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Tandem amine propargylation-Sonogashira reactions: new three-component coupling leading to functionalized substituted propargylic amines

Nathanaël Olivi, Philippe Spruyt, Jean-François Peyrat, Mouâd Alami* and Jean-Daniel Brion

Laboratoire de Chimie Thérapeutique, BioCIS-CNRS (UMR 8076), Université Paris Sud, Faculté de Pharmacie, rue J.B. Clément, 92296 Châtenay-Malabry Cedex, France

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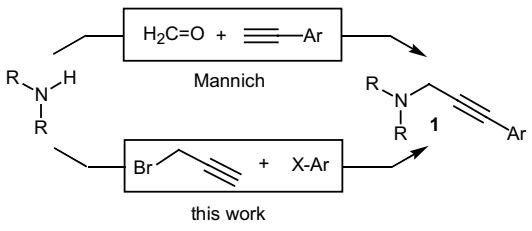
Abstract—Three-component coupling reactions of propargyl halides, amines, and organic halides in the presence of palladium–copper catalysis produced efficiently highly functionalized propargylic amines in good to excellent yields at room temperature. Extension to the synthesis of 2-(dialkylaminomethyl)benzo[*b*]furan or indole derivatives is described.

Our recent results of various hydrostannylation of disubstituted alkynes[1] have resulted in a continual requirement of substituted aryl propargylic amines **1** bearing various substituents on the aromatic ring. Such structures are of great biological interest since they display strong inhibitory activities toward several enzymes.[2] Moreover, they are synthetically key intermediates for the preparation of allylic amines and various nitrogen heterocycles (e.g., pyrroles, β-lactams, and pyrrolidines).[3]

In recent years, great efforts have been made to devise new routes to propargylic amines including amination of propargylic electrophiles (halides, triflates, or phosphates),[4] $TiCl_4$ mediated amination of propargyl ester,[5] addition of 1-alkynes to pre-formed imines,[6] or Sonogashira coupling of aryl halides with propargyl amines.[7] While these reactions are suitable methods, they require the preparation of either or both reagents. The most obvious and certainly the most popular way to prepare propargylic amines is the Mannich three-component condensation of 1-alkynes, aldehydes, and amines (Scheme 1).[8] While there are many commercially available amines and aldehydes, the number of terminal alkynes is limited (particularly functionalized terminal arylalkynes) and their preparation requires multistep sequence synthesis. Moreover, such terminal alkynes are sensitive substrates when bearing an electron-withdrawing substituent (NO_2, CN, CF_3...) on the aromatic ring.[9] From the standpoint of flexibility, a method employing a common starting material as a precursor would have obvious advantages. Herein, we wish to report a three-component synthesis of highly functionalized substituted aryl propargylic amines **1**. The basic concept of our process, illustrated in Scheme 1 is based on a tandem amine propargylation-Sonogashira reaction using amines, propargyl bromide, and functionalized aryl halides under palladium–copper catalysis. The commercial availability of such compounds makes this approach sufficiently diversity oriented, thus fulfilling the recent demand for the generation of large combinatorial chemical libraries.[10]



Scheme 1.

Keywords: Sonogashira; Propargyl halides; Propargylic amines; Palladium; 2-(Dialkylaminomethyl)indoles; 2-(Dialkylaminomethyl)benzofuranes.

* Corresponding author. Tel.: +33-146835887; fax: +33-146835828; e-mail: mouad.alami@cep.u-psud.fr

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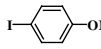
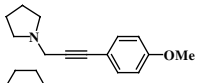
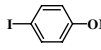
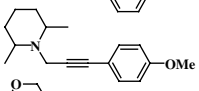
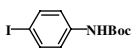
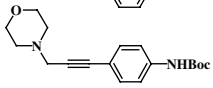
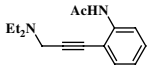
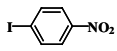
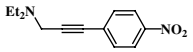
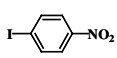
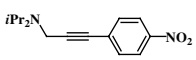
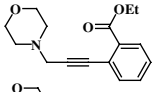
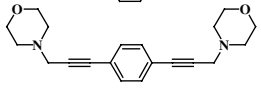
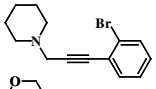
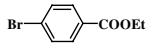
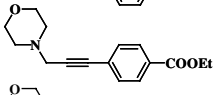
Typically the reaction of aryl halides (1 equiv), propargyl bromide (1.2 equiv) and amine in the presence of $PdCl_2(PPh_3)_2$ (5 mol%) and CuI (10 mol%) resulted in the formation of the propargylic amines **1** in excellent yields. As shown in Table 1, this process can be applied to a broad range of secondary amines and functionalized aryl iodides or aryl bromides. For the aryl iodides, the reactions proceeded at ambient temperature and were completed in a short period time (15–30 min). Both aromatic iodides bearing an *ortho* or a *para* electron-donating or electron-withdrawing substituents afforded the coupling product in excellent yields (entries 1–7). For the aryl bromides, the reaction required heating and proceeded at 60 °C for several hours to give the desired coupling product efficiently. In contrast to 1,4-diiodobenzene[11] (entry 8), the reaction of 1,2-dibromobenzene

Table 1. Synthesis of functionalized propargylic amines **1** by a three-component assembling process under palladium–copper catalysis

Entry	Amine	Propargyl halide	RX	Propargylic amine **1**	Yield (%)[a]
1					80[b]
2					87[c]
3					83
4					95
5					94
6					69
7					78
8					98
9					69
10					93
11					86[d]
12					74
13					74
14					89
15					63[e]
16					76[f]

[a] Isolated yield based on arylhalide. Propargylic amines **1** synthesized are new compounds except those of entries 5, 8, 11, and 12. All new compounds exhibited satisfactory spectral properties. For a general procedure, see Ref. 15.

[b] Reaction performed without copper iodide; see Ref. 16.

[c] Reaction performed at 60 °C.

[d] Reaction performed at room temperature.

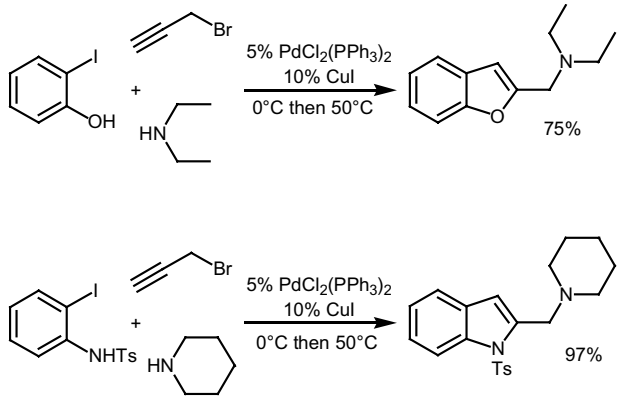
[e] Isolated yield based on propargyl bromide (1 equiv). Reaction performed in the presence of an excess (10 equiv) of 1,2-dichloroethylene (*E*/*Z* 1/1), see Ref. 12.

[f] $PdCl_2(PhCN)_2$ was used instead of $PdCl_2(PPh_3)_2$, see Ref. 13.

(entry 9) allows the selective obtention of the mono-coupling product even when using an excess of propargyl bromide (3 equiv). Under similar conditions, heteroaromatic bromides such as 2-bromopyridine underwent the three-component reaction and afforded the coupling product in 74% yield (entry 12). On the other hand, this process is also effective even when using the less reactive vinyl chlorides including 1,2-dichloroethylene[12] (entry 15) or chloroenynes (entry 16). In the latter case, $PdCl_2(PhCN)_2$[13] was used as catalyst instead of $PdCl_2(PPh_3)_2$. It should be noted that this three-component procedure with substituted propargyl chlorides such as 3-chloro-oct-1-yne is also effective to give the expected products. Its coupling with methyl 4-iodobenzoate (entry 13) or 4-iodobenzonitrile (entry 14) provided the desired three-component coupling compound in 74% and 89%, respectively.

Finally, under these reaction conditions, it was also possible to extend the scope of this three-component assembling process to perform a tandem amine propargylation-Sonogashira-cyclization sequence to obtain 2-(dialkylaminomethyl)benzo[*b*]furan or indole derivatives, an important class of heterocycles that exhibit a wide range of activity[14] (Scheme 2). Thus, when *ortho* iodophenol was used as substrate, the cyclized benzofuran was obtained in a 75% yield. Similarly, 2-iodo substituted aniline yielded 2-substituted indole derivative quantitatively. It should be noted, that the effect of the functional group on the nitrogen atom toward the cyclization step is crucial since no cyclization reaction occurred from the compound having an acetyl function on the nitrogen atom (Table 1, entry 4).

In conclusion, we have successfully developed a new three-component assembling of amines, organic halides and propargyl halides for the preparation of functionalized propargylic amine, indole, and benzofuran derivatives in high yields. Variation is allowed in each of the three components, thus making a wide range of accessible products. This process is not only of interest for combinatorial synthesis of propargylic amines and heterocycles, but in many cases also offers considerable synthetic advantages in terms of yield, selectivity, and simplicity of the reaction procedure. Extension of this process to the preparation of other heteroatom-containing cyclic compounds is already underway.



Scheme 2.

Acknowledgements

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15. General procedure: Under an inert atmosphere, propargyl bromide (1.2 equiv) purchased from Aldrich was slowly added, at 0 °C, to a solution containing aryl iodide (1 equiv), $PdCl_2(PPh_3)_2$ (5 mol %), CuI (10 mol %), and amine (used as a solvent). The reaction mixture was stirred at room temperature (or heated at 60 °C when using an aryl bromide) and monitored by TLC until complete consumption of starting materials then concentrated in vacuo. Purification by chromatography on silica gel afforded pure propargylic amine **1**.

Ethyl 4-(3-morpholin-4-ylprop-1-ynyl)benzoate (entry 10): ^{1}H NMR (200 MHz, $CDCl_3$, δ ppm) 7.86 (d, $J = 8.5$ Hz, 2H), 7.37 (d, $J = 8.5$ Hz, 2H), 4.25 (q, $J = 7.1$ Hz, 2H), 3.64 (t, $J = 4.7$ Hz, 4H), 3.40 (s, 2H), 2.51 (t, $J = 4.7$ Hz, 4H), 1.26 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$, δ ppm) 165.5, 131.2, 129.6, 129.1, 127.2, 87.0, 84.6, 66.5, 60.7, 52.1, 47.7, 14.0.

Methyl 4-(3-diethylaminooct-1-ynyl)benzoate (entry 13): ^{1}H NMR (200 MHz, $CDCl_3$, δ ppm) 7.94 (d, $J = 8.0$ Hz, 2H), 7.44 (d, $J = 8.0$ Hz, 2H), 3.88 (s, 3H), 3.67 (t, $J = 7.3$ Hz, 1H), 2.80 to 2.35 (m, 4H), 1.70 to 1.30 (m, 8H), 1.08 (t, $J = 7.2$ Hz, 6H), 0.89 (t, $J = 7.0$ Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$, δ ppm) 166.4, 131.5, 129.3, 129.0, 128.4, 92.7, 84.0, 53.7, 52.0, 44.9, 34.0, 31.5, 26.4, 22.5, 13.9, 13.7.

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