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IMPROVED METHOD FOR THE SYNTHESIS OF N-METHYL-2-OXOALKANESULFONAMIDES.

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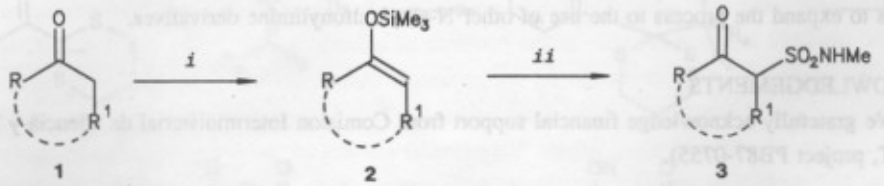
Key words: N-methyl-2-oxoalkanesulfonamides; improved; synthesis; silyl enol ethers; N-Methylsulfonylimine

Abstract: A series of N-methyl-2-oxoalkanesulfonamides was prepared by reaction between silyl enol ethers and N-methylsulfonylimine. In all cases yields were comparatively higher to those obtained by a previously described procedure

The sulfonamide group is incorporated in a variety of compounds having therapeutical application as antibacterials, diuretics, oral antidiabetic agents and antibiotics.[1] Our initial interest in the group came from the potential of 2-oxoalkanesulfonamide derivatives **3**, as intermediates in the synthesis of heterocyclic drugs.

In this report we describe a general procedure for the synthesis of N-methyl-2-oxoalkanesulfonamide derivatives. In comparison with the unique previously reported synthetic procedure,[2] the method is also based on the formation of a carbon-sulphur bond but it uses silyl enol ethers instead of enamines as enolate anion equivalents. With a variety of easily prepared silyl enol ethers from the corresponding ketones, we study the scope and limitation of the procedure. Results are summarized in table 1.

The reaction was tested under different conditions and solvents. Acetonitrile was proved to be the best solvent and reflux temperature was necessary to complete the reaction. Using these conditions a variety of ketones were routinely transformed into the N-methyl-2-oxoalkanesulfonamide derivatives **3a-j** by reaction of the corresponding silyl enol ethers[3,4] and N-methylsulfonylimine generated *"in situ"* from N-methylsulfamoyl chloride.[5,6]

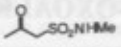
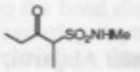
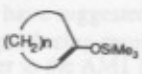
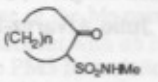
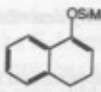
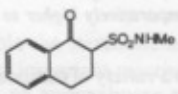
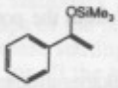
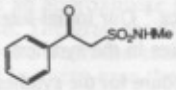
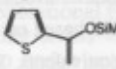
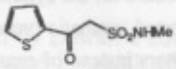


1 **2** **3**

Scheme. i) Et_3N, Me_3SiCl, NaI, MeCN [ref.3]; ii) $MeNHSO_2Cl$, Et_3N, MeCN.

The experimental procedure for the synthesis of compounds **3a-j** is as follows: To a stirred solution of the silyl enol derivative (2 mmol) and triethylamine (2.2 mmol) in acetonitrile (2 ml) a solution of N-methylsulfamoyl chloride (2.2 mmol) in acetonitrile (1 ml) was added dropwise under argon atmosphere. The mixture was stirred 2 hours at room temperature an then refluxed for the time listed in table 1. Then the reaction mixture was left at 5°C overnight and the precipitate was filtered off. The filtrate was evaporated and chromatographed on silica gel using hexane/ethyl acetate as eluent. Pure compounds were obtained by vacuum distillation or recrystallization.

Table 1. N-Methyl-2-oxoalkanesulfonamides **3a-j** prepared

Entry	Silyl enol ether	Reaction Time (h)	Product[a]		Yield(%)[b]	mp(°C)/Solvent bp(°C)(mmHg)[c]
1		5		**3a**	81	203-205/0.8
2		20		**3b**	65[64]	128-130/0.2
						
3	*n=2*	6		**3c**	67[31]	146-150/0.1
4	*n=3*	24		**3d**	85[68]	72-73 (i-PrOH)
5	*n=4*	20		**3e**	61	195-197/0.4
6	*n=5*	26		**3f**	60	220/1
7	*n=9*	24		**3g**	28[19]	129-131 (Hexane/EtOAc)
8		9		**3h**	75[50]	141-143 (i-PrOH)
9		5		**3i**	50	146-147 (EtOAc)
10		2		**3j**	60	119-120 (Hexane/EtOAc)

[a]Satisfactory spectra and analytical data were obtained for all compounds. [b]All yields refer to pure products. In brackets, yields given in ref.2. [c]Kügelrohr distillation.

In summary, we describe a general method for the preparation of N-methyl-2-oxoalkanesulfonamides derivatives by reaction between silyl enol ethers and N-methylsulfonylimine generated "*in situ*". The procedure is an improvement, in terms of yield, over the previously reported method. Further developments are in progress to expand the process to the use of other N-alkylsulfonylimine derivatives.

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