Pergamon

Tetrahedron Letters 39 (1998) 5779–5780

TETRAHEDRON LETTERS

A New Synthesis of α,β-Unsaturated N-methoxy-N-methylamides

Chantal Beney, Ahcène Boumendjel* and Anne-Marie Mariotte

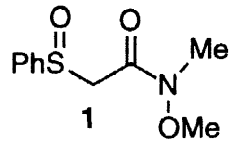
Laboratoire de Pharmacognosie, UFR de Pharmacie de Grenoble, Université Joseph Fourier.

38706 La Tronche - France.

Received 4 May 1998; accepted 3 June 1998

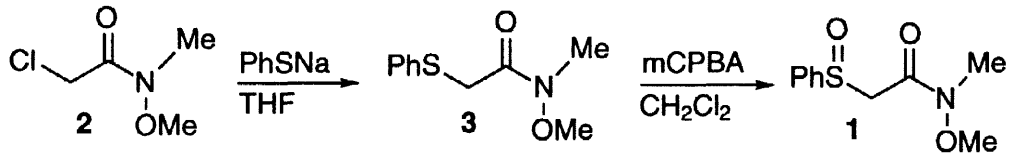
Abstract: phenyl(N-methoxy-N-methylcarbamoylmethyl)sulfoxide **1** is prepared in 2 steps starting from N-methoxy-N-methylchloroacetamide and thiophenol. Reagent **1** is useful for homologation of alkyl halides to α,β-unsaturated N-methoxy-N-methylamide compounds.

Since the initial report of Weinreb on the preparation and use of N-methoxy-N-methylamide as carbonyl equivalent, this functional group found a large applications in organic synthesis.[1] This success is due to the ease of preparation and its versatile reactivity like nucleophilic additions and selective reduction to form aldehydes. Following Weinreb's report, α,β-unsaturated N-methoxy-N-methyl amides were found to be a useful intermediates in synthesis of natural products and therapeutics.[2] Up to now, they were prepared from their corresponding acids or from carbonyls using a reagent that combines Weinreb and Wittig-Horner chemistry.[3] Owing to their utility, we wish to report a new synthesis from alkyl halides by using phenyl(N-methoxy-N-methylcarbamoylmethyl)sulfoxide **1**. The presence of the N-methoxy N-methylamide and a sulfoxide makes **1** a useful reagent for homologation of alkyl halides to α,β-unsaturated N-methoxy N-methyl amides.[4]



1

Reagent **1** is easily prepared in two steps (scheme 1): reacting N-methoxy-N-methyl 2-chloroethanamide **2** [3] with thiophenol sodium salt afford N-methoxy-N-methylphenylsulfinylethanamide **3**. Oxydation of **3** with m-chloroperbenzoic acid (mCPBA) gives **1** in 45% overall yield after purification. Reagent **1** is very stable at room temperature, as it remains intact after several months storage at room temperature.[5]



2 **3** **1**

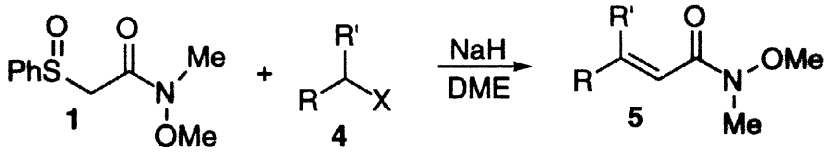
Scheme 1.

Reagent **1** reacts readily with a variety of alkyl halides (Scheme 2) to give exclusively the

Fax (33) 04 76 63 71 65. e-mail. Ahcene.Boumendjel@ujf-grenoble.fr

0040-4039/98/$19.00
PII: S0040-4039(98)01208-8

expected E stereochemistry about the newly formed double bond as determined by ^{1}H NMR.[6]



Scheme 2.

The alkylation-elimination sequence was carried out with various substances according to the conditions given in table 1 where no over alkylation was observed.

Table 1. Alkylative Elimination of Alkyl Halides **4** with Reagent **1**.

alkyl halide 4	temperature (°C)	time	%yield 5
benzylbromide	60	30 min	76
octylbromide	80	2 h	45
ethyl chloroacetate	60	30 min	80
crotylchloride	70	1 h	63
3,3-dimethylallylbromide	60	1.5 h	54
cyclohexylbromide	120[a]	3 h	18
ethyl-4-chlorobut-2-enoate	70	2 h	71
isobutylbromide	120[a,b]	2 h	49
myristyl bromide	120	2 h	45

[a] trimethylphosphite added prior temperature raising. [b] product not isolated but detected by ^{1}H NMR.

References and Notes:

1. Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815-3818.
2. Sibi, M. P. *Org. Prep. Proced. Int*. **1993**, *25*, 15-40.
3. a. Nuzillard, J-M.; Boumendjel, A.; Massiot, G. *Tetrahedron Lett.* **1989**, *30*, 3779-3780.
   b. Jacobi, P. A.; Zheng, W. *Tetrahedron Lett.* **1991**, *32*, 1279-1282.
   c. Netz, D. F.; Seidel, J. L. *Tetrahedron Lett.* **1992**, *33*, 1957-1958.
4. Trost, B. M.; Leung, K. K. *Tetrahedron Lett.* **1975**, *16*, 4197-4200
5. Preparation of reagent 1: To a stirred solution of **2** (10 g, 72.7 mmol) in THF (50 mL) is added benzenethiol sodium salt (9.64 g, 73 mmol). The solution is stirred at room temperature for 12 h and diluted with $CHCl_3$ (100 mL), washed with H_2O and concentrated to afford 13.4 g of **3** as an oil. Compound **3** is dissolved in CH_2Cl_2 (200 mL) and treated with mCPBA (8.76 g, 50.73 mmol). After the mixture stirred for 15 min, potassium fluoride (2.5 g, 50 mmol) was added. The solid is filtred off and the organic layer is washed with $NaHCO_3$, dried and concentrated. The residue is flash-chromatographed (ethyl acetate:hexane 1:1) to afford 7.5 g of reagent **1** as a clear-yellow oil. Overall Yield 45 %. ^{1}H NMR ($CDCl_3$, 200MHz) δ 7.48 (m, 2H); 7.85 (m, 3H); 3.71 (AB, 2H, J = 13.94 Hz); 3.41 (s, 3H); 2.93 (s, 3H). ^{13}C NMR ($CDCl_3$, 50MHz). δ 165.97 (C-1); 144.62 (C-1'); 132.33 (C-2'+ C-6'); 131.70 (C-5'+C-3'); 125.08 (C-4'); 62.58 (C-2); 61.75 (OCH_3); 32.83 (N-CH_3). Elemental analysis. $C_{10}H_{13}NO_3S$. Calculated. **C**: 52.85; **H**: 5.76; **N**: 6.16; **S**: 14.11. Found. **C**: 52.84; **H**: 5.80; **N**: 6.19; **S**: 13.98.
6. Preparation of α,β-unsaturated N-methoxy-N-methylamide: To a solution of NaH in dry DME was added reagent **1** (0.9 eq). The solution was stirred under N_2 for 20 min. The alkyl halide in DME (1 mL/mmol) was added dropwise. The solution was stirred for 10 min and heated at temperature and time indicated in table 1. DME was evaporated and the residue is dissolved in AcOEt, washed with HCl (2%) and brine. The organic layer was separated and concentrated. The crude material was chromtographed on silica gel using AcOEt:hexane (1:1) as eluant to give α,β-unsaturated amide.