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A Novel Two-step Preparation of Enaminoketones by Amination of α,β-Unsaturated Ketones with Methoxyamine

Shinzo Seko* and Nobuhiro Tani

Organic Synthesis Research Laboratory, Sumitomo Chemical Co., Ltd., Tsukahara, Takatsuki, Osaka 569-1093, Japan

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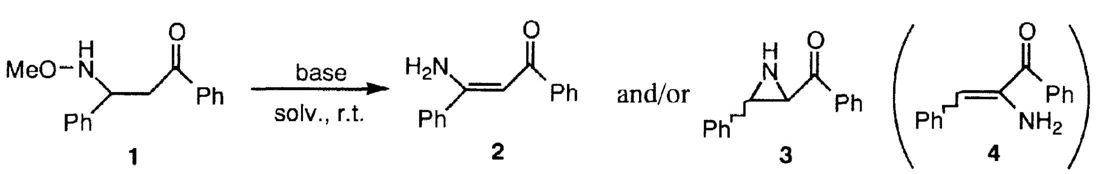
Abstract: β-Methoxyaminoketones, derived from the addition of methoxyamine to 1,3-diaryl-2-propen-1-one, underwent base-induced β-elimination to furnish the corresponding enaminoketones in good to moderate yields. The reaction conditions and substituents on the substrates significantly influenced the selectivity in the production of enaminoketone and/or aziridineketone.

In the course of our studies on amination with methoxyamine, we found that methoxyamine aminated nitroarenes and nitroolefins to give aminonitroarenes[1a,b] and β-nitroenamines,[1c] respectively. We next focused on the amination of α,β-unsaturated ketones to give enaminoketones, which are important synthetic intermediates as a "push-pull" alkene in organic synthesis.[2] As one of the most useful methods for the synthesis of enaminoketones,[2a,3] amination of 1,3-diketones with amines has been known. With unsymmetrical 1,3-diketones, however, regioselectivity becomes a major problem. Furthermore, formation of enamines by an intermolecular direct amination of alkenes is one of the most simple methods. However, there are few examples of a direct amination of α,β-unsaturated ketones possessing no leaving group at β-position to give enaminoketones. Most of these examples are limited to the palladium-catalyzed arylamination[4] or amidation,[5] and no previous reports concerning introduction of an unsubstituted amino group by replacement of vinylic hydrogen at the β-position in an α,β-unsaturated ketone have been published.[6] We report here a novel two-step preparation of enaminoketones by amination of 1,3-diaryl-2-propen-1-one with methoxyamine followed by treatment with two equivalents of ^{t}BuOK in relatively polar aprotic solvents.

It has so far been reported[7] that some base-induced reactions of 3-methoxyamino-1,3-diphenyl-1-propanone **1** did not produce the enaminoketone **2** but rather the corresponding aziridineketone **3** or α-amino α,β-unsaturated ketone **4**, which was produced *via* isomerization of **3**. At first, we examined various reaction



Scheme 1

conditions in the reaction of **1** to give the enaminoketone **2**. According to the literature,[7] the β-methoxyaminoketone **1** was easily obtained in quantitative yield by refluxing a mixture of chalcone and excess methoxyamine[8] in ethanol for 4-5 hours. We found that base-treatment of **1** gave enaminoketone **2**[9] and/or

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aziridineketone **3** with high selectivity depending on the base and solvent used (Scheme 1). Table 1 summarizes the yields of **2** and/or **3** under various reaction conditions. A previous paper reported[7b] that treatment of **1** with NaOMe in methanol gave **3**. We also found that the use of NaOMe gave **3** exclusively (entry 9). Surprisingly, however, the use of ^{t}BuOK in THF or DMF predominantly gave the enaminoketone **2** (entries 4 and 5). This is the first example of a synthesis of **2** from 3-methoxyamino-1,3-diphenyl-1-propanone **1**, in spite of the intensive studies of the reactions of **1**.[7] The enaminoketone **2** would not be produced *via* isomerization of aziridineketone **3**, because even prolonged treatment of **3** with the base did not give **2**, and Reichel previously reported[7c] that the isomerization of **3** gave α-amino α,β-unsaturated ketone **4**. The high basicity, which depended on the combination of the bases and the solvents, was needed to obtain **2** with high selectivity, since ^{t}BuOK was favored over NaOMe or KOH, and the relatively polar aprotic solvents were preferable to non-polar or protic solvents in this system. It is also noteworthy that more than two equivalents of the base were required in this reaction. The selectivity was dramatically influenced by the amount of the base. Even though the reaction was carried out with ^{t}BuOK in DMF, the use of one equivalent of ^{t}BuOK gave **3** exclusively (entry 6). The presence of excess base in the reaction is a crucial point for the production of **2**. Thus, the selective synthesis of **2** was achieved only when more than two equivalents of a strong base such as ^{t}BuOK were used in a relatively polar aprotic solvent. Predicted p*K*a values of α- and β-positions of **1** in DMSO by CAMEO[10] are 25 and 32, respectively.[11] Accordingly, after abstraction of a proton at the α-position of **1** by one equivalent of a base, another equivalent of the base probably abstracts a β-proton to induce β-elimination of the methoxy group on the nitrogen atom to give **2** faster than cyclization into **3**.[12]

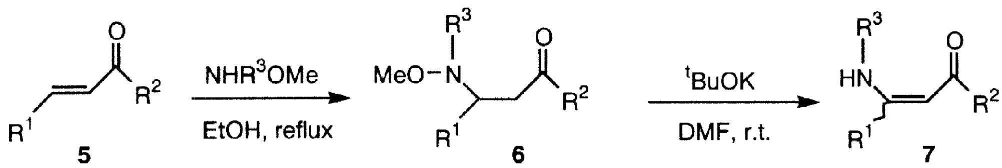
Table 1 Selective Formation of Enaminoketone **2** and/or Aziridineketone **3**[a]

entry	base	equiv.	solv.	yields(%)[b] **2**	yields(%)[b] **3**
1	^{t}BuOK	2.2	PhCl	0	67
2	^{t}BuOK	2.2	nBuOH	0	94
3	^{t}BuOK	2.2	PhMe	26	74
4	^{t}BuOK	2.2	THF	83	8
5	^{t}BuOK	2.2	DMF	55	0
6[c]	^{t}BuOK	1.0	DMF	0	53
7	KOH	2.2	THF	0	92
8	KOH	2.2	DMF	0	52
9	NaOMe	2.2	DMF	0	93

[a] Unless otherwise noted, to a solution of the base in the solvent was added a solution of **1** in the same solvent, and the mixture was stirred for 15 min ~ 48 h at room temperature. [b] Isolated yields. [c] To a solution of **1** in DMF was added ^{t}BuOK.

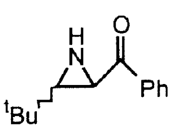
The amination of α,β-unsaturated ketones **5** with methoxyamines followed by treatment with ^{t}BuOK in DMF also furnished the corresponding enaminoketones **7**. Yields of β-methoxyaminoketones **6** and enaminoketones **7** are summarized in Table 2. Methylamination of chalcone using *N,O*-dimethylhydroxylamine proceeded to give **7a** in 64% yield, although heating was required (entry 1). Various enaminoketones **7**[13] were obtained in good to moderate yields (entries 3, 4 and 5). However, substituents R^1 and R^2 in **5** were limited to aryl groups for the successful formation of **7**. With ^{t}Bu group as R^1, aziridineketone **8** was obtained in 70% yield even with ^{t}BuOK in DMF, and the desired enaminoketone **7f** was not detected (entry 6). This may indicate that the base-induced β-elimination of the methoxy group does not take place in **6f** (R^1=^{t}Bu), since the acidity of the β-position in **6f**, in which p*K*a value in DMSO predicted by CAMEO is 44,[11] is lower than that in **6a-e** (R^1=aryl). In addition, it should be noted that R^2 also played an important role in the reaction. In the case of **6g** (R^2=^{t}Bu), a retro-aldol type reaction occurred to furnish benzaldehyde *etc.* (entry 7). The addition of methoxyamine to **5h** (R^2=Me) gave 1,2-adduct, oxime ether **9**, in a quantitative yield, but not 1,4-adduct **6h** (entry 8).

Table 2 Two-Step Synthesis of Enaminoketones **7** from α,β-Unsaturated Ketones **5**.[a]



entry		R^1	R^2	R^3	Yield of **6** (%)	Yield of **7** (%)
1	**a**	Ph	Ph	Me	99	64[b]
2	**b**	Ph	Ph	H	99	55
3	**c**	2-furyl	Ph	H	90[c]	82
4	**d**	m-$NO_2C_6H_4$	Ph	H	99	36
5	**e**	Ph	p-$MeOC_6H_4$	H	99[d]	63
6	**f**	^{t}Bu	Ph	H	97	0[e]
7	**g**	Ph	^{t}Bu	H	79	0[f]
8	**h**	Ph	Me	H	0[g]	—

[a] See ref. 14 for typical procedure, unless otherwise noted. [b] The reaction was conducted at 50°C for 5h. [c] 4.4 equiv. of methoxyamine was used. [d] 3.5 equiv. of methoxyamine was used. [e] Aziridineketone **8** was obtained in 70% yield. [f] Retro-aldol reaction took place to give benzaldehyde *etc.*. [g] Oxime ether **9** was obtained by 1,2-addition of methoxyamine to carbonyl group.



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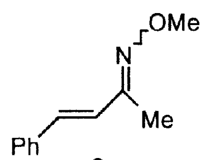

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In summary, we have demonstrated a novel two-step replacement of a vinylic β-hydrogen in an α,β-unsaturated ketone by an unsubstituted amino group to give an enaminoketone. Methoxyamine has been found to be a highly efficient aminating agent not only for nitroolefins[1c] but also for 1,3-diaryl-2-propen-1-one. In this amination, both the basicity of the base in the solvent and the acidity of β-position in 1,4-adduct of methoxyamine to α,β-unsaturated carbonyl compounds are important. Further studies on the amination with methoxyamine are actively underway.

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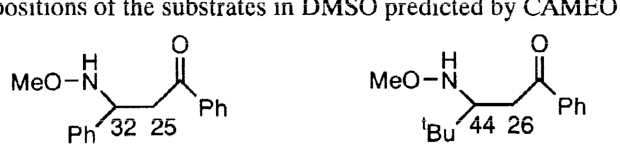
REFERENCES AND NOTES

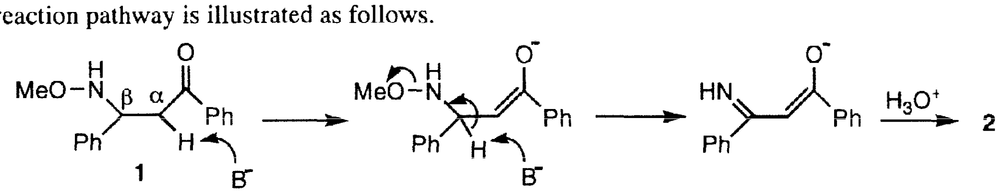
1. (a) Seko, S.; Kawamura, N. *J. Org. Chem.* **1996**, *61*, 442-443.; (b) Seko, S.; Miyake, K. *Chem. Commun.* **1998**, 1519-1520.; (c) Seko, S.; Komoto, I. *J. Chem. Soc., Perkin Trans. 1*, in press.
2. (a) Greenhill, J. V. *Chem. Soc. Rev.* **1977**, *6*, 277-294 and references cited therein.; (b) Alberola, A.; Andres, J. M.;

Gonzalez, A.; Pedrosa, R.; Vicente, M. *Heterocycles* **1990**, *31*, 1049-1058.

3. Kashima, C.; Tobe, S.; Sugiyama, N.; Yamamoto, M. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 310-313.; Honma, T.; Tada, Y. *Heterocycles* **1977**, *6*, 1985-1991.; Iimori, T.; Nii, Y.; Izawa, T.; Kobayashi, S.; Ohno, M. *Tetrahedron Lett.* **1979**, 2525-2528.; Bartoli, G.; Cimarelli, C.; Palmieri, G.; Bosco, M.; Dalpozzo, R. *Synthesis* **1990**, 895-897.; Braibante, M. E. F.; Braibante, H. S.; Missio, L.; Andricopulo, A. *Synthesis* **1994**, 898-900.
4. Bozell, J. J.; Hegedus, L. S. *J. Org. Chem.* **1981**, *46*, 2561-2563.
5. Hosokawa, T.; Takano, M.; Kuroki, Y.; Murahashi, S-I. *Tetrahedron Lett.* **1992**, *33*, 6643-6646.
6. For the aminations of α,β-unsaturated γ-dicarbonyl compounds, see: (a) Sasaki, T.; Kanematsu, K.; Kakehi, A. *Tetrahedron* **1972**, *28*, 1469-1476.; (b) Tamura, Y.; Sumoto, K.; Matsushima, H.; Taniguchi, H.; Ikeda, M. *J. Org. Chem.* **1973**, *38*, 4324-4328.; (c) Furukawa, N.; Yoshimura, T.; Ohtsu, M.; Akasaka, T.; Oae, S. *Tetrahedron* **1980**, *36*, 73-80.
7. (a) Blatt, A. H. *J. Am. Chem. Soc.* **1939**, *61*, 3494-3499.; (b) Cromwell, N. H.; Barker, N. G.; Wankel, R. A.; Vanderhorst, P. J.; Olson, F. W.; Anglin, Jr. J. H. *J. Am. Chem. Soc.* **1951**, *73*, 1044-1051.; (c) Reichel, L.; Pritze, P. *Liebigs Ann. Chem.* **1974**, 120-123.
8. CAUTION Dried methoxyamine has deflagration potential. Bissot, T. C.; Parry, R. W.; Campbell, D. H. *J. Am. Chem. Soc.* **1957**, *79*, 796-800.
9. The structure and configuration of **2** were determined by ^{1}H, ^{13}C-NMR, COLOC and NOE experiments. The structure of **2** was also confirmed by the fact that hydrolysis of **2** gave 1,3-diphenylpropane-1,3-dione.
   Spectral data of **2**: ^{1}H-NMR ($CDCl_3$, 270MHz) δ 5.71 (br.s, 1H), 6.12 (s, 1H), 7.37-7.49 (m, 6H), 7.59-7.63 (m, 2H), 7.91-7.95 (m, 2H), 10.40 (br.s, 1H).; ^{13}C-NMR ($CDCl_3$, 68MHz) δ 91.63, 126.27, 127.08, 128.16, 128.86, 130.57, 130.89, 137.36, 140.23, 162.96, 189.94.; EI-MS *m/z* 223 (M^+), 222, 146, 117, 103, 91, 77, 65, 51, 39.
10. CAMEO is an interactive computer program capable of predicting p*K*a values for organic compounds, developed by Jorgensen. See: Gushurst, A. J.; Jorgensen, W. L. *J. Org. Chem.* **1986**, *51*, 3513-3522.
11. The p*K*a values of α– and β-positions of the substrates in DMSO predicted by CAMEO are depicted as follows.



12. Probable reaction pathway is illustrated as follows.



13. **7c-e** can not be synthesized with high selectivity by amination of the corresponding 1,3-diketones. **7d** and **7e** are new compounds. Spectral data of **7d**: ^{1}H-NMR ($CDCl_3$, 270MHz) δ 5.82 (br.s, 1H), 6.12 (s, 1H), 7.39-7.51 (m, 3H), 7.62 (t, 1H, J=7.92Hz), 7.88-7.97 (m, 3H), 8.29 (m, 1H), 8.46 (m, 1H), 10.30 (br.s, 1H).; ^{13}C-NMR ($CDCl_3$, 68MHz) δ 92.45, 121.49, 125.00, 127.13, 128.30, 130.06, 131.38, 132.29, 139.12, 139.64, 148.36, 159.89, 190.42.; FD-MS *m/z* 268 (M^+). **7e**: ^{1}H-NMR ($CDCl_3$, 270MHz) δ 3.83 (s, 3H), 5.51 (br.s, 1H), 6.10 (s, 1H), 6.92 (m, 2H), 7.39-7.63 (m, 5H), 7.93 (m, 2H), 10.32 (br.s, 1H).; ^{13}C-NMR ($CDCl_3$, 68MHz) δ 55.26, 91.36, 113.39, 126.27, 128.88, 129.08, 130.48, 132.94, 137.70, 161.92, 162.34, 189.06.; FD-MS *m/z* 253 (M^+).
14. Typical procedure: A mixture of α,β-unsaturated ketone **5** (15 mmol) and methoxyamine (33 mmol) in ethanol (15 ml) was refluxed for 4 hours. After completion of the reaction, usual work-up and silica gel thin layer chromatography gave pure β-methoxyaminoketone **6**. To a solution of ^{t}BuOK (8.8 mmol) in DMF (7 ml) was added dropwise **6** (4 mmol) in DMF (3 ml) at room temperature. After 30 min at the same temperature, the reaction was quenched with saturated aq. NH_4Cl, and the product was extracted with CH_2Cl_2. Silica gel thin layer chromatography gave pure enaminoketone **7**.