yields (67–92%). The reaction of benzaldehyde and benzamides allowed for arylidenebisbenzamides **47** to be obtained, whereas acetylacetone and ethyl acetoacetate led to enamine derivatives **48** (Scheme 30).[39]

This method was modified for the synthesis of tosylformamides **49** – substituted tosylmethylisonitrile precursors. It was shown that aromatic, heteroaromatic and aliphatic aldehydes reacted with formamide (or acetamide) and chlorotrimethylsilane in toluene–acetonitrile (1:1) at 50 °C to afford the corresponding condensation products. In
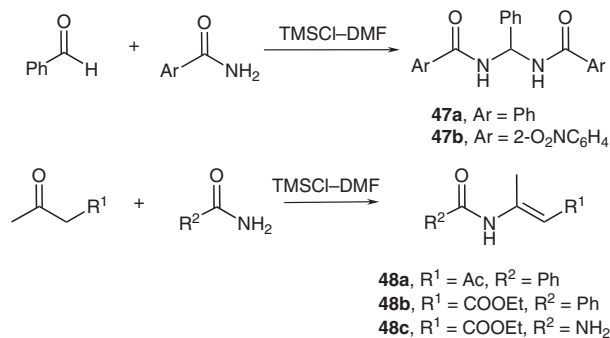
Scheme 30

situ reaction of the latter with toluenesulfinic acid allowed for compounds **49** to be obtained in excellent yields (Scheme 31).[40]
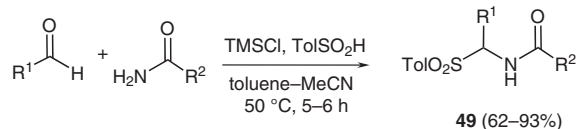
Scheme 31

Recently, tetraethylorthosilicate was used as a reaction promoter to obtain aromatic and heteroaromatic N-tosylaldimines **50** from p-toluenesulfonamide and corresponding aldehydes (Scheme 32).[41]
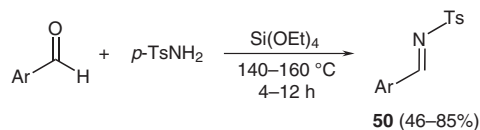
Scheme 32

Reductive alkylation of unsubstituted and monosubstituted ureas by aromatic aldehydes was achieved using chlorotrimethylsilane in combination with sodium borohydride. It should be noted that monoalkylation products **51** were obtained only when a large excess (up to 20 equiv) of urea was used; otherwise, bis-alkylation occurred (Scheme 33). The reaction was carried out under mild conditions, and the products were easily isolated from the reaction mixture. However, the method was not successful for enolizable or α,β-unsaturated aldehydes.[42]

An analogous reaction of aromatic aldehydes with thiourea and chlorotrimethylsilane followed by sodium borohydride reduction of the intermediate products afforded monosubstituted thioureas **52**. When N-monosubstituted thioureas were subjected to these conditions, N,N′-disubstituted thiuoreas **53** were formed in good yields (Scheme 34).[43]

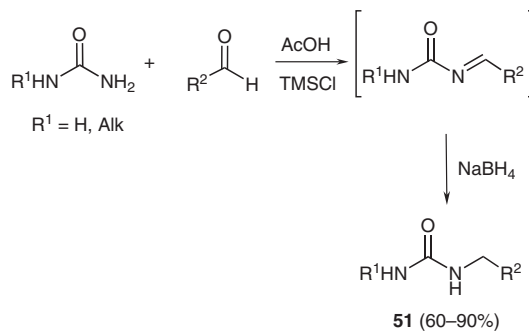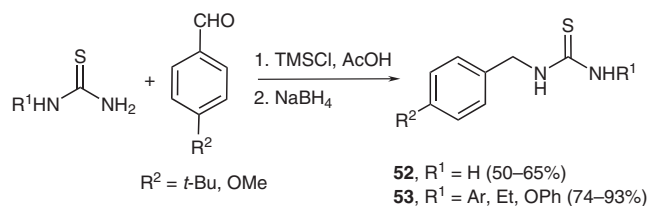The chlorotrimethylsilane-mediated construction of hydrazones was used in the syntheses of various complex organic molecules, including the macrolide antibiotics rutamycin B (obtained via intermediate **54**)[44,45] and oligo-

Scheme 33

Scheme 34

mycin C (via **55**),[45,46] the spiroketal polyketide antibiotics spirofungins A and B (via **56**),[47] the polyether antibiotic X-206 (via **57**)[48] and the secondary metabolite ulapualide A (via **58**)[49] (Scheme 35).

Reaction of aldehydes with primary or secondary amines, α-amino esters, O-trimethylsilylhydroxylamine and N,N-dimethylhydrazine in the presence of chlorotrimethylsilane and lithium perchlorate followed by reduction of the carbon–nitrogen double bond ($BH_3 \cdot NEt_3$) afforded amines **59**, α-amino esters **60**, N-substituted hydroxylamines **61** and hydrazines **62**, respectively (Scheme 36).[50]

An approach to the synthesis of iminium salts that includes the reaction of carbonyl compounds with dialkylaminotrimethylsilane and chlorotrimethylsilane has been developed. The corresponding products **63** were stable enough to be isolated in 75–93% yields and characterized (Scheme 37, see also Scheme 41). The method was applied to non-enolizable and α,β-unsaturated aldehydes and dimethylformamide. The procedure can also be utilized in the case of aldehydes capable of enolization if trimethylsilyl triflate is used instead of chlorotrimethylsilane.[51,52]

Reaction of the dialkylaminotrimethylsilane–chlorotrimethylsilane system with 3,3-dichloroacrolein afforded a mixture of salts **64** and **65** (Scheme 38). Compound **66** was isolated in 75% yield as a perchlorate salt from a mixture obtained by the reaction of dimethylaminotrimethylsilane and the precursor dialdehyde in the presence of chlorotrimethylsilane (Scheme 39).[51]

A modification of the method discussed above relies on using dialkylamines and in situ generated iodotrimethylsilane.[53,54] The first step of the reaction was amine silylation, leading to quantitative yield of the dialkylaminotrimethylsilane which then reacted with the
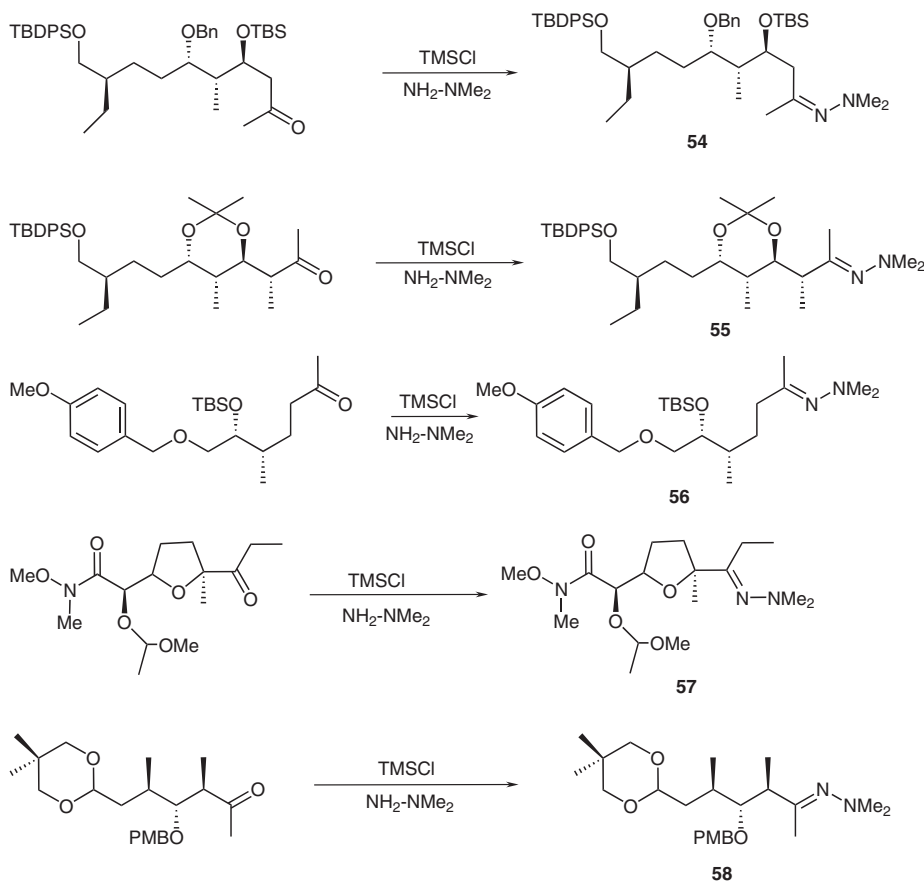
Scheme 35
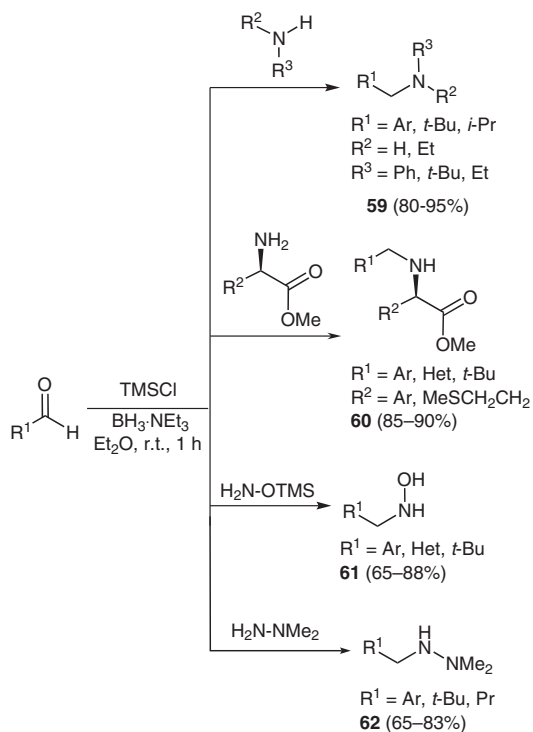
Scheme 36
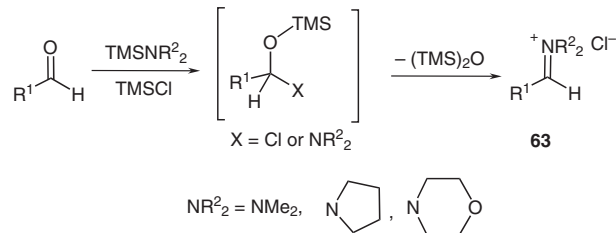
Scheme 37
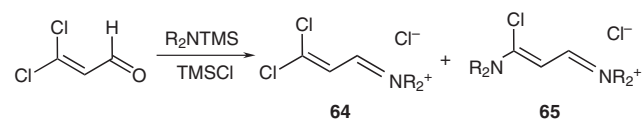
Scheme 38

aldehyde to give the iminium salt. This approach was used in the synthesis of dialkylamino-9H-pyrrolo[1,2-a]indoles **68** obtained in 68–84% yields from 2-(pyrrolyl)benzaldehydes **67** and secondary amine hydrochlorides by action of chlorotrimethylsilane in combination with sodium iodide and triethylamine, followed by intramolecular cyclization of the iminium salts thus formed (Scheme 40).[54]

Scheme 39

Scheme 40

$R^1 = R^2 = H$, $R^1 = R^2 = OMe$, $R^1 = Cl$, $R^2 = H$, $R^3 = Alk$
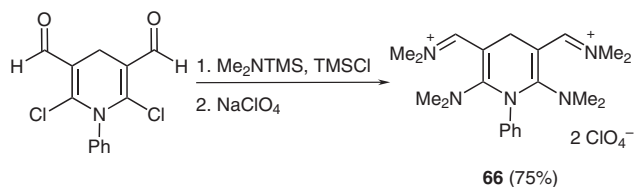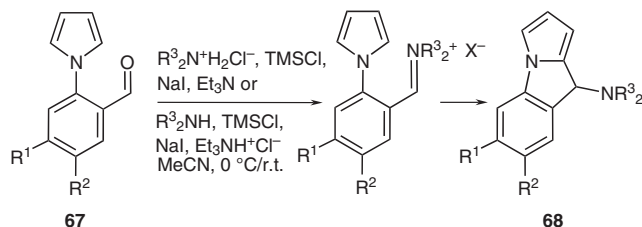
3.2 Three-Component Condensations

The transformations discussed in this section proceed in two steps: first, an imine or an iminium salt is formed, and this then reacts with a nucleophile to afford the three-component condensation product.

Chlorotrimethylsilane–lithium perchlorate in diethyl ether is a mild reagent for Mannich-type three-component condensations, and has allowed for the corresponding products to be obtained in high yields.[50,55–57] First, it was shown that aromatic and heteroaromatic aldehydes were aminoalkylated by trimethylsilylamines in the presence of lithium perchlorate.[58–63] Imines or iminium salts formed in the first step of the reaction were trapped by the corresponding nucleophile to afford corresponding amines **69**, **70** (Scheme 41). Later, the approach was modified in order to allow trimethylsilylamines to be generated in situ. In particular, reaction of aromatic aldehydes and (R)-α-phenylethylamine in the precence of chlorotrimethylsilane–lithium perchlorate led to the formation of chiral imines which reacted with organozinc compounds to give chiral amino esters **71** or amines **72** (Scheme 42).[55] It should be noted that moderate to high diastereoselectivities were achieved in these transformations (90% de for **71** and 40% de for **72**).
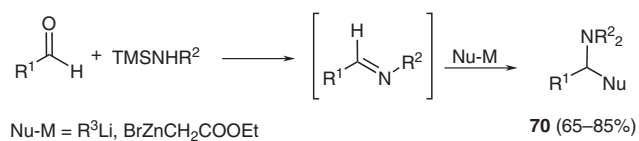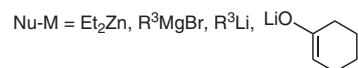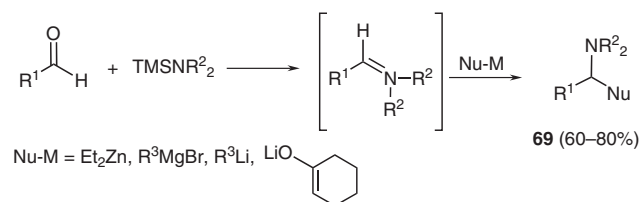
Scheme 41
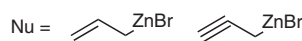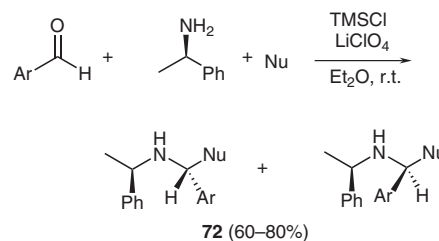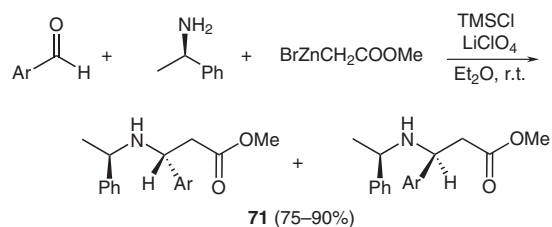
α-Aminophosphonates **73** were obtained in an analogous manner when trialkylphosphites were used as nucleophiles (Scheme 43).[56] This was a one-pot procedure and resulted in high yields and diastereoselectivities of the products, even in the case of α,β-unsaturated and some enolizable aldehydes.

Scheme 42

$R^1 = Ph, Bu; R^2 = Me, Et$ **73** (85–98%)
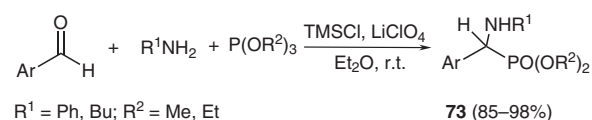
Scheme 43

A system comprising chlorotrimethylsilane, sodium iodide and triethylamine was used in the synthesis of β-amino ketones **74** from secondary amines, aldehydes and enamines (Scheme 44). The reaction resulted in high yields and diastereoselectivity; however, its use was limited to non-enolizable aldehydes.[53]
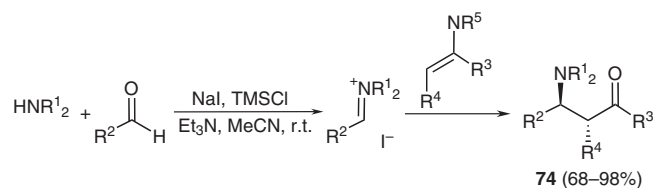
Scheme 44

3-Functionalized indoles **75** were prepared in high yields by the three-component reaction of aliphatic aldehydes, O-trimethylsilylhydroxylamine and indole by action of chlorotrimethylsilane in 5 M ethereal lithium perchlorate solution (Scheme 45).[53] α-(Hydroxylamino)alkyl/arylphosphonates **76** possessing antibacterial properties were obtained in an analogous manner (Scheme 46).[56]
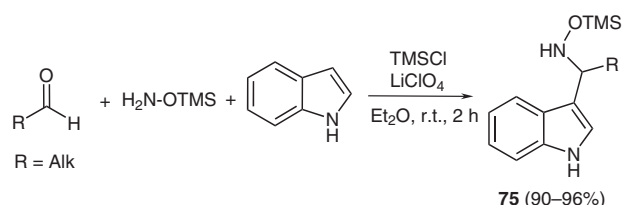
Scheme 45
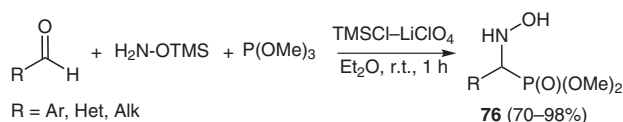
Scheme 46

4 Synthesis of Iminium Salts by Elimination Reactions

In the previous section, condensations of carbonyl compounds leading to the formation of iminium salts were mentioned. Another approach to the synthesis (or in situ generation) of iminium salts relies on the elimination of an *alcohol* or *amine* molecule from the corresponding α-amino ethers or aminals. These transformations bear resemblance to those discussed in the previous section; hence they are considered herein despite their being beyond the main goal of this review.

The first example of an iminium salt synthesis by elimination reaction involving the use of organosilicon compounds was reported in 1986 and included the reaction of dialkyl(alkoxymethyl)amines and trichloromethylsilane (Scheme 47). The corresponding iminium salts **77** were isolated in 85–98% yields and characterized.[64]
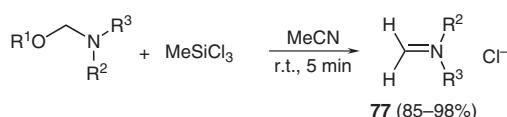
Scheme 47

The method was successfully applied to the regioselective aminomethylation of ketones. Thus, Mannich bases **78** were obtained in the reaction of silyl ethers and pre-generated iminium salts (Scheme 48).[65]

Scheme 48

The approach was extended to other chlorosilanes (Me$_3$SiCl, Me$_2$SiCl$_2$) and aminals.[66,67] Formations of iminium salts from chlorotrimethylsilane, dichlorodimethyl-

silane or trichloro(methyl)silane and dialkyl(alkoxymethyl)amines, as well as dichlorodimethylsilane or trichloro(methyl)silane and aminals were detected by spectral methods. However, in the case of chlorotrimethylsilane and aminals, the iminium ion was not observed.

The reaction of chlorotrimethylsilane with aminals and electron-rich aromatic heterocycles (i.e., *N*-methylpyrrole, furans) led to the formation of 2,5-disubstituted derivatives **83**, with chlorotrimethylsilane thus showing catalytic behavior. In the case of dichlorodimethylsilane and trichloro(methyl)silane, monosubstituted heterocycles **81** were isolated as hydrochlorides.[66,67]

To explain the results obtained, a mechanistic scheme was proposed for the transformations (Scheme 49). The first step of the reaction is supposed to be reversible aminal silylation. In the case of chlorotrimethylsilane, the concentration of the silylammonium salt **79a** is not high enough to generate iminium salt **80** due to the lowered stability of **79a**. In the presence of a nucleophile, quaternary salt **79a** reacts rapidly and irreversibly to give the product **81** and trimethylsilylamine **82a**. The hydrogen chloride formed in this step of the reaction then protonates amine **82a**, thus regenerating chlorotrimethylsilane; in other words, the latter acts as a catalyst. Compound **81** is a stronger nucleophile than the starting heterocycle, and hence reacts with quaternary ammonium salt **79** to give the 2,5-disubstituted heterocyclic derivatives **83** (Scheme 49).
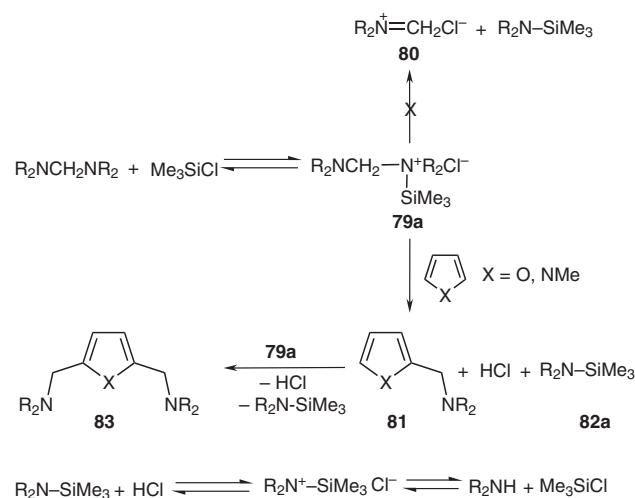
Scheme 49

In the case of dichlorodimethylsilane and trichloro(methyl)silane, the chlorine atom(s) present in the corresponding silylammonium salts **79b** weaken the neighboring carbon–nitrogen bond, thus activating the compounds towards formation of iminium salts **80**. On the other hand, (di)chloromethylsilylamines **82b** are not basic enough to capture the hydrogen chloride formed. The latter protonates amines **81**, thus preventing their further reaction with **80**, hence monosubstituted heterocycles **81** are obtained as the final products (Scheme 50).
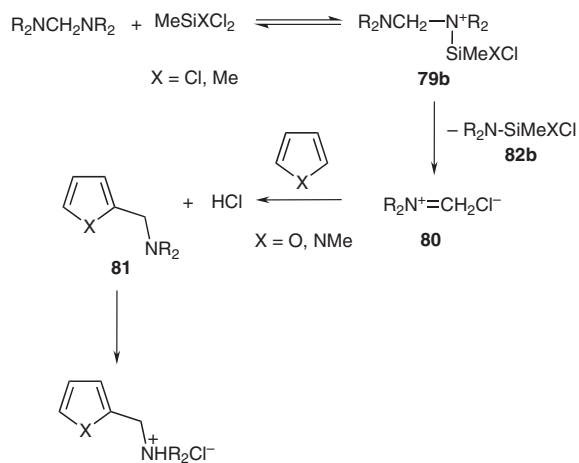
Scheme 50

Reaction of dialkyl(alkoxymethyl)amines with 1-methylpyrrole, 2-methylfuran and 1-methylindole afforded monosubstituted heterocycles as the main products (Scheme 51).[66]
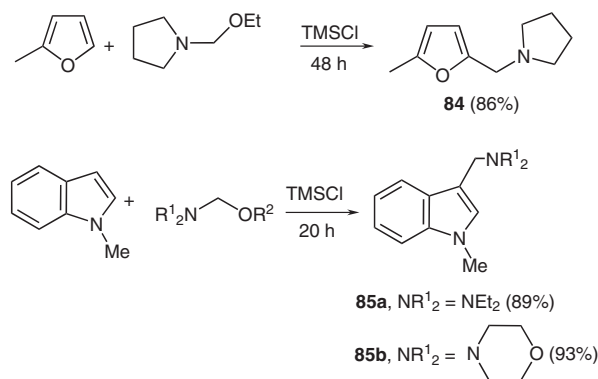
Scheme 51

1,3-Oxazolidines **86** were also shown to react with nucleophilic aromatic substrates in the presence of chlorotrimethylsilane, dichlorodimethylsilane or trichloro(methyl)silane. In particular, reaction of 3-methyl-1,3-oxazolidine (**86a**), furan and trichloro(methyl)silane allowed monosubstitution product **87a** to be obtained in 75% yield. Amino alcohol **87b** was obtained in 73–87% yields from **86a**, 2-methylfuran and either trichloro(methyl)silane or chlorotrimethylsilane. An analogous transformation of 3,4-dimethyl-5-phenyl-1,3-oxazolidine (**86b**) afforded the expected product **87c** in 80% yield (Scheme 52).[68]

N,N-Bis(alkoxymethyl)alkylamines such as **88** reacted with chlorosilanes to form α-alkoxymethyleneiminium salts **89** which are more reactive than their methyleneiminium counterparts.[69,70] In particular, a mixture of amines **90** and **91** was formed from **89** and 2-methylfuran at ambient temperature (Scheme 53). When the reaction time was increased or when an excess of chlorosilane was used, tertiary amine **91** became the main product even if
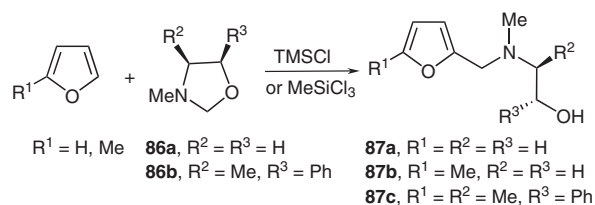
Scheme 52

salt **89** was synthesized preliminarily. That fact could be explained by generation of iminium salt **92** from the secondary amine **90**. For example, amine **91a** (R = *n*-Bu) was obtained from *N,N*-bis(methoxymethyl)butylamine (**88a**; R = *n*-Bu), 2-methylfuran and trichloro(methyl)silane in 87% yield.[70]
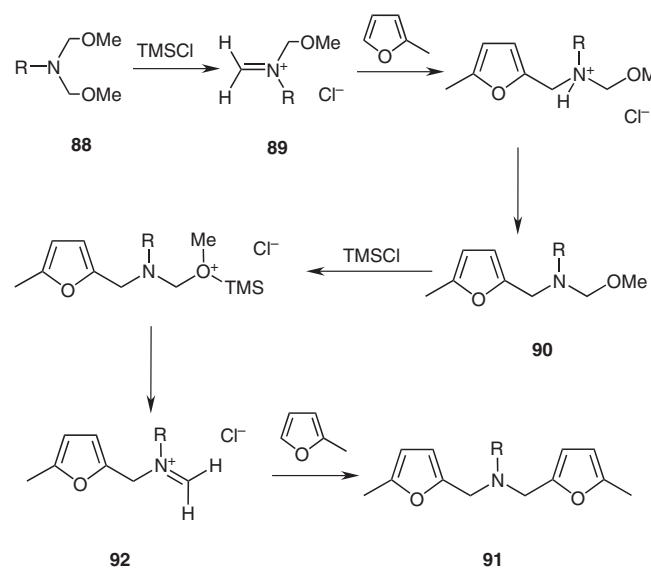
Scheme 53

This approach was recently extended to cyclic β-keto esters[71–73] and cycloalkanones.[74] In the case of cyclic β-keto esters, 3-azabicyclo[3.2.1]octanes **93a** and 3-azabicyclo[3.3.1]nonanes **93b** were obtained (Scheme 54);[71,72] these were then used in the synthesis of the alkaloid methyllycaconitine and its analogues. The method was also applied to the chiral *N,N*-bis(ethoxymethyl)(1′-phenylethyl)amine. Despite it not being possible to separate the diastereomers of the amino ketones obtained (**93**, R[1] = 1′-phenylethyl), the presence of the chiral auxiliary in the molecules was exploited in their further transformations.[73]
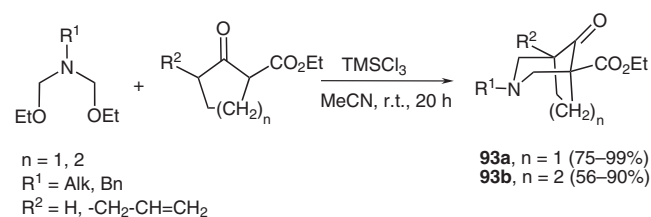
Scheme 54

The method was also applied to some cycloalkanones, including cyclooctanone, cycloheptanone and substituted cyclohexanones. In particular, azabicyclo[4.3.1]decanones **94** and azabicyclo[5.3.1]undecanone derivatives **95** were obtained from the corresponding cyclic ketones by treatment with chlorotrimethylsilane in acetonitrile at ambient temperature (Scheme 55). The scope and limitations of the approach were established; it was shown that variation of the substituent at nitrogen in *N,N*-bis(alkoxymethyl)alkylamine as well as the ring size or alkyl substituents α to the ketone did not affect the reaction progress significantly, whereas introduction unsaturated substituents or heteroatoms at that position lowered the yield of the product.[74]
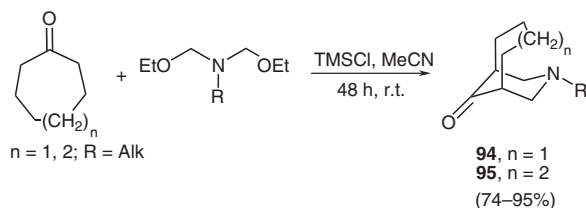
Scheme 55

5 Heterocyclizations

In this section, chlorotrimethylsilane-mediated heterocyclizations are under consideration. Modifications of classical transformations, such as the Biginelli reaction, Hantzsch and Friedlander syntheses, are among those discussed. In a separate section, 3-formylchromone recyclizations are illustrated. Some of the heterocyclization reactions were also mentioned previously (Schemes 15, 16, 28, 54 and 55).

5.1 Synthesis of O- and O,N-Containing Heterocycles

An early example of chlorosilane-mediated heterocyclization goes back to 1985 when it was shown that hydroxy and amino acid derivatives undergo cyclization upon treatment with chlorotrimethylsilane and a carbonyl compound (e.g., formaldehyde, acetaldehyde or acetone).[75] Thus, heating of paraform, lactic or mandelic acid and an excess of chlorotrimethylsilane afforded dioxolanone derivatives **96**.[76] Oxazolidines **97** and **98** were obtained from glycolic or lactic acid methylamides and acetone or formaldehyde (Scheme 56).[75,76]

X = O, NH, NMe   R² = H, Me   **96**, R¹ = Me or Ph, R² = R³ = H, X = O
R¹ = H, Me, Ph   R³ = H, Me   **97**, R¹ = Me or H, R² = R³ = H, X = NMe
                                98, R¹ = Me or H, R² = R³ = Me, X = NMe

Scheme 56

99a, R¹ = H, R² = R³ = Me (59%)
99b, R¹ = Me, R² = H, R³ = H (90%)
99c, R¹ = Me, R² = H, R³ = Me (95%)
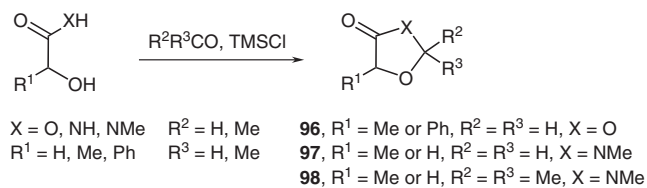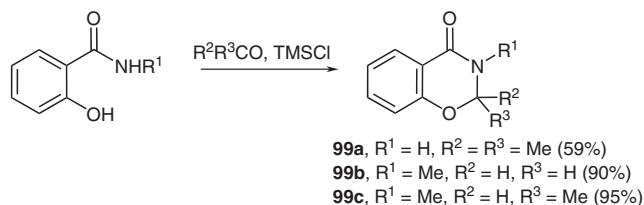
Scheme 57

An analogous transformation involving salicylic acid amides or *N*-methylamides and paraform, paraldehyde or acetone led to the formation of benzo-1,3-oxazine[2*H*]-4-ones **99** (Scheme 57).[75,76]

In the case of *N*-acetyl α-amino acids, the reaction required harsher conditions: for example, *N*-acetylvaline or *N*-acetylleucine reacted with paraform in an acetic acid–chlorotrimethylsilane mixture only under reflux. On the other hand, corresponding *N*-tosyl derivatives easily underwent cyclization at ambient temperature to give oxazolidinones **100** (Scheme 58).[76]

100a, R¹ = *i*-Pr, R² = Ac, R³ = R⁴ = H (70%)
100b, R¹ = *i*-Bu, R² = Ac, R³ = R⁴ = H (60%)
100c, R¹ = Me, R² = Ts, R³ = R⁴ = H (86%)
100d, R¹ = *i*-Bu, R² = Ts, R³ = R⁴ = Me (89%)
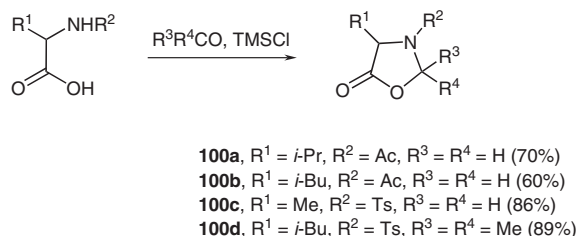
Scheme 58

4-Acetyl-2,2,5-trimethyl-2,3-dihydrofuran (**101**) was obtained in quantitative yield in a one-pot reaction involving acetylacetone, isobutyric aldehyde, a chlorotrimethylsilane–sodium iodide system and a stoichiometric amount of water. The overall process was a Knoevenagel condensation followed by cyclization (Scheme 59).[27]

101
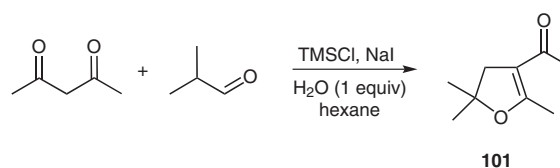
Scheme 59

An analogous transformation of dimedone led to the formation of 1,8-dioxooctahydroxanthenes **102** (Scheme 60). The reaction steps included a Knoevenagel condensation, a Michael addition and a cyclodehydration.[77]

4-Iodo-2,6-disubstituted tetrahydropyrans **103** were obtained at first by Prins cyclization of homoallyl alcohols **104** and aromatic aldehydes in the presence of in situ generated iodotrimethylsilane. The reaction was carried out in acetonitrile at ambient temperature for three to eight min-
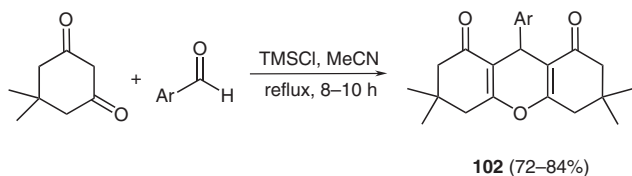
Scheme 60

utes to afford products **103** as mixtures of diastereomers. The all-*cis* isomer of **103** was the main product of the reaction, presumably due to its greater thermodynamic stability. The method appeared to be ineffective in the case of aliphatic aldehydes; however, it was successfully applied in the synthesis of the antibiotic (±)-centrolobine **105** (Scheme 61).[78]
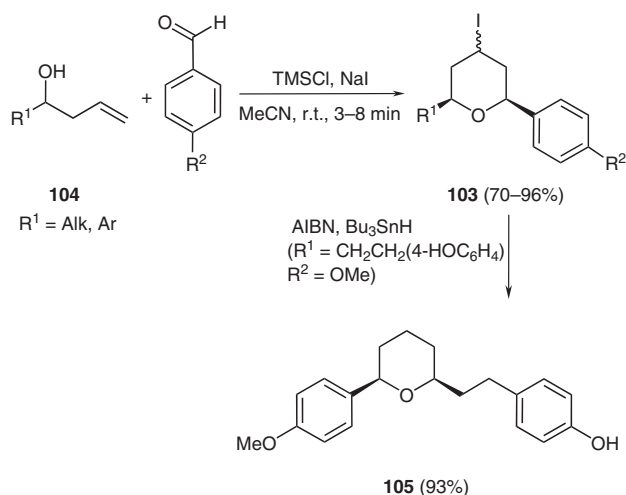
Scheme 61

5.2   Synthesis of Pyrimidines by Biginelli Reaction

One of the prevalent applications of chlorotrimethylsilane as a water scavenger is related to the Biginelli reaction and involves a three-component condensation of β-dicarbonyl compounds, aldehydes and ureas leading to the formation of 3,4-dihydropyrimidine-2-(1*H*)-one derivatives **106**. An original method included refluxing of a mixture of the starting materials in ethanol in the presence of hydrochloric acid as a catalyst and allowed the condensation products to be obtained in 20–60% yields (Scheme 62).[79]
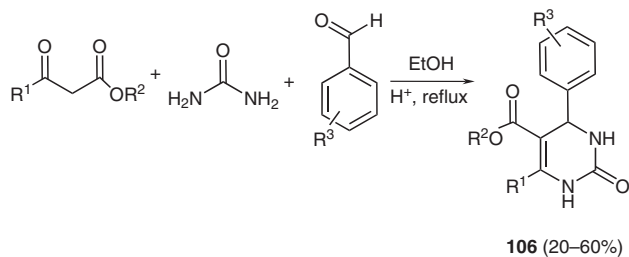
Scheme 62

In 1992, Zav'yalov and Kulikova showed that using a system of chlorotrimethylsilane and *N,N*-dimethylformamide allowed for the process to be carried out at ambient temperature. Products were obtained in 62–80% yields from aromatic aldehydes and in 32–37% from aliphatic aldehydes. The procedure included two steps: first, the β-dicarbonyl compound and the aldehyde underwent aldol condensation to give an α,β-unsaturated ketone, then urea was introduced into the reaction mixture to react with the product of the previous step. The final products were isolated and purified chromatographically.[80]

It was found that 3,4-dihydropyrimidine-2-(1*H*)-one derivatives **106** could be obtained in high (76–97%) yields using chlorotrimethylsilane in a mixture of acetonitrile and *N,N*-dimethylformamide (2:1). The method was applied to various aromatic, aliphatic and α,β-unsaturated aldehydes, ureas and thioureas, acetylacetone and ethyl acetoacetate. The products were separated from the reaction mixture simply by filtration.[81]

The reaction was also extended to N- and N,N′-(di)substituted ureas. Thus, N-substituted 3,4-dihydropyrimidine-2-(1*H*)-ones **107** were obtained in 77–97% yields using chlorotrimethylsilane (4 equiv) and *N,N*-dimethylformamide at room temperature for one to three days (Scheme 63).[82]
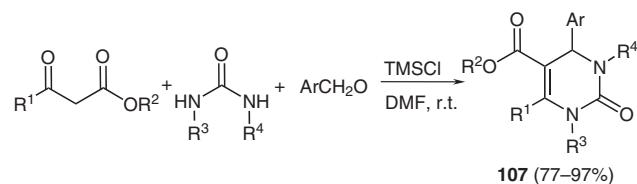
Scheme 63

Cycloalkanones can be used in the chlorotrimethylsilane-mediated Biginelli reaction in place of the β-dicarbonyl compounds. Depending on the structure of the starting compounds, three types of products can be obtained in this reaction: fused heterobicyclic structures **108**, benzylidene heterobicyclic compounds **109** or spiroheterotricyclic pyrimidines **110** (Scheme 64). In particular, cyclopentanone, urea and most aromatic aldehydes reacted in the presence of the chlorotrimethylsilane–acetonitrile–*N,N*-dimethylformamide system to afford pyrimidines **109**. Under these conditions, *p*-fluorobenzaldehyde gave a mixture of **109** and **110** in an 87:13 ratio.[83]

Aliphatic aldehydes were less reactive in these transformations: the corresponding condensation products were formed in satisfactory yields only under reflux. Cyclopentanone reacted with aliphatic aldehydes and ureas or thioureas to give the products **110**, whereas higher cycloalkanones afforded fused heterobicyclic pyrimidines **108**.[83]

Condensation of butyric or valeric aldehydes and urea in a chlorotrimethylsilane–acetonitrile–*N,N*-dimethylformamide system led to the formation of 5,6-dihydropyrimi-
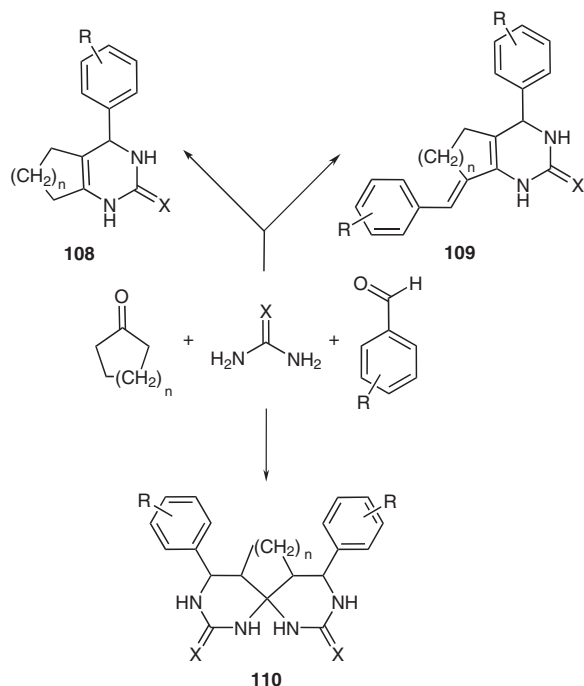
Scheme 64

din-2-ones **111** in 53% and 62% yields, respectively. Under these conditions, isovaleric aldehyde and urea or thiourea afforded 3,4-dihydro-1*H*-pyrimidin-2-ones **112**, whereas cyclohexanone and thiourea gave spirotricyclic product **113** in 78% yield (Scheme 65).[83]
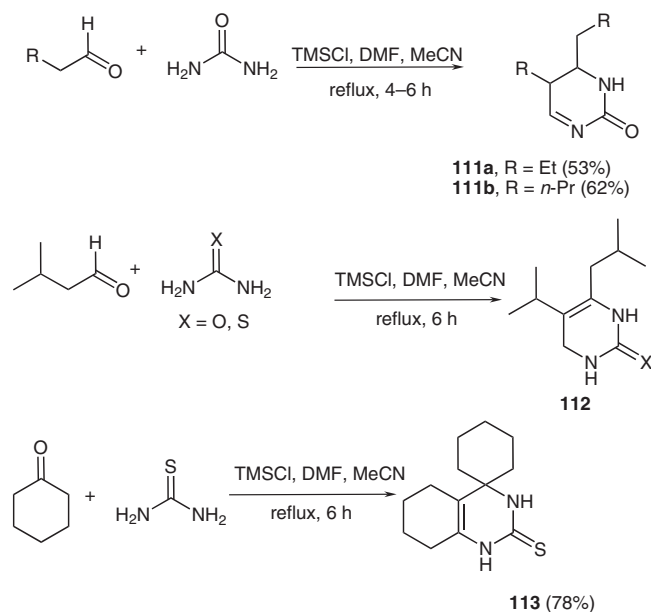
Scheme 65

Condensation of cyclohexane-1,3-dione and urea or thiourea in the presence of chlorotrimethylsilane–acetonitrile–*N,N*-dimethylformamide led to the formation of either spiro (**114**) or heterobicyclic compounds (**115**) in high yields. Whereas benzaldehyde or *para*-substituted aromatic aldehydes afforded both products, with spiro de-

rivative **114** predominating in the mixture, *ortho*- and *meta*-substituted benzaldehydes gave only the octahydroquinazolines **115** (Scheme 66).[84]
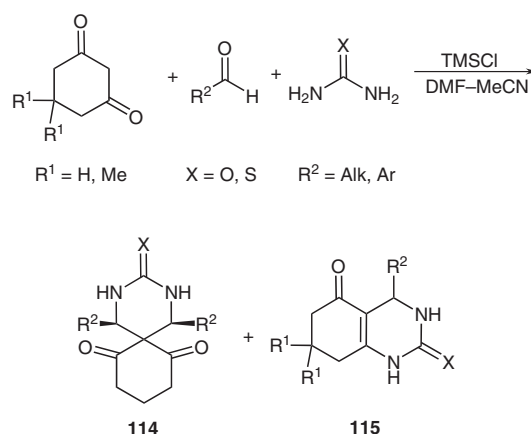
Scheme 66

In an analogous transformation involving dimedone, aromatic aldehydes and a chlorotrimethylsilane–acetonitrile–*N,N*-dimethylformamide system, octahydroquinazolines **115** (R^2 = Me) were also obtained.[77]

β-Ketonitriles were used in a Biginelli-type reaction with aromatic aldehydes and thiourea in the presence of chlorotrimethylsilane–*N,N*-dimethylformamide at 25 °C to obtain 1:2:1 condensation products **116** (Scheme 67). In the case of cyanoacetamides, one-step fusion of 1,3-thiazine and pyrimidine cycles occurred to give hydrochlorides **117** (Scheme 68). The structure of the latter products was confirmed by single-crystal X-ray analysis.[85]
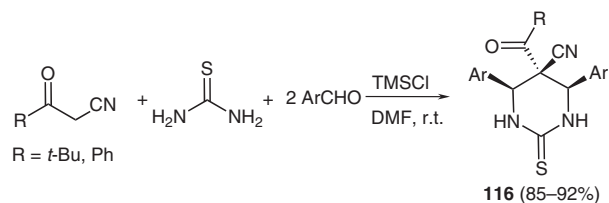
Scheme 67
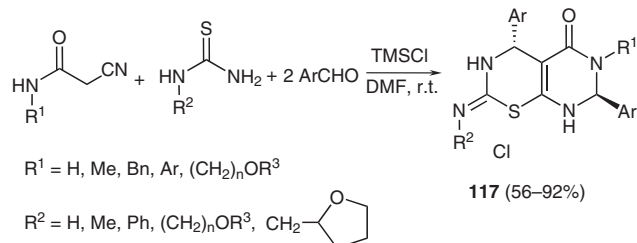
Scheme 68

When trifluoromethyl-substituted β-dicarbonyl compounds were used as substrates in the Biginelli reaction, 4-hydroxyhexahydropyrimidin-2-one derivatives **118a** were obtained in 48–82% yields. It should be noted that a

different diastereoselectivity (compound **118b**) was observed when N,N′-dimethyl(thio)urea was used instead of the unsubstituted or monosubstituted derivatives. The only exception was represented by 1,1,1-trifluoropentane-2,5-dione, which afforded classical dihydropyrimidine products **119** under these conditions (Scheme 69).[86]

R^1 = OEt, Ph, CF$_3$
X = O, S
R^2 = H, Me, Ph
R^3 = H, Me

118a (56–82%)
(R^2 = H)

118b (41–56%)
(R^1 = OEt, Ph, CF$_3$
R^2 = R^3 = Me)

119 (48–60%)
(R^2 = R^3 = Me or
R^2 = Ph, R^3 = H)

Scheme 69

Other organosilicon compounds have also been used as water scavengers in Biginelli reactions. For example, iodotrimethylsilane generated in situ from chlorotrimethylsilane and sodium iodide was successfully applied in the condensation of aromatic, heterocyclic, aliphatic or α,β-unsaturated aldehydes, urea and acetylacetone or ethyl acetoacetate, leading to the formation of dihydropyrimidine-2(1H)-ones **106**. The reaction was carried out for 30–50 minutes and afforded compounds **106** in 82–98% yields.[87]

Trimethylsilyl triflate is another effective catalyst in the Biginelli reaction. In this case, the reaction was complete within 15 minutes of the addition of 0.01 equivalent of trimethylsilyl triflate to the mixture of starting compounds (i.e., aldehyde, urea and β-dicarbonyl compound) in acetonitrile at ambient temperature. The corresponding products **106** were formed in 80–95% yields.[88]

5.3   Synthesis of Other N-Containing Heterocycles

5.3.1   Pyridines

In situ generated iodotrimethylsilane has been found to be an efficient condensing reagent in Hantzsch pyridine synthesis. The 1,4-dihydropyridines **120** were obtained from aromatic aldehydes, ethyl acetoacetate and ammonium acetate. An analogous result was obtained under modified reaction conditions starting from aldehydes and aminocrotonate (Scheme 70). Unlike the classical Hantzsch procedure or its newer modifications, the method described above afforded better yields of the products in the case of

ortho-substituted aldehydes and was efficient in the case of sensitive substrates (e.g., those containing nitro, hydroxy, alkoxy or chloro groups) due to the milder reaction conditions.[89]

R^1 = Ar, Het, i-Pr
R^2 = Me, Et
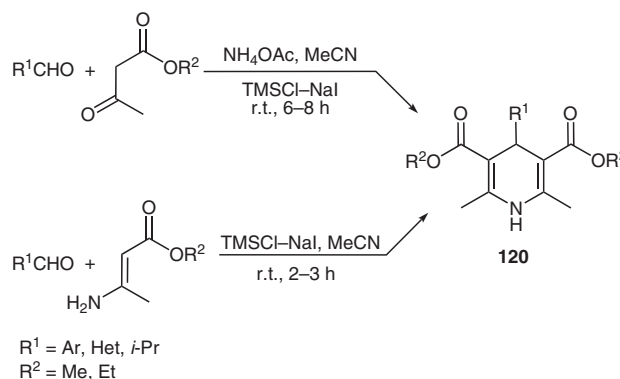
Scheme 70

5.3.2   Quinolines and Heterofused Pyridines

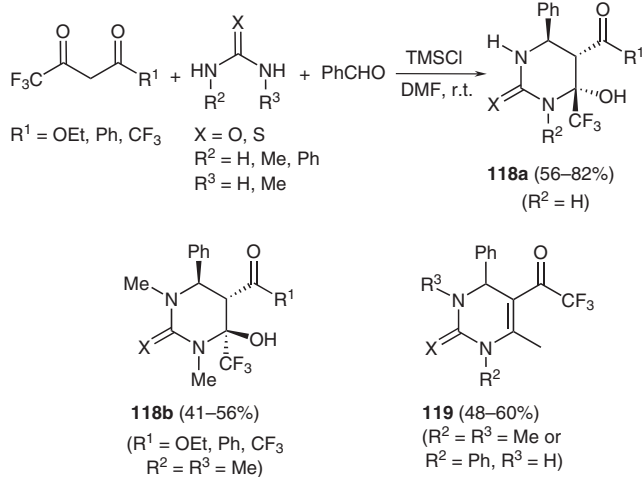Chlorotrimethylsilane was successfully applied in the Friedlander quinoline synthesis. In this case, o-aminoacetophenones reacted with a set of methylene active compounds [e.g., β-dicarbonyl compounds, acetophenones and other alkyl (het)aryl ketones, tert-butyl methyl ketone, cycloalkanones, 4-piperidones, ethyl 2-oxobutyrate, laevulinic acid, 1,3-dichloroacetone, ethyl 4-chloroacetoacetate, 2-chlorocyclohexanone] in the presence of chlorotrimethylsilane–N,N-dimethylformamide in a pressure tube to give various quinoline derivatives **121** in 76–97% yields (Scheme 71).[90,91]

Heterofused pyridines were also synthesized by this method. In particular, thieno[2,3-b]pyridines **122**, [1]benzofuro[3,2-b]pyridines **123**, 5H-chromeno[2,3-b]pyridin-5-ones **124** and pyrido[2,3-d]pyrimidin-2,4(1H,3H)-diones **125** were obtained (Scheme 71).[92]

R^1 = Me, Ph
R^2 = H, 5-Cl, 5-NO$_2$, 4,5-OCH$_2$O

121

122   **123**   **124**   **125**
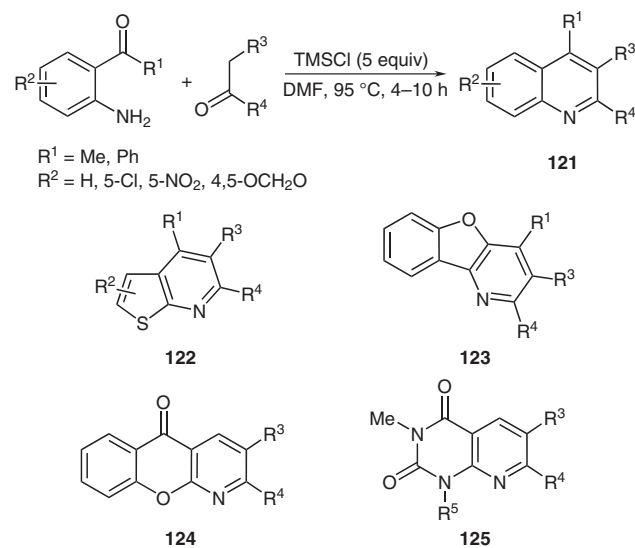
Scheme 71

In an analogous reaction, fused heterocyclic compounds **126** were obtained in 45–98% yields from *o*-amino-thiophenecarbaldehydes **127a–c** and creatinine in the presence of bis(trimethylsilyl)acetamide (Scheme 72).[93]
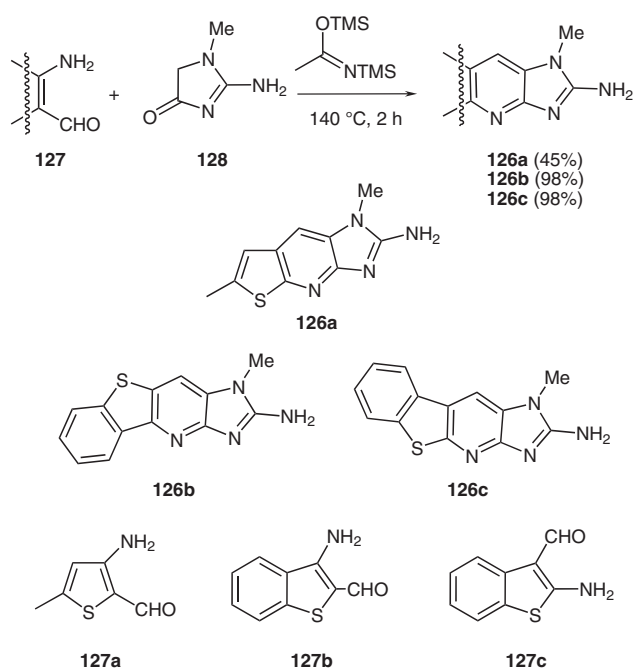
Scheme 72

Another approach to quinoline synthesis involved the chlorotrimethylsilane-promoted cyclization addition of enolizable aldehydes to arylimines, under an air atmosphere in dimethylsulfoxide, that afforded 2-arylquinolines **128** (Scheme 73). The clean and mild reaction conditions, high yields of the products and simple workup protocol are attractive features of the procedure described above which thus enable a facile preparation of the quinoline derivatives.[94]
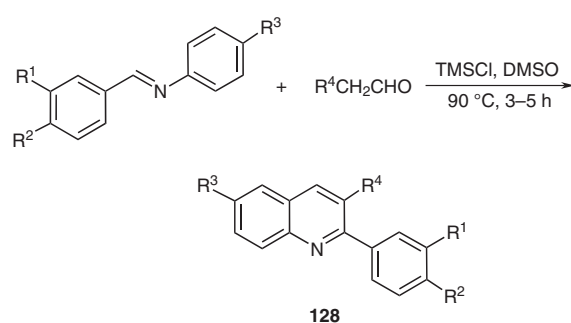
Scheme 73

5.3.3   Pyrimidines and Quinazolines

In addition to the chlorotrimethylsilane-mediated Biginelli reaction discussed in section 5.2, several examples of other pyrimidine syntheses have been reported. In particular, Zav'yalov and Kulikova successfully applied the chlorotrimethylsilane–*N,N*-dimethylformamide system in

the reaction of acetylacetone and urea that led to the formation of 1,2-dihydropyrimidin-2-ones **129** (Scheme 74).[39]
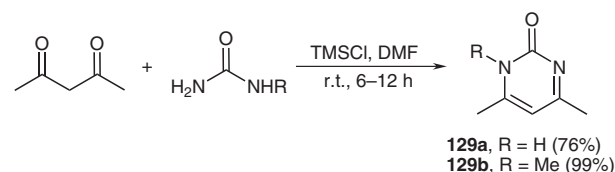
Scheme 74

Pyrimidine derivatives **130** were obtained in the reaction of azadienes **131** and acyl chlorides in the presence of chlorotrimethylsilane and triethylamine. *N,N′*-Diacylazadienes **132** were also formed as by-products; nevertheless, the use of chlorotrimethylsilane decreased the yield of **132** significantly (Scheme 75).[95]
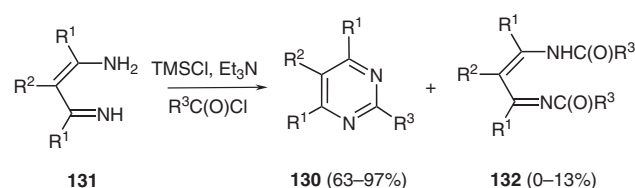
Scheme 75

A chlorotrimethylsilane-induced dehydrative cyclization of diamides **133** in the presence of *N,N*-dimethylethyl-amine (DMEA) afforded 3*H*-quinazolin-4-ones **134** (Scheme 76). The reaction appeared to be insensitive to the nature of the acyl substituent (R^3) and was also effective in the case of compounds containing OH and NH groups.[96]
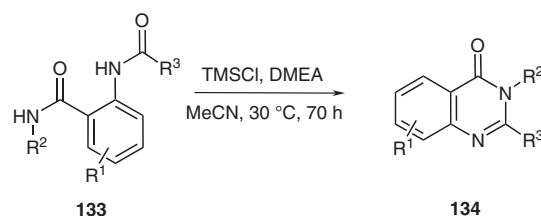
Scheme 76

Analogues of an alkaloid vasicinone **135a–c** were obtained in quantitative yields by subsequent reduction of the corresponding *N*-(2-azidobenzoyl)lactams **136** and iodotrimethylsilane-promoted reductive cyclization, with iodotrimethylsilane acting both as reaction promoter and as reducing reagent (Scheme 77).[97]

5.3.4   Azoles

2-Substituted   2,3-dihydro-3-phenyl-1,3,4-thiadiazoles **137** were obtained in high yields from *N′*-phenylthioformic hydrazide **138** and aldehydes by treatment with chlorotrimethylsilane (Scheme 78).[98]
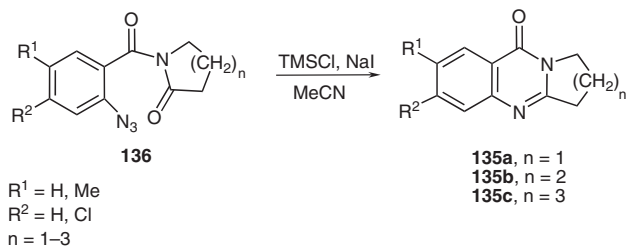
Scheme 77
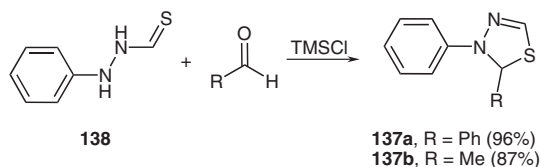
Scheme 78

Recently, it was shown that some endothiopeptides **139** were transformed into thiazoles **140** by treatment with a chlorotrimethylsilane–sodium iodide system and microwave irradiation (Scheme 79).[99]
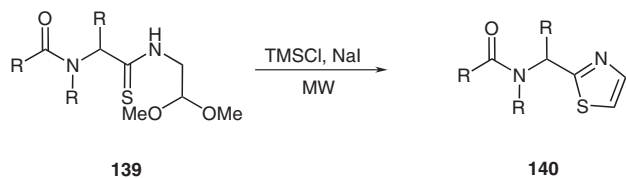
Scheme 79

The chlorotrimethylsilane-initiated [3+2]-cycloaddition reaction of imines and oxazolones **141** was shown to be a convenient method of obtaining highly substituted imidazolines **142**. The first step of the reaction was the reversible N-silylation of **141** leading to the formation of ylide **143** (so-called 'munchnone'), which acted as a 1,3-dipolar compound in the cycloaddition (Scheme 80). The diastereoselectivity of the reaction was determined by steric interactions of the bulky silyl group in **143** and the C-substituent of the imine, and led to preferential formation of the *trans*-isomer. It should be noted that in the case of R = Me or Bn instead of R = Ph, the stability of cationic center is lowered, thus resulting in diminished stereoselectivity.[100,101]

5.3.5   Benzo- and Heterofused Azoles

The chlorotrimethylsilane–*N,N*-dimethylformamide system has been applied successfully to the synthesis of benzimidazoles, 3*H*-imidazo[4,5-*b*]pyridines, purines, xanthines and benzothiazoles from the corresponding (hetero)aromatic *o*-diamines or *o*-aminothiophenols and aldehydes (Scheme 81). The reaction scope and limitations were also established. In the case of N-unsubstituted phenylenediamines, diimines were obtained as by-products, resulting in lowered yields of the desired products.

Scheme 80

R[1] = Ph, Bn
R[2] = Me, Ph, Het
R[3] = Ph, Het, COOEt
R[4] = Bn, Ar, CH$_2$COOMe
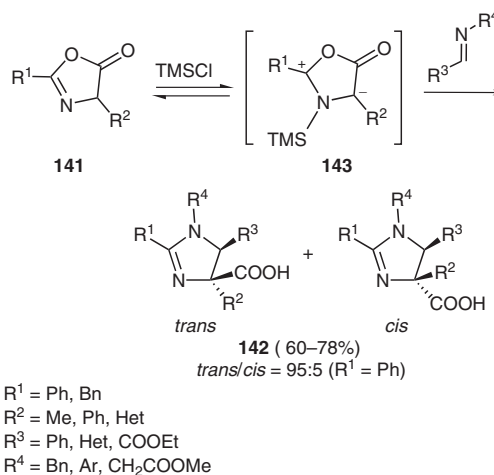
N-Aryl diamines, as well as diamines with a bulky substituent on the nitrogen, behaved poorly in the reaction: the products were formed in 10–25% yields. Only aldehydes that are sufficiently stable under reaction conditions (e.g., aromatic aldehydes) actually gave the desired products. The target products (namely, benzoxazoles) were also not formed in the case of *o*-aminophenols.[102]
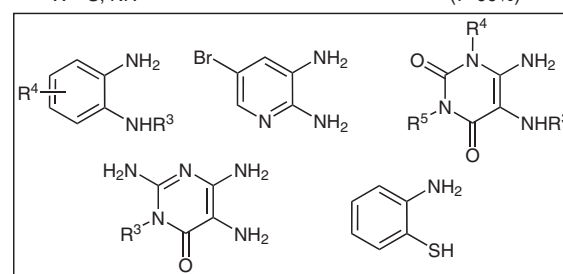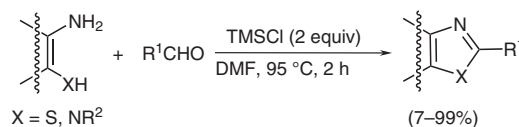
Scheme 81   Selected examples of the substrates are given

2-(Chloromethyl)indolizine-1-carbonitrile **144** was obtained from pyridin-2-ylacetonitrile and 1,3-dichloroacetone (Scheme 82). It is interesting to note that other condensing reagents used did not allow for compound **144** to be obtained.[103]
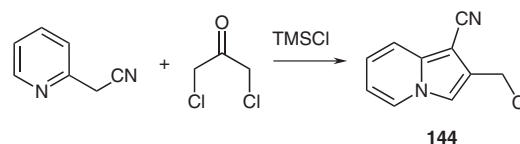
Scheme 82

Other examples of chlorotrimethylsilane- and/or hexamethyldisilazane-promoted dehydrative cyclizations leading to the formation of heterofused azoles are illustrated in Scheme 83.[104,105]
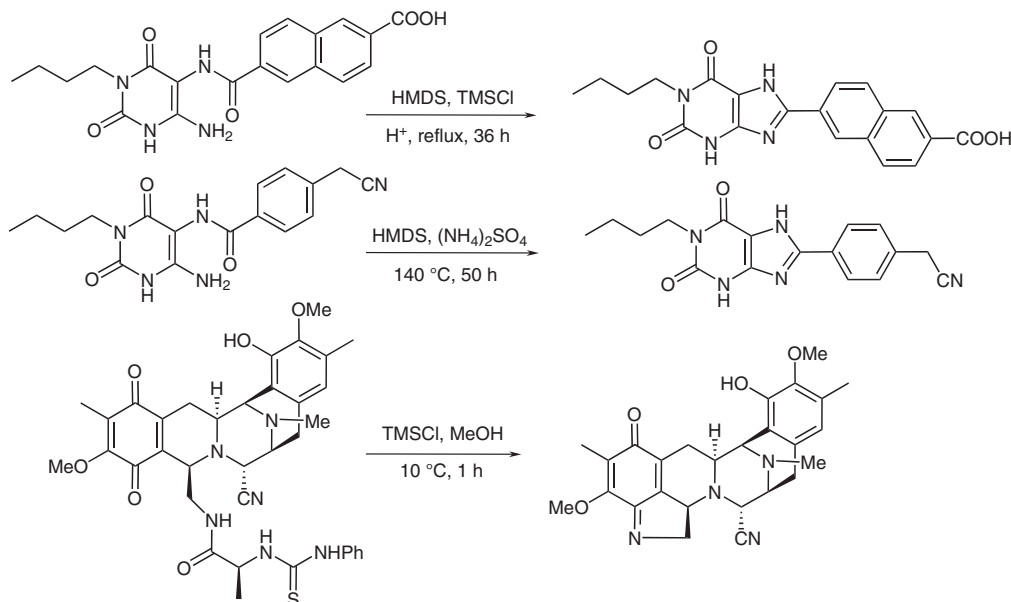
Scheme 83

5.4 Recyclization of 3-Formylchromones

The condensation of 1,3-dicarbonyl compounds is one of the most widely used reactions in the synthesis of heterocycles. In many cases, these electrophiles possess several non-equivalent reaction centers, thereby presenting a regioselectivity problem. Hence, one of the major tasks in this area is to find the substrates and the conditions that allow for single regioisomers to be obtained. 3-Formylchromone (**145**), a molecule which possesses three electrophilic centers, is that type of substrate (Scheme 84). The tendency of the chromone fragment to undergo recyclization reactions allows one to consider **145** as a synthetic equivalent of 2-(2-hydroxybenzoyl)malonic aldehyde (**146**).
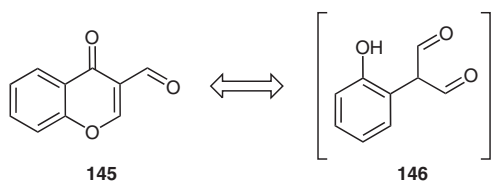
Scheme 84

The first expedient method for the preparation of the compound **145** was reported in 1973,[106] and this chromone derivative has been widely applied in heterocycle synthesis since then.[107] Nevertheless, the first example of using chlorotrimethylsilane as a promoter of the recyclization of 3-formylchromones was reported only in 2004. Specifically, the reaction of 3-formylchromones **147** and electron-withdrawing-group-substituted acetamides, in the presence of a chlorotrimethylsilane–N,N-dimethylformamide system, led to the formation of pyridone derivatives **148** as a result of a Guareschi–Thorpe condensation (Scheme 85).[108]

R¹ = H, F, Cl, Me, OMe
EWG = CN, CONHR³, COMe
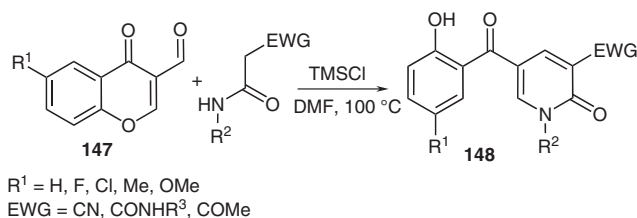
Scheme 85

In the chlorotrimethylsilane-promoted reaction of 3-formylchromone and primary hetarylmethylamines, (5-hetaryl-1H-pyrrol-3-yl)(2-hydroxyphenyl)methanones **149** were obtained in 68–91% yields (Scheme 86). With a 2:1 ratio of the reagents, fused chromonepyrroles **150** were formed in moderate yields. When secondary hetaryl-methylamines were used as substrates in this reaction, only pyrrole derivatives **149** were isolated in 65–99% yields.

An analogous transformation was also observed in the case of glycine derivatives **151** (Scheme 86).

The chlorotrimethylsilane-mediated pyrrole synthesis appeared to be also applicable to the fusion of the pyrrole and the dihydroquinoxaline rings (compounds **152**). However, in the case of prolinamide and N,N′-dimethylglycinamide, imidazolinones **153** and **154** were obtained (Scheme 87).[109]

Unexpected results were obtained in the reaction of 3-formylchromone with aromatic amines. In many cases, the target 3-(2-hydroxybenzoyl)quinolines **155** were synthesized in 35–87% yields, indicative of the amine acting first as a C-nucleophile. However, in the case of aniline derivatives possessing an electron-withdrawing group in the *meta*-position, or any *para*-substituted anilines, the fused chromenoquinolines **156** were formed in 39–67%

Scheme 86

Scheme 87

X = OH, OMe, NMe$_2$, NEt$_2$, N(CH$_2$)$_4$

Scheme 88

Scheme 89   Examples of amino heterocycles are given

Scheme 90   Examples of amino heterocycles are given

and no traces of **155** were detected, thus the amine was acting first as an N-nucleophile (Scheme 88). In the case of 3,4-disubstituted anilines, the products **155** or **156** were obtained, depending on the electronic effects of the substituents.[110]

An analogous transformation was observed in the case of heteroaromatic amines capable of acting as CCN-binucleophiles, which thus led to the formation of fused pyridines **157** (Scheme 89).[111]

Heteroaromatic amines lacking a carbon atom at the position α to the amino group showed NCN-binucleophilic behavior in the reaction with 3-formylchromone, thereby affording pyrimidines **158** (Scheme 90). An analogous

transformation was observed in the case of amidines (Scheme 91).[112]

Scheme 91

The reaction of 3-formylchromones **147** and 1-aminoimidazoles **159** in the presence of chlorotrimethylsilane and *N,N*-dimethylformamide led to the formation of imidazo[1,5-*b*]pyridazines **160** (Scheme 92). However, 1-aminobenzimidazole and 4-amino-1,2,4-triazoles did not undergo an analogous heterocyclization under these conditions; only hydrazone formation was observed.[113]

159a, R² = NH₂
159b, R² = SH

160 (81–96%)
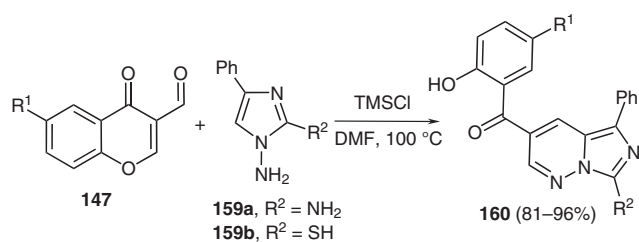
Scheme 92

Finally, in the reaction of 3-formylchromone with compounds **161** (imidazole, benzimidazole,[114] quinazolone and thieno[2,3-*d*]pyrimidin-4(3*H*)-one[115] derivatives), fused polycyclic heterocycles **162** were obtained (Scheme 93).

X = CN, COPh, CO(2-thienyl), CONH₂, CONHBn, CON(CH₂)₄O, CSNH₂, SO₂Me, SO₂Ph, 2-benzothiazolyl, Ph, SCH₂CO₂H, Cl, NHCOPh, CH₂NHCOPh, OPh, H

X = CN, H, Cl, CH₂CO₂H, (CH₂)₂CO₂H, N(CH₂)₄NH, N(CH₂)₄NMe, N(CH₂)₄O

Scheme 93   Selected examples of methylene components are given

It should be noted that the use of chlorotrimethylsilane in most of the 3-formylchromone condensations discussed above significantly improved the regioselectivity of the reaction. This is presumably due to the preliminary silylation of the carbonyl group of the chromone ring, which

thus prevents any nucleophilic attack from taking place at that site.[116]

6   Conclusions

Organosilane compounds, in particular chlorotrimethylsilane, act as very efficient water scavengers in many common reactions of carbonyl compounds, including the Knoevenagel condensation, imine and enamine syntheses, the Mannich reaction, and heterocyclizations such as the Biginelli and Friedländer reactions. The procedures developed for these syntheses are applicable to a vast range of substrate molecules. Taking into account the simplicity and generality of the methods based on organosilane-promoted condensations of carbonyl compounds, one should expect further progress in this area with regard to other reactions for which the outcome depends on the use of a water scavenger.
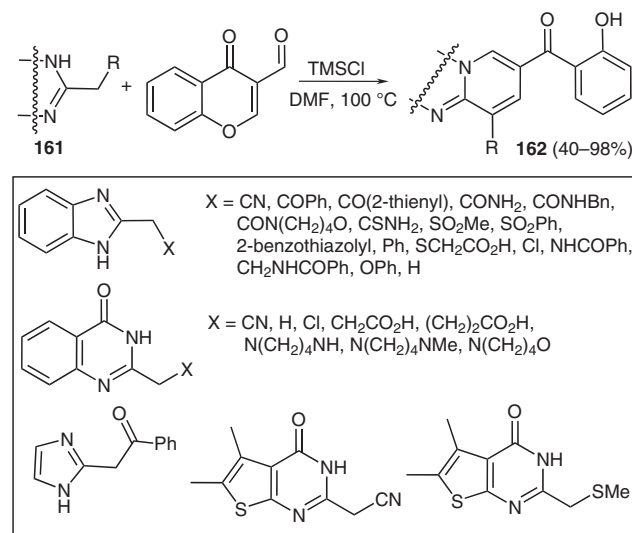
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