Pergamon

Tetrahedron Letters 43 (2002) 5731–5733

TETRAHEDRON LETTERS

# Cu(I)Br mediated coupling of alkynes with *N*-acylimine and *N*-acyliminium ions in water

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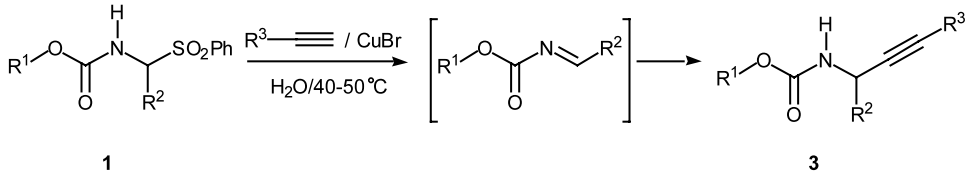
Received 12 May 2002; revised 20 June 2002; accepted 21 June 2002

**Abstract**—A coupling of alkynes with *N*-acylimines and *N*-acyliminium ions mediated by Cu(I) was developed in water to generate propargyl amide derivatives. 

The addition reaction of nucleophilic reagents to the C=N bond of imines and their derivatives has attracted considerable attention of organic chemists.[1] Such reactions can provide useful methodology for the preparation of amine compounds, which are used in organic synthesis as important intermediates. For example, the propargyl amine derivatives have been synthesized by the addition of an appropriate organometallic reagent to imine compounds.[2] Recently, we reported the copper-mediated reaction of terminal alkynes to aryl aldimines in water to produce propargyl amine derivatives, catalyzed by a co-catalyst system of Cu/Ru via alkyne C–H activation.[3] By using Cu(I)pybox as a catalyst, a highly enantioselective imine–alkyne addition was developed.[4] Unfortunately, the reactions were limited to aryl aldimines. The ineffectiveness of the aliphatic aldimines under such conditions was attributed to their low stability towards water and their low reactivity towards carbon nucleophiles. One possible approach to overcome such an obstacle is to use *N*-acylimines and *N*-acyliminium ion: the reactivity of the C=N bond in these compounds is greatly enhanced and their stability towards water is increased. In addition, *N*-acylimines or *N*-acyliminium ions can be generated conveniently in situ from amines containing a good leaving group at α position, for example, α-phenylsulfonyl *N*-acyl amine **1** and α-methoxy *N*-(alkoxycarbonyl)pyrrolidine **2**, and the products can be modified easily for various synthetic purposes.[5] Compound **1** can be prepared conveniently by the reaction of carbamate derivatives with aldehydes and sodium phenylsulfinate in the presence of formic acid.[6] Subsequent elimination of sulfinic acid under very mild conditions will generate an acylimine, which has been reacted with various nucleophiles, such as ketone enolates,[7] thiazolium-stabilized acyl anions,[8] nitromethane anion,[9] organozinc,[10] organomagnium[11] and organolithium[11] reagents under anhydrous conditions. Compound **2** and its analogues can be prepared by electrochemical or organic synthetic method.[12] The nucleophilic addition reactions to the acyliminium ions, derived from **2** and its analogues, provide an easy and promising method for the preparation of some useful intermediates in the synthesis of a variety of alkaloids and medicines.[13]

Herein we wish to report an efficient copper-mediated coupling of alkynes with *N*-acylimines and *N*-acyliminium ions, generated in situ from α-phenylsulfonyl *N*-acyl amine **1** and α-methoxy *N*-(alkoxycarbonyl)pyrrolidine **2**, in water.




**1** **3**

**Scheme 1.**

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0040-4039/02/$ - see front matter 
PII: S0040-4039(02)01197-8

An initial attempt to effect the coupling of **1** with phenylacetylene in water showed that when copper(I) bromide (10–30 mol%) was used as a catalyst, it triggered the addition reaction of phenylacetylene to **1** in water, but the yield of the desired addition product **3** was quite low (Scheme 1). It was found that compound **3** could be obtained in good yield when an excess amount of CuBr (2–3 equiv.) was employed to ensure the complete consumption of the starting material. Subsequently, various *N*-acyl amine derivatives were coupled with phenylacetylene under similar reaction conditions (Table 1).

The reaction was found to be highly sensitive to the carbamate structural portion of starting material **1** (entries 1–5). The α-phenylsulfonylamine with *n*-BOC and CBz groups can react smoothly to afford the desired coupling products in good yields. However, only low yields of propargylamides were obtained when using α-phenylsulfonylamine with *t*-BOC and an ethoxycarbonyl group; no addition product was isolated from the reaction of α-phenylsulfonylamine bearing a methoxycarbonyl group. The electronic nature of the $R_2$ of compound **1** also has a marked effect on the reaction. The α-phenylsulfonylamines derived from aromatic aldehydes provided higher yields than those derived from aliphatic aldehydes, and both strong electron-withdrawing and electron-donating groups on the aromatic rings led to decreased yield of the coupling product, possibly due to the hydrolysis of the acylimines.

**Table 1.** The addition of phenylacetylene phenylsulfonyl *N*-acylimine in water

| Entry | Sulfone (**1**) | | Alkyne | Product (**3**), yields (%)[a] |
|---|---|---|---|---|
| | $R^1$ | $R^2$ | $R^3$ | |
| 1 | *n*-Bu | Ph | Ph | **3a**, 72 |
| 2 | $PhCH_2$ | Ph | Ph | **3b**, 46 |
| 3 | *t*-Bu | Ph | Ph | **3c**, 15 |
| 4 | Et | Ph | Ph | **3d**, 20 |
| 5 | Me | Ph | Ph | 0 |
| 6 | *n*-Bu | 4-$MeC_6H_4^-$ | Ph | **3e**, 70 |
| 7 | *n*-Bu | 4-$EtC_6H_4^-$ | Ph | **3f**, 68 |
| 8 | *n*-Bu | 4-t-$BuC_6H_4^-$ | Ph | **3g**, 69 |
| 9 | *n*-Bu | 3-$MeC_6H_4^-$ | Ph | **3h**, 79 |
| 10 | *n*-Bu | 4-$PhC_6H_4^-$ | Ph | **3i**, 54 |
| 11 | *n*-Bu | 4-$ClC_6H_4^-$ | Ph | **3j**, 45 |
| 12 | *n*-Bu | 4-$BrC_6H_4^-$ | Ph | **3k**, 63 |
| 13 | *n*-Bu | 4-$MeOC_6H_4^-$ | Ph | **3l**, 10 |
| 14 | *n*-Bu | 4-$NO_2C_6H_4^-$ | Ph | 0 |
| 15 | *n*-Bu | 1-Naphth- | Ph | **3m**, 71 |
| 16 | *n*-Bu | 2-Naphth- | Ph | **3n**, 65 |
| 17 | *n*-Bu | *n*-$C_5H_{11}^-$ | Ph | **3o**, 25 |
| 18 | *n*-Bu | *n*-$C_5H_{11}^-$ | *p*-$BrC_6H_4$ | **3p**, 28 |

[a] All reactions were carried out under sonication in water. Isolated yields were reported.

Under similar reaction conditions, the coupling between α-methoxy *N*-(alkoxycarbonyl)pyrrolidine **2** and phenylacetylene in the presence of an excess amount of Cu(I)Br afforded the desired propargyl amide derivatives **4** through the *N*-acyliminium ion intermediate (Scheme 2).

In conclusion, a copper-mediated coupling of alkynes with α-phenylsulfonyl *N*-acyl amines and α-methoxy *N*-(alkoxycarbonyl)pyrrolidines in water was developed to generate propargyl amide derivatives. The scope and synthetic applications of this reaction are under investigation.

General procedure of the reaction is as follows: The mixture of α-phenylsulfonyl *N*-alkoxycarbonyl amine **1** or α-methoxy *N*-(alkoxycarbonyl)pyrrolidine **2** (1 mmol) and copper(I) bromide (2–3 mmol) was suspended in 2 mL water, then phenylacetylene (2–3 mmol) was added. The mixture was placed in a sonicator (100w, Bransonic) and sonicated overnight. After cooling to room temperature, the mixture was extracted with ethyl ether (3×10 mL) and the combined organic extract was dried over $MgSO_4$. After removal of the solvent, the residue was purified by flash chromatography with silica gel to give propargyl amide derivatives **3** and **4** (all isolated products showed satisfactory analytic characterization data).[14]

## Acknowledgements

We are grateful to NSF (CAREER Award) and NSF-EPA Joint Program for a Sustainable Environment for partial support of our research.

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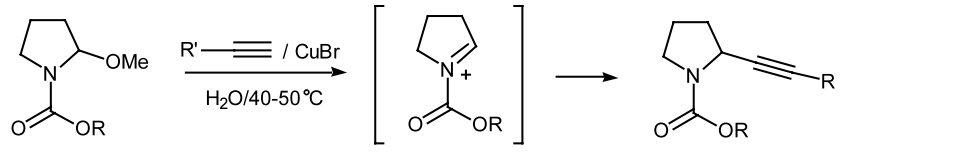


**2**

**4a**, R=Me, R'=Ph, 58%
**4b**, R=$PhCH_2$, R'=Ph, 77%
**4c**, R=Me, R'=*p*-$BrC_6H_4$-, 81%

**Scheme 2.**

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14. ***n*-Butyl 1,3-diphenylprop-2-ynyl carbamate (3a)**. IR (film): 3303, 2949, 2234, 1696, 1524, 1238 $cm^{-1}$. $^1H$ NMR ($CDCl_3$/TMS, 400 MHz): 7.58 (d, $J=7.2$ Hz, 2H, Ar-H), 7.29–7.48 (m, 8H, Ar-H), 5.94 (d, $J=8.0$ Hz, 1H, NH), 5.24 (d, $J=6.4$ Hz, 1H, PhCH), 4.13 (m, 2H, $OCH_2$), 1.62 (m, 2H, $CH_2$), 1.39 (m, 2H, $CH_2$), 0.93 (t, $J=7.4$ Hz, 3H, $CH_3$). $^{13}C$ NMR ($CDCl_3$/TMS, 100 MHz): 156.10 (-$NHCO_2^-$), 139.50, 136.86, 133.89, 132.04, 129.70, 128.99, 128.80, 128.56, 128.40, 127.82, 127.25, 122.74 (Ar-C), 87.43, 85.22 (alkyne), 65.56 (CH), 47.52, 31.26, 19.32, 14.02 (O-*n*-$C_4H_9$). EIMS ($m/z$): 307 ($M^+$), 250, 206, 191, 77. HRMS $m/z$ for $C_{20}H_{21}NO_2$ Calcd: 307.1572; Found: 307.1565.

**2-Phenylethynyl-*N*-methoxycarbonylpyrrolidine (4a)**. IR (film): 2949, 1702, 1450, 1383 $cm^{-1}$. $^1H$ NMR ($CDCl_3$/TMS, 400 MHz): 7.40 (m, 2H, Ar-H), 7.28 (m, 3H, Ar-H), 4.81, 4.71 (s, 1H, NCH), 3.76, 3.74 (s, 3H, $OCH_3$), 3.56 (m, 1H, $CH_2$), 3.39 (m, 1H, $CH_2$), 2.14 (m, 3H, $CH_2$), 1.96 (m, 1H, $CH_2$). $^{13}C$ NMR ($CDCl_3$/TMS, 100 MHz): 155.47 (-$NHCO_2^-$), 132.01, 131.88, 128.34, 123.19 (Ar-C), 89.42, 82.24 (alkyne), 52.69 ($OCH_3$), 49.33, 48.87, 46.32, 45.95, 34.26, 33.47, 24.29, 23.89. EIMS $m/z$: 229 ($M^+$), 214 (100%), 170, 115. HRMS $m/z$ for $C_{14}H_{15}NO_2$ Calcd: 229.1103; Found: 229.1094.