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A Novel Reaction of N-Phenylthiocaprolactam: The α–Sulfenylation of Ketones Under Mild Conditions

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Abstract: N-phenylthiocaprolactam (**2**) reacts with the enolate anions of aliphatic, aromatic or cyclic ketone **1a-e**, to give the corresponding α-phenylthioketones **3a-e**. This reaction proceeds with high yields of monosulphenylation (80-97%) in DMSO under mild conditions (potassium *ter*-butoxide, 25°C, 10 min) . © 1997 Elsevier Science Ltd.

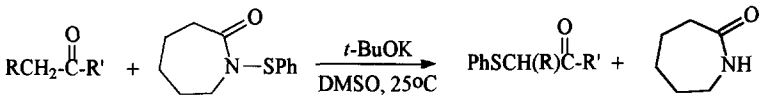
It is known that α-sulfenylketones are important intermediates[1] for: the mono- and dialkylation of ketones;[2] preparing 1,2-diketones by bis-sulfenylation;[3] alkylating on the less reactive α-position after bis-sulfenylation;[4] 1,2-carbonyl transposition;[5] and, preparing α,β-unsaturated ketones.[6]

The most common methods of α-sulfenylation of a ketone involve reaction of Ph_2S_2,[6] R_2S_2,[6] methylmethanthiosulfate ($MeS-SO_2-Me$)[7] or PhS-Cl[8] in tetrahydrofuran (THF) at 25 °C, with the enolate anion previously produced from the ketone with lithium diisopropylamide (LDA) in THF at -78 °C for one hour.

Sulfenamides[9] react with nucleophiles such as thiols, amines and with active methylene compounds[10] like malononitrile, acetylacetone and ethyl acetoacetate in variable yields (40-80%). α-Sulfenylation of ketones by N-phenylthiobenzamidine hydrochloride affords the α-phenylthioketones in poor yields (30-58%).[10] In this reaction the authors propose as sulfenyl-transfer agent the benzenesulfenyl chloride. It has also been described the preparation of α-monosulfenylated ketones by reaction of the corresponding enamines with N-phenylthiophthalimide (50-75% yields).[10]

In this communication we report a novel and easy α-sulfenylation reaction of ketones **1a-e** by N-phenylthiocaprolactam (**2**).

When to a solution of the enolate anion of ketone **1a** (6 mmol), prepared by reaction of an equimolar amount of potassium *ter*-butoxide in 50 ml of DMSO, 2 mmol of N-phenylthiocaprolactam (**2**) are added and stirred for 10 min, the corresponding α-phenylthioacetone (**3a**)[11] is isolated in 62% yield (Table 1, entry 2). This compound decomposes easily and improvement of the yield was no attempted (equation 1).



(1)

1 **2** **3** **4**

80-97%

1a R = H, R' = Me
1b R = H, R' = $C(Me)_3$
1c R = H, R' = Ph
1d R = H, R' = 2-Naphthyl
1e R-R' = $-CH_2CH_2CH_2CH_2-$

The reactions of **2** with the enolate anions of pinacolone (**1b**), acetophenone (**1c**) and cyclohexanone (**1e**) gives good yields of the corresponding α-monosulfenylated ketones **3b**[12], **3c**[11,13], and **3e**[10,6] (Table 1, entries 3, 4 and 6) that were isolated and fully characterized. With the enolate anion of **1d**, only 30% of **3d**[14] was isolated.

Whereas the recovery of **2** and **3** from DMSO by partition with water and diethyl ether was complete, the caprolactam (**4**) remains in the aqueous-DMSO layer (Table 1, entry 1). This fact is a clear advantage of the synthesis of α-sulfenylketones here described, since the reaction is monitored by TLC until no more **2** is present, and the product is easily isolated by distillation.

In order to improve the conditions described for the α-monosulfenylated derivative, the reaction of ketone **1e** with **2** was studied by changing the relation ketone **1**:*t*-BuOK: **2**. When the relation was 1:1:1, the product **3e** was quantified in 87% in only 10 minutes. After 30 minutes the reaction was complete.

Comparison with other methods described in literature for the preparation of **3e**, results in many advantages in favour of the reaction here reported. This reaction does not need the presence of a strong base-like LDA in THF at -78°C, instead *t*-BuOK in DMSO at room temperature is enough to generate the enolate anions; **2** is commercially available and easily handled as compare to the toxic benzenesulfenyl chloride which hydrolyses easily. The reaction proceeds rapidly, providing high yields of α-monosulfenylation in a few minutes, the corresponding products being isolated easily. Further work is in progress to extend the scope of the reaction by using different carbanions from ketones, esters and N,N-dialkylamide derivatives.

Table 1: Sulfenylation Reactions of Ketones by N-Phenylthiocaprolactam (2) in DMSO at Room Temperature.[a]

Entry	Ketone[b] RCOR'	Relation 1 : *t*-BuOK : 2	Time (min)	Products PhS-RCOR' (Yield %)[c]
1[d]	-	-	10	**2** (94)
2	MeCOMe **1a**	3 : 3.3 : 1	10	$PhSCH_2COMe$ (**3a**) (62)[e,f]
3	$MeCOC(Me)_3$ **1b**	3 : 3.3 : 1	10	$PhSCH_2COC(Me)_3$ (**3b**) (81)
4	MeCOPh **1c**	3 : 3.3 : 1	180[g]	$PhSCH_2COPh$ (**3c**) (83)
5	MeCONaph **1d**	3 : 3.3 : 1	120	$PhSCH_2CONaph$ (**3d**) (30)[e]
6	 **1e**	3 : 3.3 : 1	10	 (**3e**) (97) (82)[e]
7	 **1e**	1 : 1 : 1	10	 (**3e**) (87)
8	 **1e**	1 : 1 : 1	30	 (**3e**) (98)

[a]Reactions were performed in 50 ml of DMSO (analytical grade, dried over molecular sieves 4Å) with 2 mmol of **2** and *t*-BuOK as a base. [b]The ketones **1** were distilled and stored over molecular sieves 4Å before use. Naph = 2-naphthyl. [c]Determined by GLC using an OV 17 column by the internal standard method, unless otherwise indicated. [d]Recovery assay from the DMSO solution of **2** by partition with water and diethyl ether. [e]Isolated yield. [f]Decomposed easily. [g]Time not optimized.

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