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Modular Access to Tetrasubstituted Imidazolium Salts through Acid-Catalyzed Addition of Isocyanides to Propargylamines

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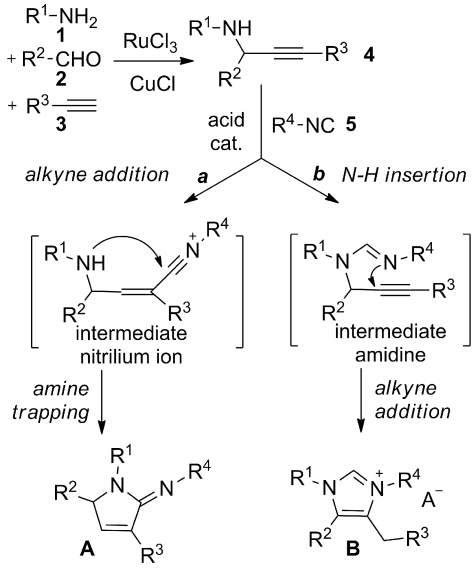
Propargylamines, prepared through A^3-coupling of primary amines, aldehydes and terminal alkynes, react with isocyanides in an HCl-catalyzed process to yield tetrasubstituted imidazolium salts. The key step of the mechanism involves the generation of an amidine intermediate, from the isocyanide insertion into the N–H bond of the propargylamine, which in situ evolves by cyclization upon the alkyne moiety. The scope of the process is analyzed and only shows restrictions for aliphatic amines, whereas it is quite general regarding the aldehyde, alkyne and isocyanide inputs. The protocol allows the preparation of a wide array of adducts, tandem one-pot processes being also feasible. Mechanistic studies using selected substrates have been used to determine the profile of the reaction and some substitution and functional group limitations. Some post-synthetic transformations of the imidazolium salts have been performed as well.

Introduction

Multicomponent reactions (MCRs) and domino processes, being transformations in which several bonds are generated in a single step, represent an optimized way for the synthesis of complex compounds in a fast manner, especially suitable for the generation of chemical libraries.[1] In this context, following our interest in isocyanide MCR chemistry,[2] we decided to tackle the interaction of these substrates with alkynes.[3] So far, this interaction mostly involves metal-catalyzed processes and conjugated additions to electron-deficient alkynes.[4] Although remarkable processes have been described by the Van der Eycken group, where the alkyne is a manifold substituent in some inputs of the Ugi MCR;[5] the direct transformation remains largely unexplored. We envisaged a new reaction profile where the isocyanide would undergo addition to an acid activated triple bond,[6] and the nitrilium ion so generated would be captured by a nucleophilic amine (Scheme 1, pathway *a*) to yield iminopyrrolines **A** or tautomeric species. Alternatively, the process may proceed by isocyanide insertion[7] into the N–H bond of the secondary amine, to trigger an intramolecular amidine addition upon the alkyne[8] through a 5-*exo-dig* route[9] (Scheme 1, pathway *b*) and [1,3]-H shift, leading to the imidazolium salts **B**. The recent report of Zhu and co-workers, describing an analogous process using double catalysis of Ag^+/Yb^{3+} cations,[10] prompted us to disclose our findings.



Scheme 1. Hypothetical mechanistic profiles on the interaction of isocyanides and propargylamines.

In this way, we prepared A^3 adducts,[11] arising from the metal-catalyzed interaction of, a primary amine **1**, an aldehyde **2** and a terminal alkyne **3**, to afford propargylamines **4** (Scheme 1). Then, these compounds were treated with isocyanides **5** under variety of acid catalysts (see below). These processes allowed the formation of imidazolium salts **6** (Scheme 2), thus revealing the prevalence of the latter mechanistic choice.

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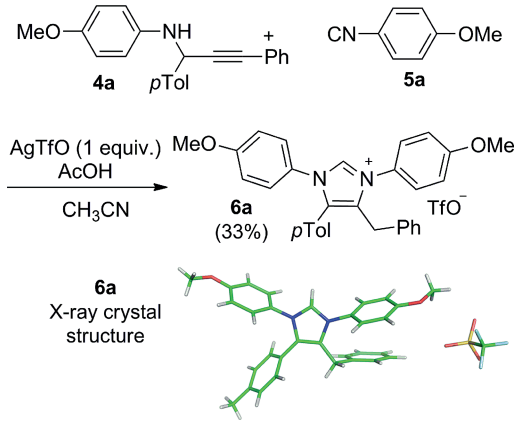


Scheme 2. Synthesis of imidazolium salts through silver-catalyzed propargylamine-isocyanide interaction.

Table 1. Range of the components.

Entry	Adduct	R^1, R^2, R^3, R^4	Yield[a]
1	**6a**	4-$MeOC_6H_4$, *p*Tol, Ph, 4-$MeOC_6H_4$	82%
2	**6b**	*p*Tol, Ph, Ph, *t*Bu	82%
3	**6c**	4-$MeOC_6H_4$, *p*Tol, Ph, *t*Bu	92%
4	**6d**	Bn, *i*Pr, Ph, *c*Hex	23%[b]
5	**6e**	4-$MeOC_6H_4CH_2$, Ph, Ph, *c*Hex	10%[b]
6	**6f**	4-$MeOC_6H_4$, 4-ClC_6H_4, *p*Tol, *t*Bu	56%[c]
7	**6g**	4-$MeOC_6H_4$, 4-ClC_6H_4, *n*-C_5H_{11}, *t*Bu	85%
8	**6h**	*p*Tol, Ph, Ph, *c*Hex	82%
9	**6i**	*p*Tol, Ph, Ph, $EtCO_2CH_2$	96%[c]
10	**6j**	*p*Tol, Ph, Ph, 2,6-$(H_3C)_2C_6H_3$	27%[d]
11	**6k**	*p*Tol, 4-ClC_6H_4, Ph, 2-naphthyl	75%[e]

[a] Obtained from general procedure A (see Supporting Information). [b] AcOH (1 equiv.) and AgTfO (20%) were used instead of HCl (see SI). [c] The hydrolyzed betaine **6i′** was also generated during purification. [d] Reaction performed at 60 °C. [e] Reaction performed with $MeSO_3H$ (1 equiv.) instead of HCl, due the low solubility of the propargylamine hydrochloride.

Results and Discussion

First the preparation of propargylamines **4** was troublesome, as there are few reports involving the participation of primary amines.[11c] We were concerned about the incompatibility of the Cu^I cation used in the A^3 couplings with isocyanides **5**, via the formation of inert complexes, therefore requiring purification of the A^3 adducts. After much experimentation, it was shown that the concomitant use of Ru^{III}/Cu^I catalysis in THF (Li-Wei method)[11d] was productive and, importantly, allowed the subsequent isocyanide interaction to be performed in tandem (see below). The aniline-derived substrates were prepared in this way, whereas those arising from benzylamine were synthesized using van Eycken conditions.[11c]

Next, the reaction of propargylamine **4a** and isocyanide **5a** was investigated (Scheme 2). Several Lewis acids such as CuBr, $InCl_3$, $AuCl_3$, AgOTf, $Sc(OTf)_3$, I_2 and ICl allowed the detection of the corresponding salt **6a** in low yields. However, the combination of AgOTf/AcOH was more productive and afforded the imidazolinium salt **6a** in 33% yield. The X-ray diffraction of a monocrystal of this compound secured the proposed structure.[12]

The best results were observed when propargylamine **4a** was treated with a stoichiometric amount of HCl (dioxane solution), in a 1:1 mixture of ACN/THF at room temp., affording the final adduct in 82% yield (Table 1). For unknown reasons, the imidazolium salts were better isolated after aqueous Na_2CO_3 extraction[13] (clean HPLC profiles), and analytical samples can be obtained by standard flash chromatography (SiO_2), although some decomposition was observed during purification. Consequently, we assume that the anion of the imidazolium species is CO_3^{2-}, although its unequivocal identification was not possible (MS-Ve technique).

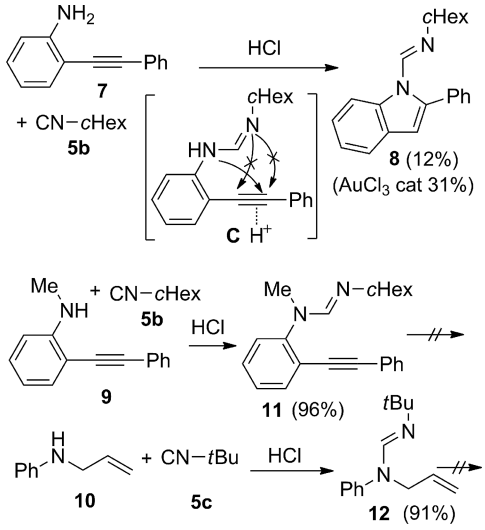
The use of imidazolium salts and their derivatives is widespread in several areas such as medicinal chemistry or biology.[14] Imidazolium salts belong to a very common class of ionic liquids,[15] and constitute the primary source of N-heterocyclic carbenes,[16] frequently used ligands in organometallic chemistry. In this respect, PEPPSI catalysts rank among the most active catalysts for Pd-coupling reactions.[17] Unfortunately the preparations of polysubstituted imidazolium salts usually involve complex multistep syntheses.[18] Therefore, many of the previously mentioned applications have been tested only on simple, easily accessible salts, usually obtained by alkylation of the parent imidazoles.[19] Thus, a general and direct access to these compounds would allow a programmed preparation of diversely substituted derivatives and hence a finer and more rational modulation of their properties.

Next the scope of the reaction was tested. Propargylamines **4** having N-aromatic residues smoothly reacted with isocyanides to afford the corresponding products (Table 1, entries 1–3, 6–11). On the other hand, the *N*-benzyl derivatives afforded imidazolium salts **6d** and **6e** in lower yields (Table 1, entries 4 and 5), whereas *N*-alkyl derivatives did not react under these conditions. The use of milder acids (AcOH, citric acid) was inefficient, *p*TosOH gave low yields and the HCl-promoted addition remained as the only productive transformation (23% and 10% respectively). This fact constitutes the main practical limitation of the procedure. Referring to the aldehyde moiety, the process allows a wider scope; including aromatic (both electron-rich and electron-poor, Table 1, entries 1–3, 5–11) and alkyl derivatives (Table 1, entry 4). With respect to the terminal alkyne substitution, a variety of aromatic (Table 1, entry 1–6, 8–11) and aliphatic residues (Table 1, entry 7) are tolerated.

Finally, a wide range of isocyanides yielded the corresponding products, allowing the introduction of bulky aliphatic groups such as *t*Bu and *c*Hex (Table 1, entries 2–8). Aromatic isocyanides were also productive, either displaying electron-donating groups (MeO) or bulky residues such as xylyl and naphthyl groups (Table 1, entries 1, 10, 11). Methyl isocyanoacetate afforded the corresponding imidazolium salt **6i** (entry 9) and partially hydrolyzed during chromatographic purification, presumably to the betaine **6i′** (see SI). Although PhosMIC and TosMIC underwent satisfactory conversions, the corresponding adducts

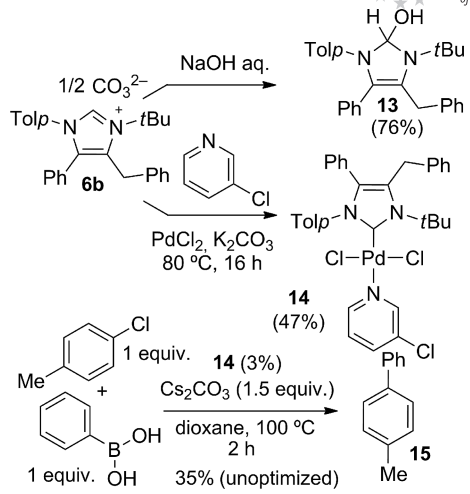
(detected by HPLC/MS) quickly decomposed during chromatographic purification.

In order to further explore the range of the reaction upon distinct substrates, we performed a series of experiments. First of all, the intermolecular version of this interaction was tested. In this way, disubstituted alkynes (diphenylacetylene or 1-phenyl-1-hexyne) were treated with primary anilines and isocyanides, under a variety of catalysts, but no imidazolium salts could be detected. This result reinforces the need of an intramolecular mode of action. The *o*-alkynylaniline **7** was treated with isocyanide **5b** to afford indole **8** in 12% yield (31% with $AuCl_3$ catalysis, Scheme 3). The process may start with an N–H isocyanide insertion to generate amidine **C**, which would subsequently cyclize (5-*endo*-*dig*) to afford the final product (Scheme 3), in a transformation related to the Larock indole synthesis.[20] Noteworthy, when 2-phenylindole reacted with isocyanide **5b** under the same conditions, product **8** was not formed, suggesting that the formation of the amidine moiety takes place first.



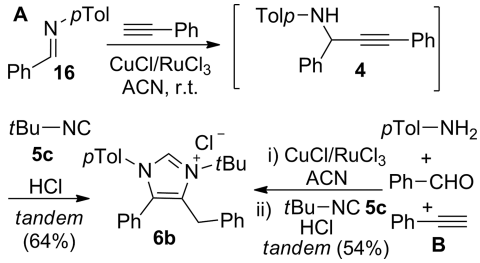
Scheme 3. Mechanistic probes.

Interestingly, the substituted anilines **9** and **10** afforded, on interaction with isocyanides **5b** and **5c**, amidines **11** (96%) and **12** (91%) respectively (Scheme 3). The processes stop at the amidine formation stage and the cyclizations upon the π systems do not proceed, although imidazolium rings have been formed this way in related systems.[21] When attempting a different extraction procedure, using aq. NaOH (1 M) as a basic quencher, the hydroxy derivative **13** (Scheme 4) cleanly precipitated, and was isolated in 76% yield and purified simply by filtration. Its structure was clearly established by spectroscopic methods. Interestingly, ^{1}H NMR showed two rotamers, probably due to the *tert*-butyl steric hindrance, albeit displaying a single peak in the HPLC profile. As a proof of concept, the PEPPSI-type catalyst **14** was prepared from imidazolinium salt **6b**, following Organ's procedure.[22] The thus prepared palladium catalyst was used in a standard Suzuki reaction using 4-chlorotoluene as representative substrate, which was successfully coupled with phenylboronic acid to furnish biphenyl **15** (35% yield, unoptimized, Scheme 4).



Scheme 4. Post-transformation reactions and application.

We next considered the feasibility of tandem procedures, to speed up the overall process. In this way, the pregenerated imine **16** was subjected to alkyne addition under Cu^I/Ru^{III} catalysis followed by in situ treatment with isocyanide **5c** and HCl to successfully afford the imidazolium salt **6b** (64%; Scheme 5, A). Furthermore, the direct synthesis of the same adduct by interaction of the four reactant inputs, without isolation of any intermediates was achieved by linking the standard A^3 reaction with the isocyanide interaction (Scheme 5, B). Interestingly, this tandem/one-pot procedure, albeit less productive (54%) and clean than the original stepwise reaction, does not show synthetic restrictions due to incompatibilities of isocyanides with metal cations present in the medium. Likewise, imidazolium salts **6h** (49%) and **6i** (68%) were also prepared following this protocol.



Scheme 5. Tandem multicomponent approaches.

Conclusions

In conclusion, the formation of tetrasubstituted imidazolium salts by an HCl-promoted isocyanide/propargylamine interaction has been described. The scope of the process has been analyzed and some synthetic uses of the corresponding adducts determined. The reaction is not productive for aliphatic amines, whereas the Zhu reaction[10] works well for these substrates. However, the milder condi-

tions used in our transformation allow the preparation of *N*-*tert*-butylimidazolium salts without elimination problems. Overall, our process shows that the stoichiometric use of HCl leads to the desired products, however in lower yields and parallels the mechanistic profile described for this interaction. Although for some sensitive substrates, the protic acid may be deleterious, the soft activation needed and the consumption of this reagent may prevent unwanted decomposition. Finally, tandem/one-pot protocols linking the synthesis of the propargylamines, by an A^3 reaction, with the isocyanide addition step have been developed.

Experimental Section

Preparation of Propargylic Amines (4): *N*-(aryl)propargylamines were prepared using a modification of Li and Wei's procedure[11d] in non-aqueous media: In a Schlenk tube, 2.0 mmol (1.00 equiv.) of aldehyde and 2.2 mmol (1.1 equiv.) of amine were dissolved in 5 mL of THF under inert atmosphere. The tube was sealed and the mixture was heated at 60 °C until complete consumption of the aldehyde (2 h). Next CuCl (30 mol-%), $RuCl_3$ (3 mol-%) and the alkyne (2.4 mmol, 1.2 equiv.) were added. The mixture was stirred at room temp. (30 min), and then heated at 50 °C until consumption of the imine (24 h). The solution was cooled, poured into water, and extracted with DCM. The combined organic phases were washed with water, dried with $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography on silica gel (hexanes/AcOEt) afforded the corresponding propargylamines.

N-benzylpropargylamines were prepared following the procedure reported by Van der Eycken et al.[11c]

General Procedure A: Propargylamine **4** (0.5 mmol, 1 equiv.) was dissolved in THF (1.5 mL) and ACN (1.5 mL) under inert atmosphere. Next isocyanide **5** (0.5 mmol, 1 equiv.) was added. A 4 M HCl solution in dioxane (125 μL, 1 equiv.) was added and the mixture stirred at room temp. until consumption of the propargylamine (4 h). Next the reaction was quenched with saturated Na_2CO_3 aq. solution (20 mL) and extracted with AcOEt (3 × 10 mL). The combined organic phases were dried with $MgSO_4$ and concentrated in vacuo to afford the corresponding imidazolium salts. Analytically pure samples of the products were obtained by flash chromatography on silica gel (hexanes/EtOH).

General Procedure B (tandem): In a Schlenk tube, the aldehyde (1.0 equiv.) and the amine (1.05 equiv.) were dissolved in THF (3 mL) under inert atmosphere. The tube was sealed and the mixture was heated at 60 °C until complete aldehyde consumption (2 h.). Next CuCl (30 mol-%), $RuCl_3$ (3 mol-%.) and the alkyne (1.2 equiv.) were added. The mixture was first stirred at room temp. for 30 min, and then heated at 50 °C (24 h). The solution was cooled to room temp. and diluted with ACN (3 mL). The isocyanide (1.1 equiv.) was then added, followed by a 4 M HCl solution in dioxane (0.125 μL, 1 equiv.). The solution was stirred at room temp. until reaction completion (24 h) and then quenched with Na_2CO_3 (saturated aq. solution, 40 mL) and extracted with AcOEt (3 × 20 mL). The combined organic phases were dried with $MgSO_4$ and concentrated in vacuo, to afford the corresponding imidazolium salts. Analytically pure samples were obtained by flash chromatography on silica gel (hexanes/EtOH). In this way, from the corresponding inputs, imidazolium salts **6b** (54%), **6h** (49%), **6i** (68%) were obtained.

Typical Procedure C (tandem from the imine): In a Schlenk tube, imine **16** (204 mg, 1.05 mmol.), phenylacetylene **3** (122 mg, 1.2 mmol), CuCl (31 mg, 30 mol-%), $RuCl_3$ (6.5 mg, 3 mol-%.) were dissolved in THF (3 mL) under inert atmosphere. The mixture was then stirred at 50 °C for 24 h. The solution was cooled to room temp. and diluted with ACN (3 mL). Then, *tert*-butyl isocyanide (91 mg, 1.1 mmol.) was then added, followed by a 4 M HCl solution in dioxane (0.125 mL, 1 equiv.). The resulting solution was stirred at room temp. until reaction completion (24 h) and then quenched with Na_2CO_3 (saturated aq. solution, 40 mL) and extracted with AcOEt (3 × 20 mL). The combined organic phases were dried with $MgSO_4$ and concentrated in vacuo, to afford imidazolium salt **6b** (412 mgs, 64%). Analytically pure sample was obtained by flash chromatography on silica (hexanes/EtOH).

Preparation of Hydroxyldihydroimidazole (13): *N*-(1,3-diphenylprop-2-ynyl)-4-methylaniline (149 mg, 0.5 mmol) was dissolved in 1.5 mL of THF and ACN (1.5 mL) under inert atmosphere. *tert*-butyl isocyanide (50 mg, 0.6 mmol) was added, followed by a 4 M HCl solution in dioxane (0.125 μL, 1 equiv.). The solution was stirred at room temp. until reaction completion (24 h) and then quenched with a NaOH aq. solution (1 M, 3 mL) was added and the solution was stirred vigorously at room temperature overnight. Hydroxyldihydroimidazole **13** (151 mg, 76%), precipitated in the reaction mixture and was recovered by filtration, washed with hexanes (1 mL) and dried in vacuo.

Preparation of 2-(Phenylethynyl)aniline (7): Compound **7** was prepared through a Sonogashira coupling reaction as reported by Liang[23] et al. in good yield (87%).

Preparation of *N*-[(2-Phenyl-1*H*-indol-1-yl)methylene]cyclohexanamine (8): 2-(Phenylethynyl)aniline (**7**) (97 mg, 0.5 mmol), and $AuCl_3$ (15 mg, 0.05 mmol), were dissolved in ACN (1 mL) under inert atmosphere in a microwave tube. Cyclohexyl isocyanide (82 mg, 0.75 mmol) was added. The sealed tube was irradiated for 2 h at 75 °C (power: 80 W). The reaction was quenched with saturated aq. $NaHCO_3$ (10 mL) and extracted with AcOEt (3 × 10 mL). The combined organic phases were dried with $MgSO_4$, filtered, concentrated in vacuo and purified by flash chromatography on silica gel (hexanes/AcOEt) to afford compound indole **8** (47 mg, 31% yield). Unreacted starting material was also recovered (58%). The same reaction catalyzed by HCl (dioxane solution,1 equiv.) gave the same compound in a modest 12% yield.

***N*-Methyl-2-(phenylethynyl)aniline (9):**[24] 2-(Phenylethynyl)aniline (**7**) (193 mg, 1.0 mmol) was dissolved in THF (5 mL) under inert atmosphere and cooled to –78 °C. *n*BuLi solution (10 M in hexanes, 0.11 mL, 1.1 equiv.) was added dropwise and the mixture was stirred for 1 h. Methyl iodide (213 mg, 1.5 mmol) was added and the mixture was stirred at room temp. for 2 h. Upon reaction completion, the reaction was carefully quenched by dropwise addition of NH_4Cl aq. solution (1 mL) at 0 °C. A precipitate was filtered off, and the solution was added to of saturated aq. solution $NaHCO_3$ (10 mL) and extracted with AcOEt (3 × 10 mL). The combined organic phases were dried with $MgSO_4$, filtered, and concentrated in vacuo to yield aniline **9** (190 mg, 91% yield). The crude was used without further purification as the spectroscopic data matched with those described in the literature.

Preparation of *N*′-Cyclohexyl-*N*-methyl-*N*-[2-(phenylethynyl)phenyl]formimidamide (11) and *N*-Allyl-*N*′-*tert*-butyl-*N*-phenylformimidamide (12): Amidines **11** and **12** were prepared from *N*-methyl-2-(phenylethynyl)aniline (**9**) and *N*-allylaniline (**10**) respectively in 96% and 91% yield using general procedure A.

6b-$PdCl_2$-(3-chloropyridine) Complex (14): This catalysts was prepared from imidazolium salt **6b**, 3-chloropyridine and $PdCl_2$ following Organ's procedure[25] (yield 47%).

4-Methyl-1,1′-biphenyl (15): A mixture of 4-chlorotoluene (24 mg, 0.205 mmol), phenylboronic acid (25 mg, 0.205 mmol), complex [**6b**-$PdCl_2$-(3-chloropyridine)] (**14**) (4 mg, 0.006 mmol), Cs_2CO_3 (99 mg, 0.307 mmol) in dioxane was heated at 100 °C for 2 h under nitrogen atmosphere. The mixture was filtered through a celite pad and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexanes/ethyl acetate) to obtain the desired product whose spectroscopic properties matched with the described in the literature[26] (12 mg, 35%).

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