Insertion of Isocyanides into N-Si bonds: Azine MultiComponent Reactions Leading to Potent Anti-parasitic Compounds

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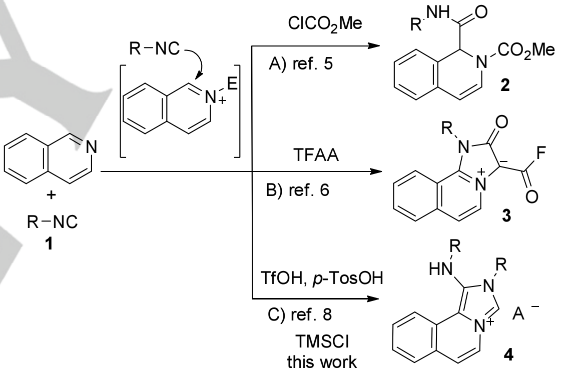
Abstract: Trimethylsilyl chloride is an efficient activating agent for azines in isocyanide-based reactions, involving a key insertion of the isocyanide into an N-Si bond. The reaction proceeds through *N*-activation of the azine, followed by concomitant nucleophilic attack of an isocyanide in a Reissert-type 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 nucleophilies leads to a variety of α-substituted dihydroazines after a selective cascade process. Computational studies and a unified mechanistic hypothesis account for the course of these reactions. The resulting products exhibit significant activity against *Trypanosoma brucei* and *T. cruzi*, featuring favourable drug-like and safety profiles.

Isocyanides hold a central role in several chemistry-related fields.[1] Their formal divalent character makes them ideal partners for multicomponent reactions (MCRs).[2] However, their mild nucleophilicity, together with their affinity to metals, complicate the activation of many MCRs, often requiring harsh conditions. Transition metal-catalyzed isocyanide processes are synthetically useful,[3] although complex, in part due to the metal coordination. In this context, the search for new facilitated MCR transformations is actively pursued, particularly those involving heterocycles, due to their relevance in biological/medicinal chemistry.

As a testing ground for developing new activation modes, we selected isocyanide variants of the Reissert MCR.[4] In this way, 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 its α-position (Scheme 1A).[5] However, interaction with trifluoroacetic anhydride, a stronger electrophilic agent, gives rise to mesoionic acid fluorides **3** (Scheme 1B).[6] Interestingly, strong Brønsted acid activation (TfOH, *p*TosOH) of isoquinoline, allowed an ABB' reaction[7] with isocyanides (Scheme 1C), leading to isoquinoline-fused imidazolium salts.[8] The latter reactions were productive, but mechanistic and selectivity issues remain unsolved. Furthermore, the drastic conditions required in these MCRs prevent applications to sensitive substrates.



Scheme 1. Reissert-isocyanide multicomponent reactions.

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 exclusively to activate carbonyls.[9] 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. Due to the relevance of this new activation mode, we studied further these processes.

To determine the scope of the reaction, we screened a wide array of isocyanides and azines. In this way, isoquinoline reacted with aliphatic isocyanides (cyclohexyl-, *t*-butyl- and benzyl-) to generate the expected adducts (**4a-c**, Figure 1) in good yields. The use of functionalized isocyanides (isocyanoacetate and PhosMIC) is compatible with the reaction, the corresponding imidazolium salts (**4d, 4e**) being produced in slightly lower yields. Aromatic isocyanides, such as 2,6-

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Supporting information for this article is given via a link at the end of dimethylphenyl-, 2-naphtyl- and 4-methoxy-phenylisocyanide also yielded the expected compounds (**4f-4h**). We then examined the azine component. In this way, bromo-, carboxy- or hydroxy-isoquinolines reacted to yield salts **4i-4k** and **4n**. These adducts can be derivatized in conventional post-transformation reactions. Thus, the acid **4i** was converted into ester **4l** and amide **4m** using standard protocols. Furthermore, arylisoquinolines reacted to generate the corresponding derivatives **4o** and **4p**. In this regard, 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 performance in Suzuki couplings (see SI).

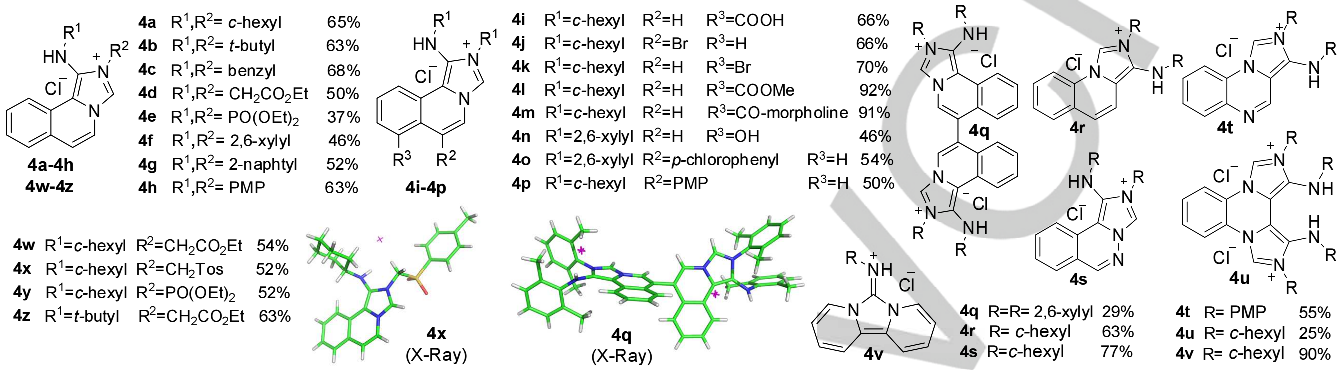


Figure 1. Reaction scope: azines and isocyanides

Remarkably, 4,4'-biisoquinoline underwent a double reaction generating salt **4q** in a single step. Other azines were also tested and, although pyridine was unreactive even under forced conditions, quinoline generated the adduct **4r** in good yields. Interestingly, phthalazine reacted with two equivalents of cyclohexyl isocyanide to selectively yield the salt **4s,** no trace of the double reaction product being detected. Conversely, quinoxaline reacted with an excess of the same isocyanide to rend the double imidazolium salt **4u**. However, 4-methoxyphenyl-isocyanide, yielded monoadduct **4t**. Interestingly, the reaction with 2,2'-bipyridine afforded in high yield the guanidinium salt **4v**, likely generated via 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 *p*-methoxyphenyl) was reacted with isoquinoline and TMSCl, a roughly equimolecular mixture of the four possible products was obtained (see SI). However, the use of one equivalent of an aliphatic isocyanide plus another one of reduced nucleophilicity (isocyanoacetate, TosMIC or PhosMIC) dramatically changed the outcome and we found one 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. 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, so far restricted to the use of two equivalents of the same input or requiring the separation of complex mixtures. Furthermore, the connectivity pattern outlined above was tested in other reactive combinations. When different nucleophiles (indole, dimedone) and one equivalent of an isocyanide were reacted with isoquinoline in TMSCl-promoted reactions,[14] adducts **5a-5e** (Figure 2) were conveniently obtained in high yields.

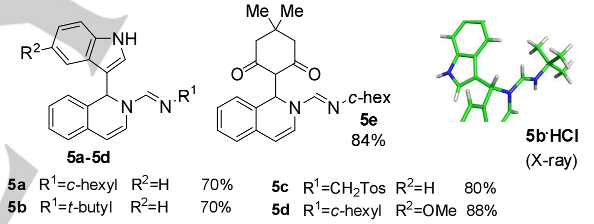
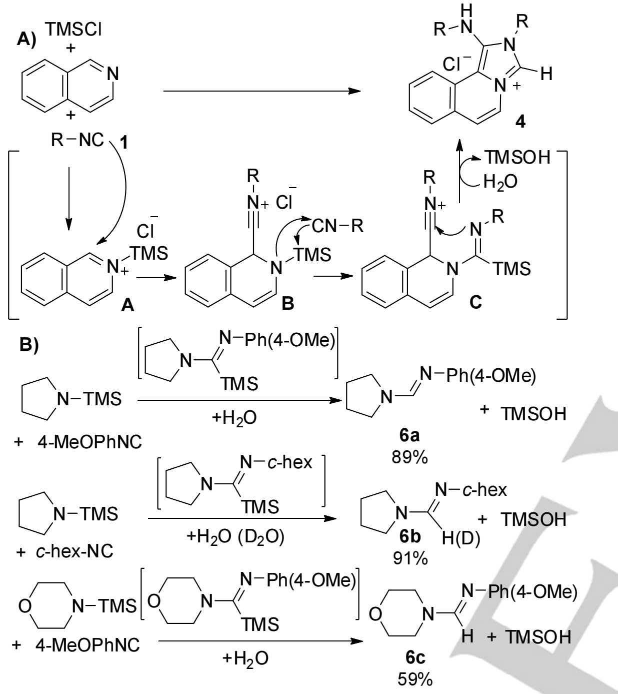


Figure 2. Interception of the MCR cascade with different nucleophilic species.

Control experiments involving a proton scavenger, support the participation of TMSCl as the activating agent (see SI). We suggest a novel mechanistic proposal that accounts for the experimental outcome (Scheme 2A). It starts with the activation of the azine by TMSCl, to generate *in situ* an *N*-silylazinium ion **A**,[15] subsequently attacked by an isocyanide (or another nucleophilic species) yielding a nitrilium cation **B**, likely stabilized by a chloride counterion. This intermediate may undergo the insertion of a second (less nucleophilic) isocyanide into the N-Si bond to yield a 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 the resulting intermediates are known,[4] the N-Si isocyanide insertion[16,17] is unprecedented.[18] All attempts to isolate the silyl-imidazolium salts under anhydrous conditions were unsuccessful, likely due 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 suitable generation of amidines **6a-c** through reaction of isocyanides with *N*-silylamines, although at higher temperatures (toluene, 110 °C, Scheme 2B).[19] In agreement with the proposed mechanism, deactivated or sterically hindered N-Si derivatives failed to undergo the insertion reaction (see SI). The course of the reaction was followed by NMR, the silylated intermediates were detected and in situ evolved to the C-H amidines by spontaneous hydrolysis with adventitious water. Although GC/MS analysis of crude reaction mixtures showed the existence of silylated species and D_2O quenching gave amidine **6b** with a partial isotopic labelling (see SI), it was impossible to characterize the intermediates or trap them with distinct electrophiles.

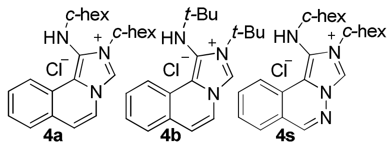


Scheme 2. Mechanistic proposal and reactivity probes.

Pivotal to this chemistry is the novel isocyanide insertion step, which, contrary to the standard nucleophilic behavior commonly exhibited by isocyanides, seems to be electrophilic in nature, 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 (see SI) were performed. For the sake of simplicity, computations were performed for methyl isocyanide and dimethylamine-TMS (DMA-TMS) as reagents. The reactive channel starts with the attack of the DMA-TMS amine nitrogen on 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 (Figure 3). These structural changes are the major contribution to the reaction barrier. Further, they afford the geometrical arrangement needed for the formation of the transition state (TS), where the isocyanide C is located at 1.54 Å from the amine N, while it faces the Si atom (distance of 2.10 Å; Figure 3C). Attack of the isocyanide C on Si then leads to insertion between the N_{amine}-Si bond, which is enlarged up to 2.84 Å in the final product, while the C-N_{amine} and C-Si bond lengths are 1.41 and 1.94 Å, respectively. Noteworthy, the product is energetically favored by *ca.* 3.7 kcal/mol with regard to the pre-reactant complex (Table S1 in SI). These calculations support the mechanistic proposal, which involves the nucleophilic addition of the amine lone pair to the isocyanide, and the configuration of a transition state with a unique azasilaiminocyclopropane connectivity.

Recently, Wipf and Robello reported the chemotherapeutical activity of imidazolium salts against *Trypanosoma cruzi*.[20] Inspired by their results, and considering the need of effective medicines for neglected tropical diseases,[21] we tested the bioactivity of the synthesized series against the causative agents of two trypanosomiases: *T. brucei*, for African trypanosomiasis, and *T. cruzi*, for Chagas disease. Infecting 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* trypanocydal activity of adducts **4** against bloodstream forms of *T. brucei* and the epimastigote form of *T. cruzi*. The results revealed an interesting spectrum of activity across the whole series, with many compounds having low micromolar (even submicromolar) EC_{50} and EC_{90} values (Figure 4, see also SI) against both parasites. We observed clear associations between structural features and bioactivity. Interestingly, the selectivity indexes, a measure of the differential activity against parasite and mammalian cells, were significantly high, with values 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 (see SI), in spite of the reasonable physicochemical profile [24] (see SI). Metabolic turnover and/or 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 and computational justification for this novel process. We have applied this activation mode to Reissert–type isocyanide MCRs, now taking place with improved selectivity and expanded synthetic outcome. Some compounds display a potent and selective in vitro activity against the causative agents of the African sleeping sickness and the Chagas disease, opening the way for more detailed structure-activity relationship studies en route to convenient leads.



	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 (CNS+), Pe >5.16 and CNS MPO score ≥ 4 suggest favourable pharmacokinetic attributes (see SI).

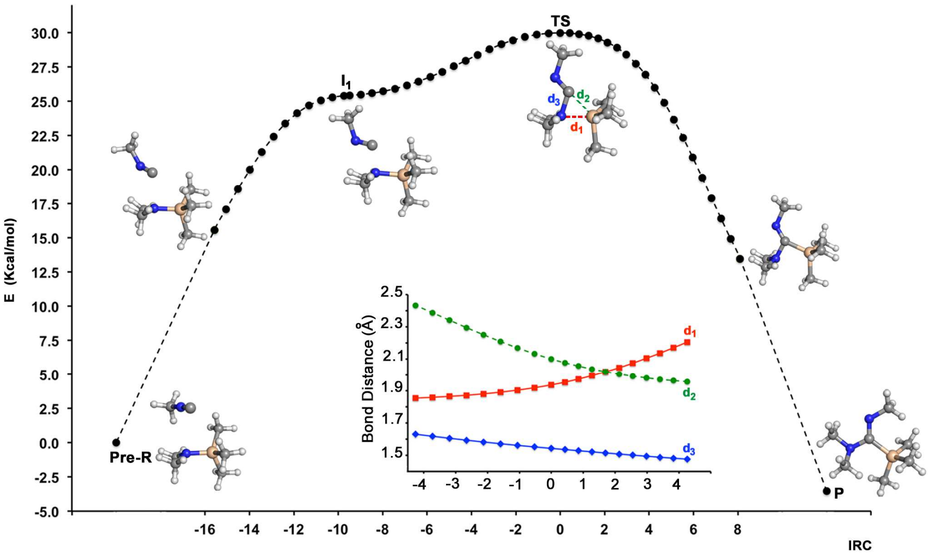


Figure 3. Reactive pathway along the intrinsic reaction coordinate (IRC) for the insertion of Me-N=C into DMA-TMS. Conversion of the pre-reactant complex (Pre-R) to the transition state (TS) occurs through a metastable intermediate (I1) orienting the isocyanide C towards Si, allowing the insertion between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

Acknowledgements

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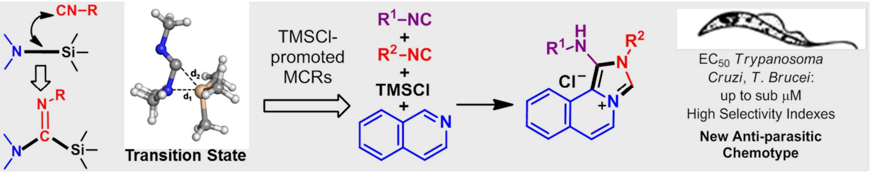
COMMUNICATION



Insert here! Isocyanides undergo insertion into N-Si bonds allowing an efficient promotion of Multicomponent Reactions with isoquinoline and other azines. This novel activation mode allows a variety of transformations which take place with high selectivity under mild conditions. A new chemotype for Trypanosoma diseases has been discovered using these processes.

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Supporting Information