Abstract: Trimethylsilyl chloride is an efficient activating agent for azines in isocyanide-based reactions, which then proceed through a key insertion of the isocyanide into a N–Si bond. [1] The reaction is initiated by N activation of the azine, followed by concomitant “followed by” or “concomitant” [2] nucleophilic attack of an isocyanide in a Reissert-type process. Finally, a second equivalent of the same or a different isocyanide inserts into the N–Si bond leading to the final adduct. The use of distinct nucleophiles leads to a variety of “followed by” or “concomitant” [3] reactions conditions required for the course of these reactions was proposed. [4] The resulting products exhibit significant activity against Trypanosoma brucei and T. cruzi, featuring favorable drug-like properties and safety profiles.

Insertion of Isocyanides into N–Si Bonds: Multicomponent Reactions with Azines Leading to Potent Antiparasitic Compounds


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Scheme 1. Reissert-type isocyanide multicomponent reactions. p-TsOH = para-toluenesulfonic acid, TFA = trifluoroacetic anhydride, N–Si bond.

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In this context, we investigated the use of trimethylsilyl chloride (TMSCl) as a new activating agent in these transformations, looking for milder conditions, wider synthetic scope, and selective processes. Incidentally, TMSCl and related derivatives have been used in MCRs almost exclusively to activate carbonyl compounds,\(^{[10a,10b]}\) although Krasavin and co-workers reported an elegant example with imines.\(^{[9c]}\) The interaction of isoquinoline and cyclohexyl isocyanide with one equivalent of TMSCl in acetonitrile readily generated imidazolium salts (4a) in good yields. Interestingly, phthathomopholine reacted to yield the salts 4i, –biisoquinoline underwent a double reaction to generate salt 4l, and the observation that 2,2′-bipyridine afforded the guanidinium salt 4v in high yield, which is likely generated in a formal [4+1] cycloaddition (Figure 1).\(^{[11,12]}\)

Finally, we explored the possibility of introducing two distinct isocyanide residues. When a mixture of two isocyanides of similar nucleophilicity (cyclohexyl and para-methoxyphenyl) was reacted with isoquinoline and TMSCl, a roughly equimolecular mixture of the four possible products was obtained (see the Supporting Information). However, the use of one equivalent of an aliphatic isocyanide with another one of reduced nucleophilicity (isocyanoacetate, TosMIC (TosMIC = \[\text{Cl}_{2}CH=\text{C(OH)}\text{CO}_2\text{H}\]), or PhosMIC (PhosMIC = \[\text{C}_2\text{H}_5\text{N}=\text{CH\text{Ph}}\]) dramatically changed the outcome, and we observed the formation of a single adduct in good yields. In this way, the isoquinoline-imidazolium salts 4w–4z were obtained without detectable amounts of the homoaducts. The residues arising from the more nucleophilic species were attached to the azine α-position, whereas the less nucleophilic ones ended up linked to the heterocyclic nitrogen atom. Unequivocal structural assignment was achieved by X-ray diffraction of a monocystal of salt 4x (Figure 1). These results represent a breakthrough in the programmed synthesis of ABB′ adducts, which had thus far been restricted to the use of two equivalents of the same input or required the separation of complex mixtures. Furthermore, the connectivity pattern outlined above was tested in other reactant combinations. When different nucleophiles (indole, dimesone) and one equivalent of an isocyanide were reacted with isoquinoline in TMSCl-promoted reactions,\(^{[14]}\) the adducts 5a–5e (Figure 2) were conveniently obtained in high yields.
Control experiments with a proton scavenger support the participation of TMSCl as the activating agent (see the Supporting Information). We propose a novel mechanism that accounts for the experimental outcome (Scheme 2A).

The reaction starts with the activation of the azine by TMSCl to generate in situ N-silyl azinium ion A which is subsequently attacked by an isocyanide (or another nucleophilic species) to yield nitrilium cation B, likely stabilized by a chloride counterion. A second (less nucleophilic) isocyanide may insert into the N–Si bond of this intermediate to yield silylated amine C, giving rise to the fused imidazolium salt 4 by intramolecular N-addition to the nitrilium moiety and spontaneous hydrolysis of the resulting adduct. Although the azine activation by electrophiles and the isocyanide attack upon formation of the resulting intermediate are known, the N–Si isocyanide insertion is unprecedented. All attempts to isolate the silyl-substituted imidazolium salts under anhydrous conditions were unsuccessful, likely owing to the instability of the putative structure. Similarly, experiments performed to trap this silylated intermediate with a variety of electrophiles were unproductive, always leading to salts 6.

However, the likelihood of the insertion step was supported by the generation of amidines 6a–6c through reaction of isocyanides with N-silyl amines, albeit at higher temperatures (toluene, 110 °C; Scheme 2B). In agreement with the proposed mechanism, deactivated or sterically hindered N-silyl derivatives failed to undergo the insertion reaction (see the Supporting Information). The course of the reaction was followed by NMR spectroscopy; the silylated intermediates were detected and evolved in situ into the C–H amidines by spontaneous hydrolysis with adventitious water. Although GC/MS analysis of the crude reaction mixtures confirmed the presence of silylated species and D2O quenching gave amide 6b with partial isotopic labeling (see the Supporting Information), it was impossible to characterize the intermediates or trap them with distinct electrophiles.

Pivotal to this chemistry is the novel isocyanide insertion step, as contrary to the standard nucleophilic behavior commonly exhibited by isocyanides, the isocyanide seems to act as an electrophile in spite of the absence of metal cations or strong bases. To gain insight into the insertion process leading to amidines, quantum-mechanical calculations were performed (see the Supporting Information). For the sake of simplicity, computations were performed with methyl isocyanide and trimethylsilyl dimethylamine (DMA-TMS) as the reagents. The reactive channel starts with the attack of the DMA-TMS amine nitrogen atom at the isocyanide in a process that involves the progressive loss of the sp hybridization of this latter reagent and the increased pyramidalization of the amine nitrogen atom (Figure 3). These structural changes are the major contribution to the reaction barrier. Furthermore, they afford the geometrical...
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Remarkably, this compound was also synthesized by Berthet and co-workers (Ref. [8a]) in a TfOH-promoted reaction at 100°C with an excess of the isocyanide.


Amidines can also arise from isocyanide insertion into N–H bonds; see: F. Medda, C. Hulme, Tetrahedron Lett. 2014, 55, 3328–3331.


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Insert here! Multicomponent reactions (MCRs) with isocyanolines and other azines that proceed through the insertion of an isocyanide into a N–Si bond are described. This novel activation mode enables a variety of transformations to take place with high selectivity under mild reaction conditions. Some of the products showed in vitro activity against the causative agents of trypanosomiasis. TMS = trimethylsilyl. ❌ graphic had to be cropped ❌


#MulticomponentReactions of #isoquinolines and other azines via #isocyanide insertion

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