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.

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Key words: carbonyl compounds, condensation, organosilicon compounds, water scavengers, chlorotrimethylsilane

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 (H₂SO₄, H₃PO₄, etc.) and alkalis [e.g., NaOH, KOH, Ba(OH)₂]. 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.). 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 zeolites 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 reagents include Al₂O₃, MgO, TiCl₄, cation-exchanged zeolites, SiO₂, calcite, fluorite, modified Mg-Al hydrotalcite, and Lewis acidic ionic liquids. 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.

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 remov- 
ABLE hydrogen halide is formed upon hydrolysis of 
halogenosilanes (Scheme 1), which increases the catalytic 
activity of the system further. The advantages that halo-
ogenosilanes have as water scavengers in reactions of car-
bonyl compounds are summarized in Figure 2.

Scheme 1 Hydrolysis of chlorotrimethylsilane

\[ 2 \text{TMSCl} + \text{H}_2\text{O} \rightarrow (\text{TMS})_2\text{O} + 2 \text{HCl} \]

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 elimina-
tion reactions, and heterocyclizations are all considered. 
In some cases, related transformations resulting in elimi-
nation of small molecules other than water are also dis-
cussed. 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

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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. Aliphatic and aromatic aldehydes reacted with ethyl acetoacetate under mild conditions to give Knoevenagel adducts in 70–75% yields (Scheme 2).

The method was extended to some other carbonyl compounds. In particular, Knoevenagel adduct 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 co-catalyst; compounds were obtained from these reactions in 60–70% yields. Reaction of benzaldehyde with acetylacetone, acetophenone and a-bromoacetophenone afforded the β-chloro ketones , respectively (Scheme 3).

A chlorotrimethylsilane-N,N-dimethylformamide system was applied to the synthesis of 5-(arylmethylene)hexahydropyrimidine-2,4,6-triones (from barbituric acid and the corresponding aromatic aldehydes) possessing immunosuppressive, fungicidal and anti-inflammatory activities (Scheme 4). Combinations of chlorotrimethylsilane with other Lewis acids (e.g., SnCl₂, BF₃·OEt₂, TiCl₄ or InCl₃) 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. For example, adduct 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).
Recently, a system of chlorotrimethylsilane, \(N,N\)-dimethylformamide 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 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-alkylidenecycloalkanones 11 (Scheme 7). These products were also obtained when a chlorotrimethylsilane–ytterbium(III) triflate system was used as reaction promoter.\(^{18}\)

\(\alpha,\alpha'\)-Bis(benzylidene)cyclokanones 8 were also obtained, in 70–95% yields, by the reaction of alicyclic ketones and aromatic aldehydes in the presence of iodonitrilisilane, generated in situ from chlorotrimethylsilane and sodium iodide in acetonitrile (Scheme 8).\(^{19}\)

The chlorotrimethylsilane-induced condensation of 2,5-dihydro-2,5-dimethoxyfuran (12) and aromatic or heteroaromatic aldehydes led to the formation of the corresponding \(\gamma\)-arylidene-\(\alpha,\beta\)-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-
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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 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 cyanoacetic 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 p-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.,...
acetylaceton 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
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).  

Scheme 18

In some cases, the Knoevenagel reactions discussed above were accomplished by self-condensation of the starting aldehydes.  

 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).  

Scheme 19

Aldehydes of the formula RCH_{2}CHO formed self-condensation products 26 in 78–89% yields in the presence of iodo(trimethyl)silane. A mechanistic scheme of the reaction was suggested. The key step of the transformation was postulated to be the reaction between trimethylsilyliodohydrine 27 (formed by TMSI addition to the starting aldehyde) and trimethylsilyl enolate 28 (formed from 27 by HI elimination) (Scheme 20).  

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-diarylethenes led to the formation of complex mixtures that include 1,1-bis(2,2-diarylethyl)alkanes 29 and cyclic ketal 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

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 α-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 condensations 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, dimesone) and aromatic amines to give N-arylenamino ketones 39, which are intermediates in the syntheses of some analgesics (Scheme 24).34
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

Tetraethylorthosilicate \([\text{Si(OEt)}_4]\) 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.

Reactions of \(\text{o-}(\text{dialkylamino})\text{anilines and aromatic aldehydes performed in sealed reactors at 100 °C resulted in the } T\text{-amino effect, thus leading to the formation of dihydrobenzimidazoles 44. To avoid the acid-catalyzed dismutation 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\text{-amino effect was also not observed in the case of } \text{o-}
\pi\text{-peridinylanilines as amine components; usual imine formation was observed instead.38

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

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 aryldenebisbenzamides 47 to be obtained, whereas acetylacetone and ethyl acetooacetate 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
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 were obtained only when a large excess (up to 20 equiv) of urea was used; otherwise, bis-alkylation occurred (Scheme 31).40

A modification of the method discussed above relies on using dialkylamines and in situ generated iodotrimethylsilane system with 3,3-dichloroacrolein afforded a mixture of salts that in the case of aldehydes capable of enolization if trimethylsilyl triflate is used instead of chlorotrimethylsilane.51,52 The first step of the reaction was amine silylation using dialkylamines and in situ generated iodotrimethylsilane which then reacted with the chloride obtained by the reaction of dimethylaminotrimethylsilane and chlorotrimethylsilane has been developed. The corresponding products were isolated in 75–93% yields and characterized (Scheme 37, see also Scheme 41). The method was applied to non-enolizable and N,N'-disubstituted thioureas 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-myacin 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 (BH₃·NEt₃) 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 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...
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
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. First, it was shown that aromatic and heteroaromatic aldehydes were aminoalkylated by trimethylsilylamines in the presence of lithium perchlorate. Imines or iminium salts formed in the first step of the reaction were trapped by the corresponding nucleophile to afford corresponding amines. 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 presence of chlorotrimethylsilane–lithium perchlorate led to the formation of chiral imines which reacted with organozinc compounds to give chiral amino esters or amines in moderate to high diastereoselectivities (90% de for 71 and 40% de for 72).

α-Aminophosphonates were obtained in an analogous manner when trialkylphosphites were used as nucleophiles. 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.

A system comprising chlorotrimethylsilane, sodium iodide and triethylamine was used in the synthesis of α-amino ketones 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.

3-Functionalized indoles 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. α-(Hydroxylamino)alkyl/arylphosphonates possessing antibacterial properties were obtained in an analogous manner.
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 were isolated in 85–98% yields and characterized.

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

In the case of dichlorodimethylsilane and trichloro(methyl)silane, the chlorine atom(s) present in the corresponding silylammonium salts weaken the neighboring carbon–nitrogen bond, thus activating the compounds towards formation of iminium salts. On the other hand, (di)chloromethylsilylamines are not basic enough to capture the hydrogen chloride formed. The latter protonates amines, thus preventing their further reaction with, hence monosubstituted heterocycles are obtained as the final products (Scheme 50).
Reaction of dialkyl(alkoxymethyl)amines with 1-methylpyrrole, 2-methylfuran and 1-methylindole afforded monosubstituted heterocycles as the main products (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).

\[
\text{Scheme 52}
\]

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. 89 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 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.

This approach was recently extended to cyclic β-keto esters71–73 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, R1 = 1'-phenylethyl), the presence of the chiral auxiliary in the molecules was exploited in their further transformations.73
The method was also applied to some cycloalkanones, including cyclooctanone, cycloheptanone and substituted cyclohexanones. In particular, azabicyclo[4.3.1]decanes 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 \( a \) 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

Scheme 56

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 \( \alpha \)-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

Scheme 57

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).77

Scheme 58

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 \( \text{in situ} \) generated iodotrimethylsilane. The reaction was carried out in acetonitrile at ambient temperature for three to eight min-

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

Scheme 60

An analogous transformation of dimerone 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 \( \text{in situ} \) generated iodotrimethylsilane. The reaction was carried out in acetonitrile at ambient temperature for three to eight min-

Scheme 60

An analogous transformation of dimerone 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 \( \text{in situ} \) generated iodotrimethylsilane. The reaction was carried out in acetonitrile at ambient temperature for three to eight min-

Scheme 60

An analogous transformation of dimerone 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 \( \text{in situ} \) generated iodotrimethylsilane. The reaction was carried out in acetonitrile at ambient temperature for three to eight min-

Scheme 60

An analogous transformation of dimerone 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 \( \text{in situ} \) generated iodotrimethylsilane. The reaction was carried out in acetonitrile at ambient temperature for three to eight min-

Scheme 60

An analogous transformation of dimerone 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 \( \text{in situ} \) generated iodotrimethylsilane. The reaction was carried out in acetonitrile at ambient temperature for three to eight min-

Scheme 60

An analogous transformation of dimerone 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 \( \text{in situ} \) generated iodotrimethylsilane. The reaction was carried out in acetonitrile at ambient temperature for three to eight min-
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 \((\pm)\)-centrolobine \(105\) (Scheme 61).

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 \(\beta\)-dicarbonyl compound and the aldehyde underwent aldol condensation to give an \(\alpha,\beta\)-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.

It was found that 3,4-dihydropyrimidine-2-(1H)-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 \(\alpha,\beta\)-unsaturated aldehydes, ureas and thioureas, acetylaceton and ethyl acetooacetate. The products were separated from the reaction mixture simply by filtration.

The reaction was also extended to \(N\) - and \(N,N\)’-(di)substituted ureas. Thus, \(N\)-substituted 3,4-dihydropyrimidine-2-(1H)-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).

Cycloalkanones can be used in the chlorotrimethylsilane-mediated Biginelli reaction in place of the \(\beta\)-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, cyclopantenone, 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.

Aliphatic aldehydes were less reactive in these transformations: the corresponding condensation products were formed in satisfactory yields only under reflux. Cyclopantenone reacted with aliphatic aldehydes and ureas or thioureas to give the products \(110\), whereas higher cycloalkanones afforded fused heterocyclic pyrimidines \(108\). Condensation of butyric or valeric aldehydes and urea in a chlorotrimethylsilane–acetonitrile–\(N,N\)dimethylformamide system led to the formation of 5,6-dihydropyrimi-
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Scheme 64

Condensation of cyclohexane-1,3-dione and urea or thiourea in the presence of chlorotrimethylsilane–acetonitrile–N,N-dimethylformamide system, octahydroquinazolines 115 (R² = Me) were also obtained.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.

Scheme 65

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
differential 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).

**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 \( \alpha,\beta \)-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.

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 \( \beta \)-dicarbonyl compound) in acetonitrile at ambient temperature. The corresponding products 106 were formed in 80–95% yields.

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 aminoacetonitrile (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 \( \alpha \)-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.

**Scheme 70**

5.3.2 Quinolines and Heterofused Pyridines

Chlorotrimethylsilane was successfully applied in the Friedlander quinoline synthesis. In this case, \( \alpha \)-aminoceto-phenones reacted with a set of methylene active compounds [e.g., \( \beta \)-dicarbonyl compounds, acetoephones 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).

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).
In an analogous reaction, fused heterocyclic compounds 126 were obtained in 45–98% yields from \( \text{o-ami}-\)

nothiophenecarbaldehydes 127a–c and creatinine in the presence of bis(trimethylsilyl)acetamide (Scheme 72). 93

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 work-up protocol are attractive features of the procedure described above which thus enable a facile preparation of the quinoline derivatives. 94

A chlorotrimethylsilane-induced dehydrative cyclization of diamides 133 in the presence of \( \text{N,N}-\)

dimethylformamide (DMEA) afforded \( 3H-\)quinazolin-4-ones 134 (Scheme 76). The reaction appeared to be insensitive to the nature of the acyl substituent (R3) and was also effective in the case of compounds containing OH and NH groups. 96

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

Pyrimidine derivatives 130 were obtained in the reaction of azadienes 131 and acyl chlorides in the presence of chlorotrimethylsilane and triethylamine. \( \text{N,N}'-\)Diacylaza-
dienes 132 were also formed as by-products; nevertheless, the use of chlorotrimethylsilane decreased the yield of 132 significantly (Scheme 75). 95

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–\( \text{N,N}-\)

dimethylformamide system in the reaction of acetylacetone and urea that led to the formation of 1,2-dihydropyrimidin-2-ones 129 (Scheme 74). 39

Pyrimidine derivatives 130 were obtained in the reaction of azadienes 131 and acyl chlorides in the presence of chlorotrimethylsilane and triethylamine. \( \text{N,N}'-\)Diacylaza-
dienes 132 were also formed as by-products; nevertheless, the use of chlorotrimethylsilane decreased the yield of 132 significantly (Scheme 75). 95

A chlorotrimethylsilane-induced dehydrative cyclization of diamides 133 in the presence of \( \text{N,N}-\)
dimethylformamide (DMEA) afforded \( 3H-\)quinazolin-4-ones 134 (Scheme 76). The reaction appeared to be insensitive to the nature of the acyl substituent (R3) and was also effective in the case of compounds containing OH and NH groups. 96

Analogues of an alkaloid vasicinone 135a–c were obtained in quantitative yields by subsequent reduction of the corresponding \( \text{N-}(2-\text{azidobenzoyl})\)lactams 136 and iodo(trimethyl)silane-promoted reductive cyclization, with iodo(trimethyl)silane 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 \( \text{N}-\)phenylthioformic hydrazide 138 and aldehydes by treatment with chlorotrimethylsilane (Scheme 78). 98

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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, 3H-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 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
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 regiosomers 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).

The first expedient method for the preparation of the compound 145 was reported in 1973, and this chromone derivative has been widely applied in heterocycle synthesis since then. 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).

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 hetarylmethylamines 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).

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% yields.
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.\textsuperscript{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).\textsuperscript{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).\textsuperscript{112}
silane and thieno[2,3-d] not undergo an analogous heterocyclization under these conditions; only hydrazone formation was observed.\textsuperscript{113}

Finally, in the reaction of 3-formylchromones 147 and 1-aminimidazoles 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.\textsuperscript{113}

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

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.\textsuperscript{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 Friedlander 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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References


Organosilicon Compounds as Water Scavengers


(95) Barluenga, J.; Pozo, C.; Olano, B. Synthesis 1996, 133.


(103) Tereschenko, A. D.; Sysoiev, D. A.; Tverdokhlebov, A. V.; Tolmachev, A. A. Synthesis 2006, 349.


