# A Highly Chemo- and Regioselective *N*-Acylative Alkynylation of Quinolines with Alkynylsilanes Promoted by Triflate Ion

Ryohei Yamaguchi,* Yoshikazu Omoto, Masahiro Miyake, and Ken-ichi Fujita
*Faculty of Integrated Human Studies and Graduate School of Human and Environmental Studies*
*Kyoto University, Yoshida, Kyoto 606-8501*

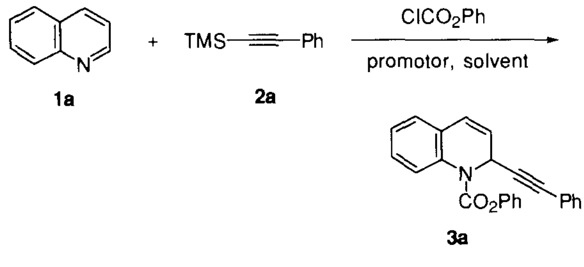
(Received March 11, 1998; CL-980178)

Reactions of quinolines activated by phenyl chloroformate and silver triflate with 1-alkynylsilanes proceed smoothly at 83 °C to afford 1-alkynyl-1,2-dihydroquinolines in highly chemo- and regioselective manners.

---

Introduction of functional carbon substituents into nitrogen heterocycles has been one of the most important issues for synthesizing physiologically active nitrogen heterocycles including alkaloids. Recently, Dynemicin A has attracted a considerable attention due to a potent anti tumor activity and its unique structure of the enediyne system.[1] In almost all of synthesis of Dynemicin A and its analogs, reactions of quinoline activated by acyl chloride with alkynyl Grignard reagents have been utilized to introduce alkynyl groups to quinoline systems as a key-step.[1,2,3] Meanwhile, we have also developed the reactions of *N*-acylpyridinium chloride with alkynyltin reagents,[4,5] because it has been shown that Grignard reagents suffer from less chemoselectivity. We have recently disclosed that *N*-acylquinolinium ion is so activated by exchange of chloride ion to triflate ion to readily react with allylsilanes.[6,7] We wish to report here that the highly activated *N*-acylquinolinium ions react with alkynylsilanes in chemo- and regioselective manners to provide an alternative method for introduction of alkynyl groups to quinoline systems.[8]

When quinoline (**1a**) activated by phenyl chloroformate and silver triflate was allowed to react with phenylethynyltrimethylsilane (**2a**) at rt, no reaction was observed.[9] We have found, however, that the reaction heated at 83 °C in $ClCH_2CH_2Cl$ proceeded smoothly to give 2-(2-phenylethynyl)-1-phenoxycarbonyl-1,2-dihydroquinoline (**3a**) in 91% isolated yield (Scheme 1). Thus, we examined other promoters and solvents and the results are summarized in Table 1.



**Scheme 1.**

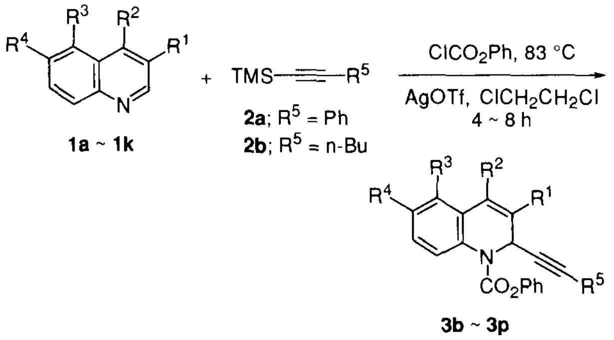
As shown in Table 1, the highest yield was obtained with silver triflate. The yields were moderate with trimethylsilyl triflate and silver tetrafluoroborate. Among the solvents used, 1,2-dichloroethane is the solvent of choice, while the good yields were obtained in chloroform and acetonitrile. Thus, silver triflate as the promoter and 1,2-dichloroethane as the solvent were used in the following reactions.[10]

**Table 1.** Reactions of **1a** activated by phenyl chloroformate and promoter with **2a** to give **3a**

| entry | promoter | solvent | temp / °C [a] | time / h | yield / % [b] |
|---|---|---|---|---|---|
| 1 | AgOTf | $ClCH_2CH_2Cl$ | rt | 24 | 0 |
| 2 | AgOTf | $ClCH_2CH_2Cl$ | 83 | 4 | 91 |
| 3 | $AgBF_4$ | $ClCH_2CH_2Cl$ | 83 | 24 | 56 |
| 4 | TMSOTf | $ClCH_2CH_2Cl$ | 83 | 10 | 59 |
| 5 | NaOTf | $ClCH_2CH_2Cl$ | 83 | 24 | 36 |
| 6 | AgOTf | $CHCl_3$ | 55 | 5 | 80 |
| 7 | AgOTf | $CH_3CN$ | 83 | 5 | 79 |

[a] Bath temperature. [b] Isolated yield.

We next examined reactions of other quinolines having a variety of functional groups with **2a** as well as 1-hexynyltrimethylsilane (Scheme 2). The results are summarized in Table 2.



**Scheme 2.**

**Table 2.** Reactions of substituted quinolines activated by phenyl chloroformate and AgOTf with 1-alkynylsilanes

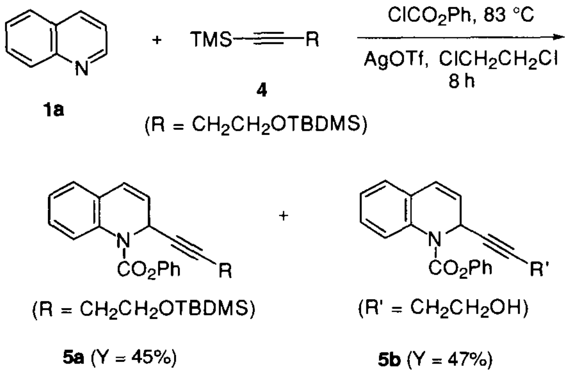
| entry | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ | product | yield / % [a] |
|---|---|---|---|---|---|---|---|
| 1 | CN | H | H | H | Ph | **3b** | 97 |
| 2 | Me | H | H | H | Ph | **3c** | 96 |
| 3 | $CO_2Me$ | H | H | H | Ph | **3d** | 84 |
| 4 | H | CHO | H | H | Ph | **3e** | 85 |
| 5 | H | H | $NO_2$ | H | Ph | **3f** | 90[b] |
| 6 | H | H | H | OMe | Ph | **3g** | 75 |
| 7 | H | H | H | $NO_2$ | Ph | **3h** | 90 |
| 8 | H | H | H | H | n-Bu | **3i** | 85 |
| 9 | Br | H | H | H | n-Bu | **3j** | 83 |
| 10 | CN | H | H | H | n-Bu | **3k** | 90 |
| 11 | Me | H | H | H | n-Bu | **3l** | 80 |
| 12 | $CO_2Me$ | H | H | H | n-Bu | **3m** | 93 |
| 13 | H | CHO | H | H | n-Bu | **3n** | 91 |
| 14 | H | H | $NO_2$ | H | n-Bu | **3o** | 90[b] |
| 15 | H | H | H | $NO_2$ | n-Bu | **3p** | 92 |

[a] Isolated yield. [b] The reaction was conducted at 60 °C.

As shown in Table 2, a variety of functional groups can be tolerated to afford the 1,2-adducts in good to excellent yields. While electron-withdrawing groups such as cyano and nitro groups are favorable for the reactions, an electron-donating group such as methoxy group is not.

A typical experimental procedure is as follows: To a solution of **1a** (129 mg, 1.0 mmol) in dry $ClCH_2CH_2Cl$ (5 mL) was added $ClCO_2Ph$ (188 mg, 1.2 mmol) under ice-cooling and the mixture was stirred for 1 h. Then, to the mixture were added **2a** (349 mg, 2.0 mmol) and AgOTf (308 mg, 1.2 mmol), and the reaction mixture was stirred at 83 °C for 4 h. Usual work-up followed by column chromatography on silica gel gave **3a** (320 mg, 91%): mp 159 - 161 °C; IR 1722 $cm^{-1}$; $^{1}H$ NMR ($CDCl_3$) $\delta$ 7.78 (1H, br s), 7.14 - 7.41 (m, 13H), 6.63 (1H, d, $J$ = 9.1 Hz), 6.22 (1H, d, $J$ = 6.7 Hz), 6.17 (1H, dd, $J$ = 9.2 and 6.7 Hz); $^{13}C$ NMR ($CDCl_3$) $\delta$ 152.3 (C), 151.0 (C), 133.9 (C), 131.8 (CH), 129.4 (CH), 128.4 (CH), 128.1 (CH), 128.0 (CH), 126.8 (C), 126.7 (CH), 126.0 (CH) 125.8 (CH), 125.0 (CH), 124.4 (CH), 122.4 (C), 121.7 (CH), 85.1 (C), 83.8 (C), 45.4 (CH). Anal. Found: C, 82.25; H, 5.11%. Calcd for $C_{24}H_{17}NO_2$: C, 82.03; H, 4.88%.

We next examined the reaction with an alkynylsilane having hydroxy functionality. The reaction of **1a** activated by phenyl chloroformate and silver triflate with 4-*tert*-butyldimethylsiloxy-1-butynyltrimethylsilane (**4**) was conducted in a similar manner to the above to afford the 1,2-adduct **5a** and its desilylated derivative **5b** in 45% and 47% yields, respectively.



**Scheme 3.**

In summary, we have developed a highly chemo- and regioselective reaction for introducing alkynyl groups into a variety of quinolines. The present reaction may provide an alternative effective method for synthesis of Dynemicin A and its analogs.

This work was supported by Grant-in-Aid for Scientific Research from the Ministry of Education, Science, and Culture (No. 08455415). We also thank to Professor Sinpei Kozima (Fukui University) for valuable discussions.

## References and Notes

1 A. G. Myers, N. J. Tom, M. E. Fraley, S. B. Cohen, and D. J. Mader, *J. Am. Chem. Soc.*, **119**, 6072 (1997) and references cited therein.

2 a) T. Okita and M. Isobe, *Tetrahedron*, **51**, 3737 (1995) and references cited therein. b) T. Takahashi, Y. Sakamoto, H. Yamada, S. Usui, and Y. Fukazawa, *Angew. Chem., Int. Ed. Engl.*, **34**, 1345 (1995). c) H. Mastalerz, T. W. Doyle, J. F. Kadow, and M. V. Dolatrai, *Tetrahedron Lett.*, **37**, 8687 (1996).

3 R. Yamaguchi, Y. Nakazono, and M. Kawanisi, *Tetrahedron Lett.*, **24**, 1801 (1983). R. Yamaguchi, Y. Nakazono, T. Matsuki, E. Hata, and M. Kawanisi. *Bull. Chem. Soc. Jpn.*, **60**, 215 (1987). R. Yamaguchi, E. Hata, T. Matsuki, and M. Kawanisi, *J. Org. Chem.*, **52**, 2094 (1987).

4 R. Yamaguchi, E. Hata, and K. Utimoto, *Tetrahedron Lett.*, **29**, 1785 (1988).

5 T. Nishikawa, M. Yoshikai, K. Obi, T. Kawai, R. Unno, T. Jomori, and M. Isobe, *Tetrahedron*, *51*, 9339 (1995).

6 R. Yamaguchi, B. Hatano, T. Nakayasu, and S. Kozima, *Tetrahedron Lett.*, **38**, 403 (1997).

7 For general reviews on *N*-acyliminium ions, see W. N. Speckamp and H. Hiemstra, *Tetrahedron*, **41**, 4367 (1985). H. Hiemstra and W. N. Speckamp, in "Comprehensive Organic Synthesis," ed by B. M. Trost and I. Fleming, Pergamon Press (1991), Vol. 2, p. 1047.

8 For reactions of *N*-acyliminium ions with alkynylsilanes, see T. Nishikawa, M. Isobe, and T. Goto, *SYNLETT*, **1991**, 99.

9 It has been supported that an alkynylsilane is $10^8$ less reactive than an alkynylstannane: C. Dallaire and M. A. Brook, *Organometallics*, **12**, 2332 (1993). However, a more recent report suggests that the former is only $2.1 \times 10^2$ less reactive than the latter: I. Egle, V. Gabelica, A. J. Kresge, and T. T. Tidwell, *Can. J. Chem.*, **74**, 1366 (1996).

10 An use of a smaller amount (0.3 eq) of AgOTf lowered the yield to 45%.