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Lewis acid promoted alkynylation of imines with terminal alkynes: simple, mild and efficient preparation of propargylic amines

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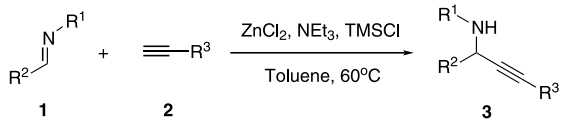
Abstract—A mild and efficient addition of terminal alkynes to imines in the presence of $ZnCl_2$, Et_3N and TMSCl gives propargylamines in good yields.

Addition of carbanions to imines and imine derivatives has attracted the attention of organic chemists and is still a very active field of investigation. Propargyl amines are not only synthetically important intermediates for preparation of various nitrogen compounds such as (*E*)-allylamines, pyrroles, β-lactams, and pyrrolidines,[1] but also biologically important.[2] Recently, great efforts have been made on developing methodology for generating propargyl amines. These reactions include amination of propargylic halide[3] and allenyl halide,[4] propargyl phosphates[5] and propargyl triflate,[6] and $TiCl_4$ mediated amination of propargyl ester.[7] On the other hand, direct nucleophilic 1,2-addition of alkyne to an imine double bond via activation of C–H bond in terminal alkynes is a valuable method for the synthesis of propargylamines. For generation of propargyl amines, a Grignard-type direct addition of alkynes to imines catalyzed by iridium or Cu–Ru was reported, respectively, by Carreira[8] and Li.[9] Herein, we wish to report that the direct addition of terminal alkynes to imines using trimethylsilyl chloride as activator in the presence of $ZnCl_2/Et_3N$.



Scheme 1.

We have been interested in the developing of practical C–C bond formation reaction by combination of zinc salt and tertiary amine onto a mixture of a terminal alkyne and a carbonyl group.[10] Initially, we examined the addition reaction of phenyl acetylene with *N*-benzyl imine derived from benzaldehyde. Treatment of 1 equiv. each of phenyl acetylene, $ZnCl_2$, Et_3N and the imine at room temperature or elevated temperature did not lead to the desired addition reaction due to the poor electrophilicity of the azomethine carbon. To increase the scope of organometallic addition to imines, several methods have been explored, for example, activation of the C=N bond either by *N*-substitution with an electron-withdrawing group or by *N*-coordination to a Lewis acid. Lewis acids, such as TMSOTf, BF_3–Et_2O have been reported for activation of imine in the addition reaction of Grignard reagent to imine.[11] It was found that after addition of an activator, namely chlorotrimethylsilane, the reaction was dramatically improved. The addition of a terminal alkyne to a imine could be proceeding smoothly to give desired propargylamines in high yields when 1.5 equiv. of chlorotrimethylsilane was added to the reaction mixture (Scheme 1).

A variety of substrates were examined in the reaction. The results were summarized in Table 1. All reactions could be carried out in high yields for imines either derived from alkyl or aryl aldehydes. The aromatic imines with electron-withdrawing groups are more reactive compared to those with electron-donating groups. It is worthy to note that alkyl imines could react under such condition and gave high yield of propargyl amines (up to 93% yield). Phenyl acetylene is more reactive than alkyl acetylenes.

Keywords: alkynylation; imine; propargylic amine; Lewis acid.
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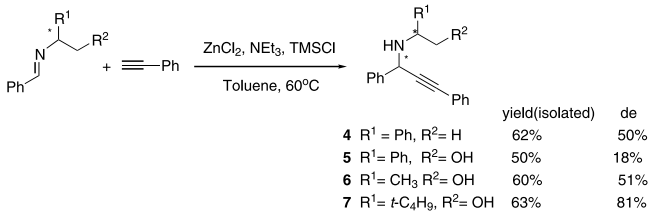

Scheme 2.

Table 1. Alkynylation of the imines promoted with $ZnCl_2$ and TMSCl[a]

Entry	R^1	R^2	R^3	Yield (%)[b]
1	Bn	Ph	Ph	81
2	Bn	*p*-CNC_6H_4	Ph	84
3	Bn	*p*-$MeOC_6H_4$	Ph	62
4	Bn	*c*-Hexyl	Ph	91
5	Bn	*i*-Propyl	Ph	93
6	Bn	*i*-Propyl	*c*-Propyl	78
7	Bn	*i*-Propyl	*n*-Butyl	60

[a] Typical procedure in detail see Ref. 13.
[b] Isolated yields.

Diastereoselective addition of organometallic reagents to the C=N bond of chiral imines and their derivatives has been the subject of considerable interest because they might provide synthetically useful methodology for the preparation of pharmaceutically important enantiopure amines.[12] With the above results in hand, our attention was turned to the asymmetric synthesis of a propargyl amine using a chiral imine as substrate. The imine, derived from (*R*)-α-methyl-benzylamine and benzylaldehyde, was allowedto react with phenyl acetylene to give propargyl amine **4** in 62% yield with 50% de (determined by 300 MHz ^1H NMR of the crude reaction mixture). When the amine was changed to the β-hydroxy amine, namely (*S*)-*t*-butyl amino ethanol, the diastereoselectivity was increased to 81%, while methyl amino-alcohol and (*R*)-phenyl glycinol only gave 51 and 18% de, respectively (Scheme 2).

In conclusion, we have described a simple and efficient addition of terminal alkynes to imines in the presence of $ZnCl_2$, Et_3N and TMSCl, which gives propargyl amines in high yields. The present entry to propargyl amines has the advantage of mild reaction conditions and readily available reagents.

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13. A representative procedure: Under argon atmosphere, anhydrous $ZnCl_2$ (164 mg, 1.2 mmol) was added to a flame dried bottle, then Et_3N (168 μl, 1.2 mmol) was added. The mixture was stirred in toluene at 30°C for 0.5 h, phenylacetylene (164 μl, 1.2 mmol) was added. After stirring for 1 h at 30°C, imine derived from isobutyraldehyde and NH_2Bn (201 mg, 1.0 mmol, freshly distilled at 82–84°C/3 mmHg) and TMSCl (189 μl, 1.5 mmol, freshly distilled from CaH_2) was added. Then the mixture was stirred in toluene at 60°C for 5 h and cooled to room temperature. Then NH_4Cl (satd aqueous) was added. The mixture was extracted with EtOAc (5 mL×3). After working up as usual, the crude product was purified by chromatography on silica gel (hexane:EtOAc=40:1) to give the adduct proparglic amine (281 mg, 93%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.57–7.30 (m, 10H), 4.19 (d, J=12.9 Hz, 1H), 3.97 (d, J=12.6 Hz, 1H), 3.48 (d, J=5.5 Hz, 1H), 2.09–1.98 (m, 1H), 1.59 (s, br, 1H), 1.17 (d, J=1.8 Hz, 3H), 1.15 (d, J=1.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.5, 132.0, 128.7, 128.6, 128.5, 128.2 123.9, 90.1, 84.9, 56.5, 52.1, 33.3, 20.1, 18.4; MS (EI) m/e 264 (M+1, 4), 220 (90), 91 (100); HREIMS calcd for $C_{19}H_{21}N$ 263.1628, found 263.1673.