Multicomponent Reactions Hot Paper

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

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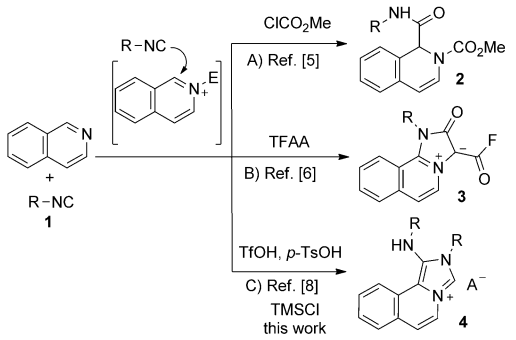
Abstract: *Trimethylsilyl chloride is an efficient activating agent for azines in isocyanide-based reactions, which then proceed through a key insertion of the isocyanide into a N–Si bond. The reaction is initiated by N activation of the azine, followed by nucleophilic attack of an isocyanide in a Reissert-type 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 α-substituted dihydroazines after a selective cascade process. Based on computational studies, a mechanistic hypothesis for the course of these reactions was proposed. The resulting products exhibit significant activity against Trypanosoma brucei and T. cruzi, featuring favorable drug-like properties and safety profiles.*

Isocyanides hold a central role in several fields of chemistry.[1] Their formally divalent character makes them ideal partners for multicomponent reactions (MCRs).[2] However, their mild nucleophilicity, together with their affinity to metals, complicates their activation for many MCRs, which hence often require harsh reaction conditions. Transition-metal-catalyzed processes that involve isocyanides are synthetically useful,[3] but complex, which is in part due to the metal coordination. In this context, the development of new facilitated MCR transformations is actively pursued, particularly those involving heterocycles, owing to their relevance in biological and medicinal chemistry.

As a testing ground for developing new activation modes, we selected isocyanide variants of the Reissert MCR.[4] The interaction of isoquinoline with chloroformates or similar reagents and isocyanides gives the MCR adduct **2**, following the typical mechanism of N activation and isocyanide attack at the α-position (Scheme 1 A).[5] However, interaction with trifluoroacetic anhydride (TFAA), a stronger electrophilic agent, gives rise to mesoionic acid fluorides **3** (Scheme 1 B).[6] Interestingly, strong Brønsted acid activation (TfOH, *p*-TsOH) of the isoquinoline enables an ABB′ reaction[7] with isocyanides (Scheme 1 C), leading to isoquinoline-fused imidazolium salts.[8] The latter reactions were productive, but mechanistic and selectivity issues have remained unsolved. Furthermore, the harsh reactions conditions required for these MCRs prevent the use of sensitive substrates.

In this context, we investigated the use of trimethylsilyl chloride (TMSCl) as a new activating agent in these trans-



Scheme 1. Reissert-type isocyanide multicomponent reactions. *p*-TsOH = *para*-toluenesulfonic acid, Tf = trifluoromethanesulfonyl, TFAA = trifluoroacetic anhydride, TMS = trimethylsilyl.

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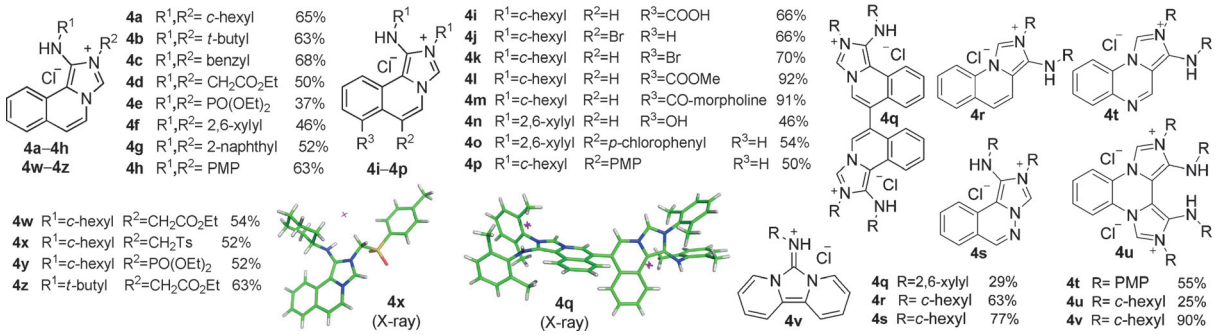


Figure 1. Reaction scope: azines and isocyanides. *c*-hex = cyclohexyl, PMP = *para*-methoxyphenyl.

formations, 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,[9a,b] 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 salt **4a** (65%; Scheme 1C, Figure 1), which precipitated as the chloride salt, presumably after spontaneous hydrolysis of the initial TMS adduct. Owing to the relevance of this new activation mode, we further studied this process.

To determine the scope of the reaction, we screened a wide array of isocyanides and azines. Isoquinoline reacted with aliphatic isocyanides (cyclohexyl, *tert*-butyl, and benzyl isocyanides) to generate the expected adducts (**4a**–**4c**) in good yields (Figure 1). Functionalized isocyanides (ethyl isocyanoacetate and diethyl isocyanomethylphosphonate (PhosMIC)) are compatible with the reaction conditions, and the corresponding imidazolium salts (**4d**, **4e**) were obtained in slightly lower yields. Aromatic isocyanides, such as 2,6-dimethylphenyl-, 2-naphthyl-, and 4-methoxyphenylisocyanide, also yielded the expected compounds (**4f**–**4h**). We then examined the azine component. Bromo-, carboxy-, and hydroxy-substituted isoquinolines reacted to yield the salts **4i**–**4k** and **4n**. These adducts can be derivatized in conventional post-transformation reactions. The acid **4i** was thus converted into ester **4l** and amide **4m** using standard procedures. However, the halogenated salts **4j** and **4k** do not react with boronic acids in standard Suzuki couplings, probably because their imidazolium moieties form stable NHC–Pd complexes.[10] Experimental support came from the characterization of the Pd complex of **4s** and the observation of its low catalytic activity in Suzuki couplings (see the Supporting Information).

Furthermore, aryl-substituted isoquinolines reacted to generate the corresponding derivatives **4o** and **4p**. Remarkably, 4,4′-biisoquinoline underwent a double reaction to generate salt **4q** in a single step. Other azines were also tested, and whereas pyridine was unreactive even under forcing conditions, quinoline generated the corresponding adduct **4r** in good yields. Interestingly, phthalazine reacted with two equivalents of cyclohexyl isocyanide to selectively yield the salt **4s**, with no trace of the double reaction product being detected. Conversely, quinoxaline reacted with an excess of the same isocyanide to render the double imidazolium salt **4u**. 4-Methoxyphenylisocyanide, however, yielded monoadduct **4t**. Interestingly, the reaction with 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[13] (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, toluenesulfonylmethyl isocyanide (TosMIC), or PhosMIC) 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 homoadducts. 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 monocrystal 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, dimedone) 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

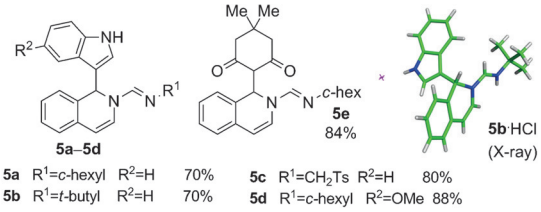
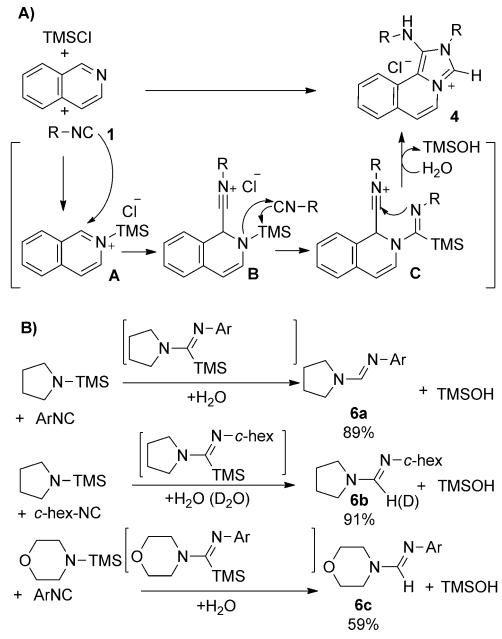


Figure 2. Interception of the MCR cascade with different nucleophilic species.



Scheme 2. Mechanistic proposal and control experiments. Ar = 4-$MeOC_6H_4$.

Supporting Information). We propose a novel mechanism that accounts for the experimental outcome (Scheme 2 A). The reaction starts with the activation of the azine by TMSCl to generate in situ *N*-silyl azinium ion **A**,[15] 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 amidine **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,[4] the N–Si isocyanide insertion[16,17] is unprecedented.[18] 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 **4**. 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 2 B).[19] 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 D_2O quenching gave amidine **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 **6**, 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 arrangement needed for the formation of the transition state (TS), where the isocyanide C atom is located 1.54 Å away from the amine

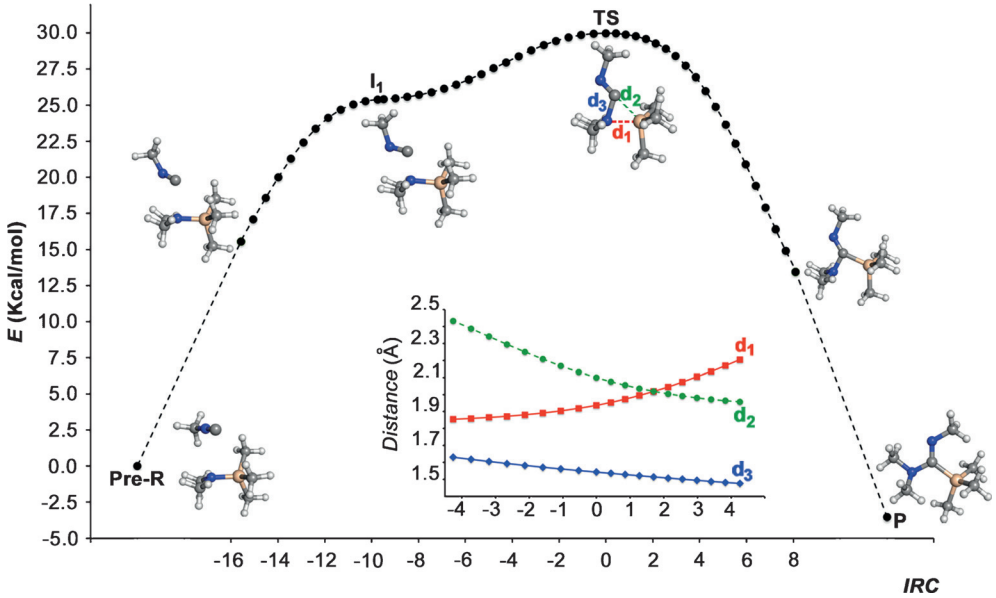
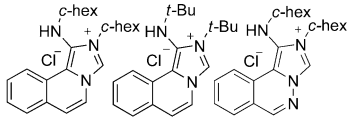


Figure 3. Reactive pathway along the intrinsic reaction coordinate (IRC) for the insertion of Me–N=C into DMA-TMS. Conversion of the pre-reactant (Pre-R) into the transition state (TS) occurs through a metastable intermediate (I1) orienting the isocyanide C atom towards the Si atom, enabling the insertion between the amine N and Si atoms in the final product (P). Inset: Changes in the distances between the isocyanide C atom and DMA-TMS (Si and N) around the TS (IRC = 0).

N atom, while it faces the Si atom (distance of 2.10 Å; Figure 3). Attack of the isocyanide C atom on the Si atom then leads to insertion into the N_{amine}–Si bond, which is enlarged to 2.84 Å in the final product, whereas the C–N_{amine} and C–Si bond lengths are 1.41 and 1.94 Å, respectively. The product is energetically favored by approximately 3.7 kcal mol^{-1} with regard to the pre-reactant complex (see the Supporting Information, Table S1). These calculations support the mechanistic proposal, which involves the nucleophilic addition of the amine lone pair on the isocyanide and a transition state with a unique azasilaiminocyclopropane connectivity.

Recently, Wipf, Robello, and co-workers reported the activity of imidazolium salts against *Trypanosoma cruzi*.[20] Inspired by their results, and considering the need for effective medicines for neglected tropical diseases,[21] we tested the bioactivity of the synthesized compounds against the causative agents of two trypanosomiases, namely *T. brucei* for African trypanosomiasis and *T. cruzi* for Chagas disease, which infect several million people. The search for simple, efficient hits is appealing,[22] particularly if they can simultaneously treat more than one parasitic infection. We evaluated the in vitro trypanocidal activity of adducts **4** against bloodstream forms of *T. brucei* and the epimastigote form of *T. cruzi*. The results revealed an interesting spectrum of activities across the whole series, with many compounds having low micromolar (or even submicromolar) EC_{50} and EC_{90} values (Figure 4; see also the Supporting Information)



	4a	4b	4s
EC_{50} (*T. brucei*, μM)	0.55	0.50	0.71
EC_{50} (*T. cruzi*, μM)	1.02	1.53	1.14
SI (*T. brucei/cruzi*)	18/10	132/43	56/35
PAMPA BBB (Pe)	2.7	5.2	10.8
CNS MPO	4.8	4.8	5.5

Figure 4. Bioactivity data of selected compounds. SI = Selectivity index. High BBB permeation (Pe > 5.16) and CNS MPO scores suggest favorable pharmacokinetic properties (see the Supporting Information).

against both parasites. We observed clear correlations between structural features and bioactivity. Interestingly, the selectivity indexes, a measure of the differential activity against parasite and mammalian cells, were rather high, with values of up to 130 for *T. brucei* and up to 40 for *T. cruzi*. In a preliminary test, compounds **4b** and **4s** were found to display acceptable tolerability, although when evaluated in a bioluminescent murine model for acute *T. cruzi* infection,[23] there was little significant activity in spite of the reasonable physicochemical profile (see the Supporting Information).[24] Metabolic turnover and/or a poor biodistribution could be factors that limit efficacy, and these issues will require further assessment.

In summary, we have described the insertion of isocyanides into N–Si bonds, providing a mechanistic hypothesis and a computational justification for this novel process. We have applied this activation mode to Reissert-type isocyanide MCRs, which can now be conducted with improved selectivity and benefit from an expanded scope. Some products displayed potent and selective in vitro activity against the causative agents of the African sleeping sickness and Chagas disease, paving the way for more detailed structure–activity relationship studies towards the development of convenient lead compounds.

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