# Spontaneous Addition of Active Methine Compounds to Enol Ethers and α,β-Unsaturated Ketones in Aprotic Polar Solvent

Tsutomu Yokozawa,* Motoi Oishi, and Yasukazu Tanaka

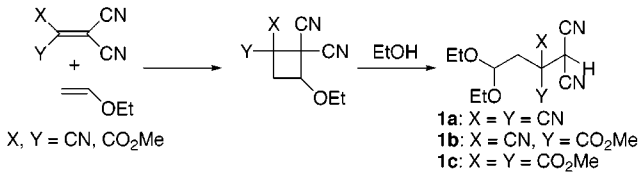
*Department of Applied Chemistry, Kanagawa University, Rokkakubashi, Kanagawa-ku, Yokohama 221-8686, Japan*

*Received November 30, 1999*

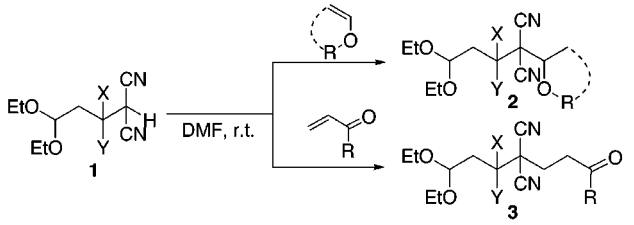
## Introduction

Active methylene and methine compounds having the electron-withdrawing groups at the α positions are easily converted to carbanions with a weak base and have been widely used for many kinds of carbon−carbon bond forming reactions. However, there are few examples of the effect of the electron-withdrawing groups at the *β* positions on the reaction of active methylene and methine compounds having the electron-withdrawing groups at the α and *β* positions, although the effect of substituents at any position on the acidity of organic compounds is well-documented.[1] We have studied the ring-opening polymerization of the cyclobutane adducts of a variety of tetrasubstituted-acceptor olefins and vinyl ethers.[2] The cyclobutanes easily undergo the ring-opening reaction with alcohols to give dicyanomethine compounds **1** having the cyano and/or methoxycarbonyl groups adjacent to the dicyanomethine group (Scheme 1).[3] We have recently reported the tandem dimerization and double annulation of 3,3,4,4-tetracyanobutanal acetal (**1a**).[4] This unusual reaction is caused by the strong acidity of the dicyanomethine group enhanced by the dicyano groups at the *β* positions. In this paper, we study the reaction of **1**, having the dicyano groups at the α positions and the different electron-withdrawing groups at the *β* positions, with donor olefins and acceptor olefins, respectively, in which **1** containing the strong electron-withdrawing groups at the *β* positions add to enol ethers and α,*β*-unsaturated ketones without any catalysts in *N*,*N*-dimethylformamide (DMF), and it reveals that the electron-withdrawing groups at the *β* positions of the active methine group affect these reactions (Scheme 2). From our survey of the existing literature, no study has been reported on the addition of active methylene and methine compounds to enol ethers to form carbon−carbon bonds. The chemistry

**Scheme 1**




**Scheme 2**




of 1,1,2,2-tetracyanoethane has been extensively studied by Nasakin and his colleague,[5] and the Michael reactions of 1,1,2,2-tetracyanoethane without catalysts have been reported.[6] The reaction of other highly acidic ethanes, however, has yet to be studied and even their synthesis has not been reported either.

## Results and Discussions

The reaction of **1** with a variety of enol ethers was carried out in DMF at ambient temperature (Table 1). *β*,*β*-Dicyano-substituted **1a** and *β*-cyano-*β*-methoxycarbonyl-substituted **1b** resulted in Markownikoff adducts **2**, whereas *β*,*β*-bis(methoxycarbonyl)-substituted **1c** did not react with ethyl vinyl ether. To the best of our knowledge, this is the first example of the addition of carbon acids to enol ethers. In the reaction of **1a** with enol ethers, bicyclic 2-aminopyridine derivative **4**, which has been reported in our previous paper,[4] was produced as a byproduct. On the other hand, the reaction of **1b** with enol ethers did not afford byproducts such as **4**, although it took longer time than the reaction of **1a**. The reactivity of **1** would be attributed to the different acidity of **1** caused by the electron-withdrawing groups at the *β* positions of the methine group. Regarding enol ethers,

(1) For examples, see: (a) Simon, W. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 661. (b) Fisher, H.; Rewicki, D. *Prog. Org. Chem.* **1968**, *7*, 116. (c) Streitwieser, A., Jr.; Chang, C. J.; Hollyhead, W. B. *J. Am. Chem. Soc.* **1972**, *94*, 5292. (d) Brückner, R.; Huisgen, R. *Tetrahedron Lett.* **1990**, *31*, 2561.

(2) (a) Yokozawa, T.; Miyamoto, Y.; Futamura, S. *Makromol. Chem., Rapid Commun.* **1993**, *14*, 245. (b) Yokozawa, T.; Fujino, T. *Ibid.* **1993**, *14*, 779. (c) Yokozawa, T.; Fukata, H. *J. Polym. Sci. Polym. Chem. Ed.* **1995**, *33*, 1203. (d) Yokozawa, T.; Mori, T.; Hida, K. *Macromol. Chem. Phys.* **1996**, *197*, 2261. (e) Yokozawa, T.; Tsuruta, E. *Macromolecules* **1996**, *29*, 8053. (f) Yokozawa, T.; Wakabayashi, Y.; Kimura, T. *J. Polym. Sci. Polym. Chem. Ed.* **1997**, *35*, 1563. (g) Yokozawa, T.; Fujino, T.; Morita, I.; Toyoizumi, T. *Macromol. Chem. Phys.* **1998**, *199*, 997.

(3) (a) Karle, I.; Flippen, J.; Huisgen, R.; Schug, R. *J. Am. Chem. Soc.* **1975**, *97*, 5285. (b) Huisgen, R. *Acc. Chem. Res.* **1977**, *10*, 117. (c) *Idem., Ibid.* **1977**, *10*, 199.

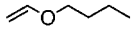
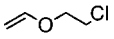
(4) Yokozawa, T.; Nishikata, A.; Kimura, T.; Shimizu, K.; Takehana, T. *Tetrahedron Lett.* **1999**, *40*, 4707.

(5) For a review, see: Zolotoi, A. B.; Zil'berg, S. P.; Lukin, P. M.; Konovalikhin, S. V.; Nasakin, O. E.; Atovmyan, L. O. *Probl. Kristallokhim.* **1989**, 85 (*Chem. Abstr.* **1990**, *113*, 96708).

(6) (a) Nasakin, O. E.; Lukin, P. M.; Terent'ev, P. B.; Bulai, A. Kh.; Sheludyakov, V. D.; Zolotoi, A. B.; Gusev, A. I.; D'yachenko, O. A.; Apal'kova, G. M. Atovmyan, L. O. *Khim. Geterotsikl. Soedin.* **1984**, 1431 (*Chem. Abstr.* **1985**, *102*, 24426). (b) Nasakin, O. E.; Lukin, P. M.; Terent'ev, P. B.; Bulai, A. Kh.; Khaskin, B. A.; Zakharov, V. Ya. *Zh. Org. Khim.* **1985**, *21*, 662 (*Chem. Abstr.* **1985**, *103*, 104528). (c) Nasakin, O. E.; Lukin, P. M.; Zil'berg, S. P.; Terent'ev, P. B.; Bulai, A. Kh.; D'yachenko, O. A.; Zolotoi, A. B.; Konovalikhin, S. V.; Gusev, A. I. *Zh. Org. Khim.* **1988**, *24*, 1007 (*Chem. Abstr.* **1989**, *110*, 38289). (d) Nasakin, O. E.; Lukin, P. M.; Zil'berg, S. P.; Terent'ev, P. B.; Bulai, A. Kh.; D'yachenko, O. A.; Zolotoi, A. B.; Konovalikhin, S. V.; Atovmyan, L. O. *Zh. Org. Khim.* **1988**, *24*, 997 (*Chem. Abstr.* **1989**, *110*, 75241). (e) Zil'berg, S. P.; Nasakin, O. E.; Lukin, P. M.; Turkhanov, V. L.; D'yachenko, O. A.; Zolotoi, A. B.; Konovalikhin, S. V.; Terent'ev, P. B.; Bulai, A. Kh. *Zh. Org. Khim.* **1988**, *24*, 1014 (*Chem. Abstr.* **1989**, *110*, 94262). (f) Zolotoi, A. B.; Zil'berg, S. P.; Lukin, P. M.; Konovalikhin, S. V.; Nasakin, O. E.; Lyshchikov, A. N.; D'yachenko, O. A.; Bulai, A. Kh.; Atovmyan, L. O.; Skvortsova, M. Yu. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1988**, 2561 (*Chem. Abstr.* **1989**, *111*, 23105). (g) Zolotoi, A. B.; Konovalikhin, S. V.; Lukin, P. M.; D'yachenko, O. A.; Zil'berg, S. P.; Nasakin, O. E. *Khim. Geterotsikl. Soedin.* **1988**, 1404 (*Chem. Abstr.* **1989**, *111*, 115085).

10.1021/jo991837j CCC: $19.00 
Published on Web 03/02/2000

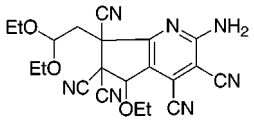
**Table 1. Reaction of 1 with Enol Ethers**[a]

| enol ether | 1 | time, h | yield, %[b] |
|---|---|---|---|
|  | **1a** | 2 | 63 |
| | **1b** | 84 | 50 |
| | **1c** | 672 | 0 |
|  | **1a** | 2 | 68 |
| | **1b** | 24 | 59 |
|  | **1a** | 2 | 28 |
| | **1b** | 29 | 42 |
|  | **1a** | 48 | 46 |
| | **1b** | 672 | 55 |
|  | **1a** | 41 | 36 |
| | **1b** | 672 | 54 |

[a] Reaction was run in DMF ([**1**]$_0$ = 1 M, [enol ether]$_0$ = 1.2 M) at room temperature. [b] Isolated by preparative HPLC.

acyclic and cyclic ones reacted with **1a** and **1b**. The yields of **2** were affected by the alkyl groups of enol ethers and decreased in the order of *n*-Bu > Et > $CH_2CH_2Cl$, which agreed with the order of electron-donating ability of the alkyl groups.

The reaction of **1a** with other donor olefins was also attempted. *N*-Vinylcarbazole (NVCZ), which is a stronger donor olefin than enol ethers, reacted with **1a** to afford not **2** but homopolymer of NVCZ. It implied that NVCZ reacted faster than the carbanion of **1a** with the carbocation of NVCZ generated by the transfer of proton of **1a** to NVCZ. In addition, the production of NVCZ polymer also implied that the reaction intermediate of **1** in the addition of **1** to enol ethers may be close to free ions. If an ion pair was the reaction intermediate, **1** should undergo similar addition to NVCZ to yield **2**. Weaker donor olefins such as *p*-methoxystyrene, ethyl vinyl sulfide, and phenyl vinyl sulfide did not react with **1a** in DMF at room temperature.



**4**

The reaction of **1** with a variety of α,*β*-unsaturated ketones was also carried out in DMF at ambient temperature (Table 2). All **1** yielded Michael adducts **3**, and the reaction became slow in the order of **1a** > **1b** > **1c** in a similar manner of the reaction of **1** with enol ethers. In *N*,*N*-dimethylacetamide, **3** was similarly obtained, but in other solvents such as acetonitrile and tetrahydrofuran, catalytic amounts of tertiary amines were needed for yielding **3**. *β*-Methyl- or phenyl-substituted α,*β*-unsaturated acyclic ketones did not react with **1a**, but **1a** underwent dimerization and annulation to afford **4**. This implies that the *β*-substituents on α,*β*-unsaturated ketones make the Michael reaction slow by virtue of steric hindrance. The reaction of **1a** with other acceptor olefins such as acrylonitrile, fumaronitrile, ethylidenemalononitrile, methyl acrylate, and phenyl vinyl sulfoxide afforded no adducts **3** under the same conditions.

**Table 2. Reaction of 1 with Enones**[a]

| enone | 1 | time, h | yield, %[b] |
|---|---|---|---|
|  | **1a** | 5 | 67 |
| | **1b** | 17 | 79 |
| | **1c** | 672 | 61 |
|  | **1a** | 6 | 61 |
| | **1b** | 29 | 63 |
|  | **1a** | 81 | 56 |
| | **1b** | 24 | 69 |

[a] Reaction was run in DMF ([**1**]$_0$ = 1 M, [enol ether]$_0$ = 1.2 M) at room temperature. [b] Isolated by preparative HPLC.

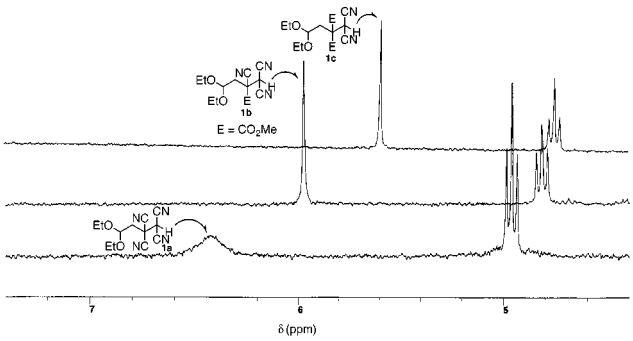



**Figure 1.** $^1$H NMR spectra of **1a**−**c** in DMF-$d_7$ ([**1**] = 0.167 M) at 23 °C.

The above results seem to stem from the differences of the acidity of the active methine groups of **1a**, **1b**, and **1c**, which may decrease in this order. The values of chemical shift of the methine groups in $^1$H NMR spectra of **1** would be helpful for estimation of the acidity. Figure 1 shows the $^1$H NMR spectra of **1** in DMF-$d_7$ at the same concentration. The signal of the methine proton of **1a** appeared broad at 6.40 ppm, and the signals of methine protons of **1b** and **1c** were shown sharply at 5.97 and 5.60 ppm, respectively. Consequently, the order of acidity of **1** was substantiated by the $^1$H NMR spectra of **1**.

In summary, we have found the spontaneous addition of **1** to enol ethers and α,*β*-unsaturated ketones in DMF at room temperature. In addition, we demonstrate that the electron-withdrawing groups at the *β* positions of the active methine group having the ones at the α and *β* positions were strongly affected on the acidity of **1** and on the above reactions.

## Experimental Section

**General.** $^1$H NMR spectra were recorded at 200, 270, and 500 MHz and $^{13}$C NMR spectra at 50 and 125 MHz in $CDCl_3$, with chemical shifts reported in ppm references to tetramethylsilane as an internal standard. Infrared spectra were recorded as thin films on NaCl plates or KBr disks containing a solid sample. Isolation of **2** and **3** was carried out with a preparative HPLC (eluent: chloroform) with the use of JA1GEK-1H and 2H columns. DMF was purified by distillation over $CaH_2$. Dicyanomethine compounds **1** were prepared according to our previous papers.[1a,e,f] Phenyl vinyl ketone was prepared by the reaction of benzaldehyde and vinylmagnesium bromide, followed by oxidation according to the reported method.[7]

**General Procedure for Reaction of 1 with Enol Ethers.** Into a round-bottomed flask equipped with a three-way stopcock was placed **1** (1.0 mmol) and purged with argon. A solution of enol ether (1.2 mmol) in dry DMF (1 mL) was added to the flask under dry nitrogen flow and the reaction mixture was stirred at ambient temperature. The reaction mixture was poured into water, and extracted with diethyl ether. Organic layer was washed with water several times and dried over $MgSO_4$. The solution was concentrated in vacuo, and the residue was purified by a preparative HPLC (eluent: $CHCl_3$) to give adduct **2**.

**3,3,4,4-Tetracyano-5-ethoxyhexanal diethyl acetal:** IR (neat) 2980, 2932, 2896, 2254, 1119, 1071 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 4.97 (t, $J$ = 4.9 Hz, 1H), 4.30 (q, $J$ = 5.9 Hz, 1H), 3.92−3.55 (m, 6H), 2.70 (dd, $J$ = 4.9 and 13.7 Hz, 1H), 2.58 (dd, $J$ = 4.9 and 13.7 Hz, 1H), 1.68 (d, $J$ = 5.9 Hz, 3H), 1.34 (t, $J$ = 7.1 Hz, 3H), 1.30 (t, $J$ = 7.1 Hz, 3H), 1.28 (t, $J$ = 7.1 Hz, 3H). $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 111.0, 110.7, 110.0, 109.2, 99.2, 78.0, 66.9, 64.3, 63.7, 50.8, 40.4, 39.4, 17.1, 15.4, 15.1, 14.8. Anal. Calcd for $C_{16}H_{22}N_4O_3$: C, 60.36; H, 6.96; N, 17.60. Found: C, 60.14; H, 6.99; N, 17.34.

**General Procedure for Reaction of 1 with Enones.** Into a round-bottomed flask equipped with a three-way stopcock was placed **1** (1.0 mmol), and the air was replaced with argon. A solution of enone (1.2 mmol) in dry DMF (1 mL) was added to the flask under dry nitrogen flow, and the reaction mixture was stirred at ambient temperature. The reaction mixture was poured into water and extracted with diethyl ether. Organic layer was washed with water several times and dried over $MgSO_4$. The solution was concentrated in vacuo, and the residue was purified by a preparative HPLC (eluent: $CHCl_3$) to give adduct **3**.

**3,3,4,4-Tetracyano-7-oxoctanal diethyl acetal:** IR (neat) 2980, 2938, 2902, 2254, 1725, 1128, 1071 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 4.92 (t, $J$ = 5.7 Hz, 1H), 3.86−3.61 (m, 4H), 2.98 (t, $J$ = 7.6 Hz, 2H), 2.67 (t, $J$ = 7.6 Hz, 2H), 2.59 (d, $J$ = 5.7 Hz, 2H), 2.29 (s, 3H), 1.29 (t, $J$ = 7.1 Hz, 6H). $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 202.9, 110.3, 110.2, 98.9, 64.0, 45.2, 41.7, 39.1, 38.8, 29.9, 29.2, 15.0. Anal. Calcd for $C_{16}H_{20}N_4O_3$: C, 60.75; H, 6.37; N, 17.71. Found: C, 60.43; H, 6.40; N, 17.51.

**Acknowledgment.** This work was supported by Grant-in-Aid for Scientific Research (No. 05750791) from the Ministry of Education, Science, and Culture, Japan and grants from the 21st Century Foundation and Shinsei Foundation.

**Supporting Information Available:** The characterization data of compounds **2** and **3**. This material is available free of charge via Internet at http://pubs.acs.org.

JO991837J

(7) (a) Skorianetz, W.; Ohloff, G. *Helv. Chim. Acta* **1975**, *58*, 1272. (b) Hammen, P. D.; Braisted, A. C.; Northrup, D. L. *Synth. Commun.* **1991**, *21*, 2157.