Acylation of Ester Enolates by N-Methoxy-N-methylamides: An Effective Synthesis of β-Keto Esters

James A. Turner* and Wendy S. Jacks

Agricultural Products Research, The Dow Chemical Company, 2800 Mitchell Drive, Walnut Creek, California 94598

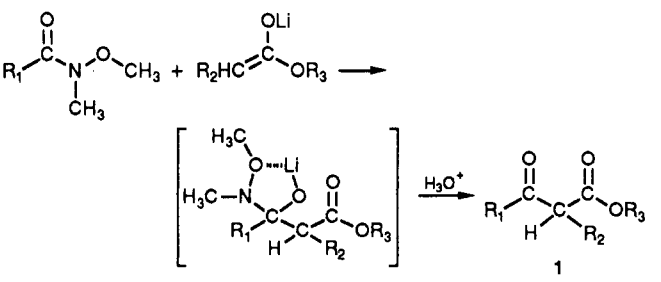
Received March 20, 1989

Acylation of ester enolates represents a straightforward method for preparation of β-keto esters. The approach is exemplified by the classic acetoacetic ester synthesis in which esters serve as both nucleophile (as an enolate) and acylating agent.[1] When the two ester fragments are different, and both contain α-hydrogens, the reaction (in fact, a series of equilibria) is complicated by the inability to control the nucleophilic and electrophilic character of each individual ester.[2] A variety of alternative β-keto ester syntheses have been developed which avoid this difficulty by effective differentiation of the electronic nature of the two carboxylic acid moieties.[3,4] The more useful of these employ enolates of malonic esters as nucleophiles and irreversible acylating agents (such as acid chlorides),[3] but α-substituted β-keto esters cannot always be prepared directly by these methods. Furthermore, additional steps are often required to convert the intermediate tricarbonyls to β-keto esters, and large excesses of base are sometimes necessary to deprotonate the acidic products.

We have found that N-methoxy-N-methylamides, first employed by Nahm and Weinreb in a superior synthesis of ketones from organometallics,[5] serve as effective acylating agents for ester enolates in a simple, one-step synthesis of β-keto esters (Scheme I). The condensation is accomplished by adding a solution of the amide to the lithium enolate of an ester in THF or ether at −78 °C.[6] The initially rapid reaction can, in certain instances, be difficult to drive to completion, but this problem is easily overcome by the use of excess enolate (1.4 equiv).

Product is isolated after hydrolysis of the intermediate chelate with 1 N aqueous HCl. The reactions are clean (VPC, TLC, NMR) with few sideproducts, although, occassionally, small amounts of unreacted starting amide are detected. There was no indication of further reaction of the product nor of products resulting from self-condensation of the amide. The results presented in Table I serve to illustrate the general utility of this simple β-keto ester synthesis.

Scheme I



Scheme II

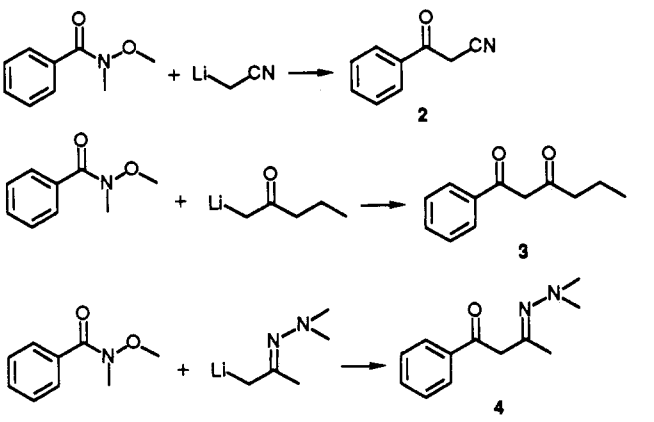


Table I. Acylation of Lithium Ester Enolates by N-Methoxy-N-methylamides (Scheme I)[a]

no.	R_1	R_2	R_3	equiv of enolate	yield, %
1a	n-C_5H_{11}	H	t-Bu	1.2	80
1b	n-C_5H_{11}	H	Et	1.2	78[b]
1b	n-C_5H_{11}	H	Et	1.4	82
1c	CH_2=$CH(CH_2)_3$	H	Et	1.5	89
1d	Ph	H	t-Bu	1.1	83
1e	Ph	CH_3	t-Bu	1.2	72
1f	Ph	CH_3	Et	1.2	84
1g	Ph	F	t-Bu	1.2	79
1h	4-CH_3Ph	H	t-Bu	1.1	73
1i	4-ClPh	H	Et	1.2	68
1j	$PhCH_2$	H	Et	1.2	63[c]
	Ph	CO_2Et	Et	1.2	0
	Et	Ph	Et	1.4	0

[a] Yields refer to isolated, purified products and are not optimized. For conditions see the Experimental Section. [b] The crude product contained approximately 10% of the starting amide (NMR). [c] The crude product contained approximately 20% of the starting amide (NMR).

Attempts to extend this reaction to more stabilized ester enolates were less satisfactory. Treatment of the lithium enolate of diethyl malonate with N-methoxy-N-methylbenzamide in THF failed to produce any new product even after a prolonged period at reflux. Likewise, the lithium enolate of ethyl phenylacetate did not react with N-methoxy-N-methylpropanamide at −78 °C, and, upon stirring at room temperature, the enolate underwent self-condensation. On the other hand, acylation of the lithium enolate of *tert*-butyl fluoroacetate with N-methoxy-N-methylbenzamide was sluggish at −78 °C but proceeded to near completion after warming to 0 °C.[8]

(1) Hauser, C. R.; Hudson, B. E. *Org. React.* **1942**, *1*, 266.
(2) For a general discussion regarding acylation of esters, see House, H. O. *Modern Synthetic Reactions*, 2nd ed.; W. A. Benjamin: Menlo Park, CA, 1972; pp 734-765.
(3) (a) Breslow, D. S.; Baumgarten, E.; Hauser, C. R. *J. Am. Chem. Soc.* **1944**, *66*, 1286. (b) Ireland, R. E.; Marshall, J. A. *J. Am. Chem. Soc.* **1959**, *81*, 2907. (c) Pollet, P.; Gelin, S. *Synthesis* **1978**, 142. (d) Wierenga, W.; Skulnick, H. I. *J. Org. Chem.* **1979**, *44*, 310. (e) Brooks, D. W.; Lu, L. D.-L.; Masamune, S. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 72. (f) Oikawa, Y.; Sugano, K.; Yonemitsu, O. *J. Org. Chem.* **1978**, *43*, 2087. (g) Houghton, R. P.; Lapham, D. J. *Synthesis* **1982**, 451. (h) Barnick, J. W. F. K.; van der Baan, J. L.; Bickelhaupt, F. *Synthesis* **1979**, 787. (i) Kim, H.-O.; Olsen, R. K.; Choi, O.-S. *J. Org. Chem.* **1987**, *52*, 4531.
(4) (a) Rathke, M. W.; Deitch, J. *Tetrahedron Lett.* **1971**, 2953. (b) Rathke, M. W.; Sullivan, D. P. *Tetrahedron Lett.* **1973**, 1297. (c) Nokami, J.; Kunieda, N.; Kinoshita, M. *Tetrahedron Lett.* **1975**, 2841. (d) Hartzell, S. L.; Rathke, M. W. *Tetrahedron Lett.* **1976**, 2757. (e) Cooke, M. P., Jr. *J. Org. Chem.* **1982**, *47*, 4963.
(5) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.
(6) In contrast, neither the sodium (from sodium bis(trimethylsilyl)-amide)[7] nor bromomagnesium (from bromomagnesium diisopropylamide) enolate of ethyl acetate gave β-keto ester product upon treatment with N-methoxy-N-methylhexanamide (−78 °C, THF or ether).
(7) The sodium enolate is much less stable than the corresponding lithium enolate. See: Rathke, M. W. *J. Am. Chem. Soc.* **1970**, *92*, 3222.
(8) This latter example is noteworthy since the product β-keto ester (**1q**) was readily converted[9] to α-fluoroacetophenone (cat. *p*-TsOH, benzene, reflux, 1 h; 91%) to demonstrate a remarkably simple two-step synthesis of an α-fluoromethyl ketone from a carboxylic acid equivalent.

0022-3263/89/1954-4229$01.50/0

Table II

compd	conditions	NMR	formula	calcd (found) C	calcd (found) H
1a	Et_2O, 2 h	3.32 (s), 2.45 (t, J = 7), 1.7–1.45 (m), 1.45 (s), 1.4–1.15 (m), 0.86 (t, J = 7)	$C_{12}H_{22}O_3$	67.25 (67.15)	10.35 (10.16)
1b	Et_2O, 5 h	4.17 (q, J = 7), 3.31 (s), 2.51 (t, J = 7), 1.7–1.45 (m), 1.4–1.15 (m), 0.87 (t, J = 7)	$C_{10}H_{18}O_3$	exact mass: 186.1256 (186.1260)	
1c	Et_2O, 7 h	5.87–5.68 (m), 5.11–4.87 (m), 4.08 (q, J = 7), 3.58 (s), 2.62 (t, J = 7), 2.20 (m), 1.18 (t, J = 7)			
1d	Et_2O, 2 h	7.98–7.32 (m), 3.88 (s), 1.38 (s)	$C_{13}H_{16}O_3$	70.88 (70.75)	7.32 (7.34)
1e	Et_2O, 6 h	8.0–7.42 (m), 4.25 (q, J = 7), 1.46 (d, J = 7), 1.34 (s)	$C_{14}H_{18}O_3$	71.77 (71.39)	7.74 (7.91)
1f	THF, 6 h	7.95 (m), 7.56–7.41 (m), 4.35 (q, J = 7), 4.12 (q, J = 7), 1.47 (d, J = 7), 1.13 (t, J = 7)	$C_{12}H_{14}O_3$	exact mass: 206.0943 (206.0947)	
1g	THF, −78 °C, 6 h; 0 °C, 1 h	8.0 (m, 2 H), 7.7–7.4 (m, 3 H), 5.75 (d, J = 47, 1 H), 1.4 (s, 9 H)	$C_{13}H_{15}FO_3$	65.33 (65.36)	6.35 (6.30)
1h	THF, 1 h	7.86–7.25 (m), 3.87 (s), 2.41 (s), 1.43 (s)	$C_{14}H_{18}O_3$	71.77 (71.80)	7.74 (7.71)
1i	Et_2O, 7 h	7.91–7.37 (m), 4.21 (q, J = 7), 3.96 (s), 1.26 (t, J = 7)	$C_{11}H_{11}ClO_3$	exact mass: 226.0397 (226.0388)	
1j	Et_2O, 36 h	7.35–7.18 (m), 4.17 (q, J = 7), 3.83 (s), 3.44 (s), 1.26 (t, J = 7)	$C_{12}H_{14}O_3$	exact mass: 206.0943 (206.0935)	

Preliminary experiments have also demonstrated the potential utility of *N*-methoxy-*N*-methylamides as acylating agents for other stabilized anions (Scheme II).[10] Thus, reaction of *N*-methoxy-*N*-methylbenzamide with the lithium enolate of acetonitrile (1.5 equiv; −78 °C, 3 h; 0 °C, 1 h) or 2-pentanone (1.2 equiv; −78 °C, 3 h; ambient temperature, 24 h) gave the corresponding β-keto nitrile (**2**, 62%) or β-diketone (**3**, 47%) along with unreacted starting amide. Reaction of the lithium enolate of acetone dimethylhydrazone with *N*-methoxy-*N*-methylbenzamide proceeded to completion in 30 min at 0 °C to give β-keto hydrazone **4** in 98% yield.

The success of this acylation procedure is presumably due to the stability of the tetrahedral intermediate (Scheme I) toward dissociation to product β-keto ester, under the reaction conditions.[5,13] This lithium chelate must effectively prevent further condensation with the enolate[4a,14] as well as deprotonation of the intermediate by the enolate. Unlike the corresponding *N*-methoxy-*N*-methylamide, *N*,*N*-dimethylhexanamide did not react with the lithium enolate of ethyl acetate (1.2 equiv) under typical reaction conditions (THF, −78 °C, 5 h). The current results represent a rare example of the successful use of an amide for acylation of an ester.[15,16]

In conclusion, we have demonstrated that *N*-methoxy-*N*-methylamides function as acylating agents for ester enolates and other stabilized anions. The reaction provides a versatile synthesis of β-keto esters, which is devoid of many of the complications typically associated with acylation of esters.[2]

Experimental Section[17]

General Procedure for Acylation of Ester Enolates with *N*-Methoxy-*N*-methylamides. A solution of diisopropylamine (11–15 mmol) in 20 mL of THF or ether was cooled under N_2 to −78 °C, and *n*-butyllithium (11–15 mmol) in hexane was added. The appropriate ester (11–15 mmol) in 1 mL of THF or ether was added dropwise, and, after 15 min at −78 °C, a solution of the *N*-methoxy-*N*-methylamide (10 mmol) in 1 mL of THF or ether was slowly added. The reaction mixture was stirred at −78 °C for the specified period of time, warmed to near room temperature, and poured into 1 N HCl. The mixture was extracted twice with ether, and the combined organic layers were dried over $MgSO_4$ and evaporated to dryness. The residue was chromatographed through a short column of silica gel, eluting with 9:1 hexane–ethyl acetate (8:1 and 19:1 hexane–ethyl acetate for **1b** and **1i**, respectively; 19:1 hexane–acetone for **1h**), and then distilled in a Kugelrohr apparatus. The resulting oily β-keto esters (**1**) were characterized on the basis of their corresponding NMR spectra and appropriate element analyses (see Table II).

Attempted Acylation of Ethyl Phenylacetate with *N*-Methoxy-*N*-methylpropanamide. Ethyl phenylacetate (2.30 g, 14 mmol) in 1 mL of ether was added slowly to a −78 °C solution of LDA (14 mmol, prepared in the usual fashion) in 20 mL of ether. After 15 min, a solution of 1.17 g (10 mmol) of *N*-methoxy-*N*-methylpropanamide in 1 mL of ether was slowly added, and the reaction mixture was stirred at −78 °C for 6 h. The solution was warmed to room temperature and stirred overnight when VPC and TLC analyses showed complete loss of ethyl phenylacetate. The mixture was then treated in the usual fashion to give 1.90 g of a tan, oily mixture. Preparative-scale HPLC, eluting with 9:1 hexane–ethyl acetate, gave 0.50 g of ethyl 2,4-diphenyl-3-oxobutanoate as colorless crystals: mp 77–78.5 °C (lit.[18] mp 78–78.5 °C); NMR δ 7.40–7.05 (m, 10 H), 4.79 (s, 1 H), 4.18 (q, J = 7 Hz, 2 H), 3.83–3.66 (m, 2 H), 1.24 (t, J = 7 Hz, 3 H).

(9) Renerow, W. B.; Walker, G. B. *J. Am. Chem. Soc.* **1948**, *70*, 3957.

(10) The acylation of the anion of 1,3-dithiane[11] and the highly reactive dianions of β-keto esters[12] by *N*-methoxy-*N*-methylamides has recently been reported.

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(15) Yamaguchi, M.; Hirao, I. *J. Org. Chem.* **1985**, *50*, 1975.

(16) The highly reactive acyl imidazoles have been used for acylation of the lithium enolate of *tert*-butyl (trimethylsilyl)acetate. See: Hartzell, S. L.; Rathke, M. W. *Tetrahedron Lett.* **1976**, 2757.

(17) Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Proton NMR spectra were recorded in $CDCl_3$ at 200 MHz with a Varian XL-200 spectrometer. Chemical shifts are reported in ppm downfield from internal tetramethylsilane and coupling constants are in hertz. Most of the β-keto esters were obtained as mixtures of the keto and enol isomers with chemical shifts reported referring to the predominant keto isomer only. Tetrahydrofuran and ether ("anhydrous, gold label") and *n*-butyllithium (1.55 or 2.5 M in hexane) were obtained from Aldrich Chemical Co. Diisopropylamine was distilled from CaH_2 and stored over 4A molecular sieves. The *N*-methoxy-*N*-methylamides were prepared by minor modification of the procedure described by Nahm and Weinreb.[5] Microanalyses were performed by Mary Gade of the Dow Chemical Co., Walnut Creek, CA. High-resolution mass spectra were recorded by the Mass Spectrometry Lab at the University of California, Berkeley, CA.

(18) Shivers, J. C.; Hudson, B. E., Jr.; Hauser, C. R. *J. Am. Chem. Soc.* **1943**, *65*, 2051.

3-Oxo-3-phenylpropanonitrile (2) was prepared by the general procedure from 0.62 g (15 mmol) of acetonitrile and 1.65 g of *N*-methoxy-*N*-methylbenzamide in ether (-78 °C, 3 h: 0 °C, 1 h). After standard workup, 1.3 g (90%) of an orange solid was obtained, which was contaminated with a trace of starting amide. The solid was triturated with methylcyclohexane (2×), filtered, and then distilled in a Kugelrohr apparatus to give 0.90 g (62%) of **2** as a pale yellow solid: mp 78–80 °C (lit.[19] mp 80–81 °C); NMR δ 7.90 (m, 2 H), 7.65 (m, 1 H), 7.50 (m, 2 H), 4.09 (s, 2 H).

1-Phenyl-1,3-hexanedione (3) was prepared by the general procedure from 1.03 g (12 mmol) of 2-pentanone and 1.65 g of *N*-methoxy-*N*-methylbenzamide in ether (-78 °C, 3 h; ambient temperature, 24 h). After a standard workup, 1.5 g of an oil was isolated, which was contaminated with approximately 25% of the starting amide (NMR). The oil was purified by chromatography, eluting with 19:1 hexane–ethyl acetate, and Kugelrohr distillation to give 0.90 g (47%) of diketone **3** as a colorless oil: NMR (enol form) δ 7.88 (m, 2 H), 7.5–7.4 (m, 3 H), 6.17 (s, 1 H), 2.40 (t, J = 7.5 Hz, 2 H), 1.72 (sextet, J = 7.5 Hz, 2 H), 0.99 (t, J = 7.5 Hz, 3 H). Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.97; H, 7.45.

1-Phenyl-1,3-butanedione 3-(Dimethylhydrazone) (4). A solution of diisopropylamine (1.7 mL, 12 mmol) in 10 mL of THF was cooled under N_2 in an ice bath, and 12 mmol of *n*-butyllithium in hexane was added. The resulting solution was stirred at 0 °C for 15 min, and a solution of 1.2 g (12 mmol) of acetone dimethyl hydrazone in 1 mL of THF was added dropwise. The resulting mixture was stirred at 0 °C for 40 min, when a solution of 1.65 g (10 mmol) of *N*-methoxy-*N*-methylbenzamide in 1 mL of THF was slowly added. The resulting solution was stirred at 0 °C for 30 min, poured into aqueous NH_4Cl, and extracted with two portions of ether. The combined organic layers were dried over Na_2SO_4 and evaporated to dryness. The residue was distilled in a Kugelrohr apparatus (100 °C, 0.07 mmHg) to give 2.00 g (98%) of **4** as a yellow oil: NMR (enol form) δ 7.84 (m, 2 H), 7.38 (m, 3 H), 5.55 (s, 1 H), 2.58 (s, 6 H), 2.15 (s, 3 H). Anal. Calcd for $C_{12}H_{16}N_2O$: C, 70.55; H, 7.90; N, 13.72. Found: C, 70.16; H, 7.80; N, 13.77.

Acknowledgment. We would like to thank M. J. Ricks and J. M. Renga for generous samples of certain starting materials. In addition, special thanks are extended to M. J. Ricks for providing one of the examples.

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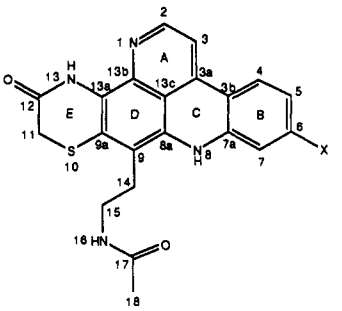
A Second Shermilamine Alkaloid from a Tunicate *Trididemnum* sp.

Anthony R. Carroll, Niranjala M. Cooray, Anthony Poiner, and Paul J. Scheuer*

Department of Chemistry, University of Hawaii at Manoa, Honolulu, Hawaii 96822

Received February 24, 1989

Recent chemical studies of colonial tunicates have shown them to be rich sources of fused tetra- and pentacyclic aromatic alkaloids.[1] In our earlier work on *Trididemnum* sp., a purple colonial tunicate from Pago Bay, Guam, we isolated a thiazinone-containing pentacyclic alkaloid, shermilamine A (**1**).[2] Further fractionation of the extracts has yielded a second shermilamine alkaloid, shermilamine B (**2**), lacking C6 bromination. The structure of shermilamine B was determined by interpretation of spectral data. Furthermore, a ^{1}H-detected heteronuclear multiple bond ^{1}H–^{13}C correlation experiment (HMBC)[3] has facilitated the complete and unambiguous assignment of ^{1}H and ^{13}C resonances for both shermilamine A and B. As a result of this experiment, a number of the spectral properties previously reported for shermilamine A have been revised.[4]



Optimized extraction of the tunicate with a mixture of chloroform/methanol (1:1) containing 1% of a concentrated ammonium hydroxide solution, followed by extraction of the orange pigments into an aqueous hydrochloric acid solution, and finally purification of the pigment fraction on normal-phase MPLC yielded shermilamine A, orange prisms from chloroform/methanol (94:6), mp >300 °C (0.006%, wet weight), and shermilamine B, orange prisms from methanol, mp 254 °C dec (0.02%, wet weight).

HREIMS established the molecular formula, $C_{21}H_{18}N_4O_2S$, for **2**, suggesting that it might be the nonbrominated analogue of **1**. This proposal was supported by close similarities in the UV, IR, ^{1}H NMR, and ^{13}C NMR spectra (Table I) of **2** with those of **1**. In particular, the ^{1}H NMR and ^{13}C NMR spectra for the two compounds were almost identical. The only major differences were the resonances associated with the spin system of the B ring. Proton decoupling and a COSY experiment indicated that the three protons on C4, C5, and C7 in the ^{1}H NMR spectrum of **1** were replaced in the ^{1}H NMR spectrum of **2** by a four-proton spin system in which the protons are attached to contiguous carbons. This is best explained by a hydrogen replacing the bromine at C6. The presence of another protonated aromatic carbon (δ 131.8) in the DEPT (distortionless enhancement of polarization transfer) spectrum and the absence of one quarternary carbon in the broad band decoupled ^{13}C NMR spectrum of **2** as compared with **1** was also in accord with the proposed structure assignment for **2**.

To complete the unambiguous assignment of structures for shermilamine A and B, ^{1}H–^{13}C long range coupling information was obtained from an HMBC experiment (Table II). Since the structure of **1** had already been solved by an X-ray crystallographic study,[2] an analysis of its long range $^{2\text{-}3}J_{C\text{-}H}$ ^{1}H–^{13}C couplings has allowed us to trace indirectly the complete carbon skeleton of the molecule, thus confirming the structure by a second method. It has also allowed us to unambiguously assign the ^{1}H and ^{13}C resonances for **1**. The ^{13}C resonances for **2**

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(4) The ^{1}H NMR data in DMSO-d_6 and the ^{13}C NMR data for shermilamine A reported previously were data for shermilamine B. The mass spectral data previously presented were those of a mixture of shermilamine A and B.

0022-3263/89/1954-4231$01.50/0