Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

α-Tolylsulfinylation of Ketones via Their Trimethylsilyl Enol Ethers. One-Step Synthesis of β-Ketosulfoxides

Romualdo Caputo [a] , Carla Ferreri [a] , Luigi Longobardo [a] , Giovanni Palumbo [a] & Silvana Pedatella [a]

[a] Dipartimento di Chimica Organica e Biologica , Università degli Studi di Napoli Federico II Via Mezzocannone , 16 I-80134, Napoli, Italy

To cite this article: Romualdo Caputo , Carla Ferreri , Luigi Longobardo , Giovanni Palumbo & Silvana Pedatella (1993) α-Tolylsulfinylation of Ketones via Their Trimethylsilyl Enol Ethers. One-Step Synthesis of β-Ketosulfoxides, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 23:11, 1515-1522, DOI: 10.1080/00397919308011245

To link to this article: http://dx.doi.org/10.1080/00397919308011245

SYNTHETIC COMMUNICATIONS, 23(11), 1515-1522 (1993)

α-Tolylsulfinylation of Ketones *via* their Trimethylsilyl Enol Ethers. One-Step Synthesis of β-Ketosulfoxides.

Romualdo Caputo, Carla Ferreri, Luigi Longobardo,
Giovanni Palumbo* and Silvana Pedatella

Dipartimento di Chimica Organica e Biologica
Università degli Studi di Napoli Federico II
Via Mezzocannone, 16 I-80134 Napoli (Italy)

ABSTRACT: Ketones are reported to be conveniently converted into their α-tolylsulfinylated derivatives. This new procedure is based on the reaction of their corresponding trimethylsilyl enol ethers with p-toluenesulfinyl p-tolylsulfone in the presence of tris(dimethylamino)sulfur trimethylsilyldifluoride (TAS-F). Considering that β-ketosulfoxides are key intermediates for the preparation of α,β-unsaturated ketones, this procedure turns out to be of rather broad synthetic relevance.

In a recent paper[1] we reported a new general and reliable regiospecific α-phenylsulfenylation of ketones that is based on the reaction of their silyl enol ether derivatives with thiosulfonic *S*-esters in the presence of tetrabutylammonium fluoride (TBAF). Actually, in organic synthesis, a

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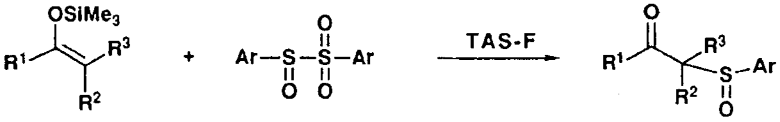
* To whom correspondence should be addressed.

preminent interest in the chemistry of β-ketosulfides lies on their prompt oxidation to β-ketosulfoxides and the subsequent mild pyrolisis of the latter to afford α,β-unsaturated ketones[2]. Thus, we consider interesting to report in this paper a ready one-step procedure we have devised for converting trimethylsilyl enol ethers of ketones directly into their corresponding β-ketosulfoxides, hence enabling to bypass the β-ketosulfide stage when unnecessary.

In fact, in this procedure the (regiospecifically generated) trimethylsilyl enol ethers[3] of various ketones (**1a-e**) are treated with the specially prepared *p*-



1 **2** **3**

Ar = *p*-Tolyl

1,3	R¹	R²	R³
a	$CH_2(CH_2)_2CH_2$		H
b	$CH_2CH_2\underset{\substack{\vert \\ Bu^t}}{C}HCH_2$		H
c	$\underset{\substack{\vert \\ CH_3}}{C}HCH_2CH_2CH_2$		H
d	$CH_2(CH_2)_2CH_2$		CH_3
e	$CH_3(CH_2)_2CH_2$	$CH_2CH_2CH_3$	H

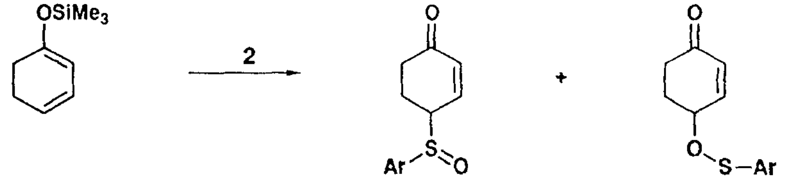
Table - β-Ketosulfoxides from Trimethylsilylenolethers (2a-e).

Sulfoxides	Yield (%)	*ax*:*eq*	^{1}H NMR
3a	86	24:76	δ 2.41 (*s*, 3H, aromatic Me), 3.32 (*dd*, 0.76H, $J_{2ax\text{-}3}$ = 9.0 Hz, H_{ax}-2), 3.48 (*t*, 0.24H, $J_{2eq\text{-}3}$ = 6.0 Hz, H_{eq}-2), 7.28 (*d*, 2H, J_{ortho} = 8.0 Hz, aromatic Hs), 7.58 (*d*, 2H, J_{ortho} = 8.0 Hz, aromatic Hs).
3b	81	20:80	δ 2.43 (*s*, 3H, aromatic Me), 3.48 (*m*, 0.8H, H_{ax}-2), 3.72 (*m*, 0.2H, H_{eq}-2), 7.30 (*d*, 2H, J_{ortho} = 8.0 Hz, aromatic Hs), 7.61 (*d*, 2H, J_{ortho} = 8.0 Hz, aromatic Hs).
3c	78	20:80	δ 1.04 (*d*, 3H, *J* = 6.0 Hz, Me), 2.40 (*s*, 3H, aromatic Me), 3.42 (*dd*, 0.8H, $J_{2ax\text{-}3}$ = 10.0 Hz, H_{ax}-2), 3.7 (*t*, 0.2H, $J_{2eq\text{-}3}$ = 5.8 Hz, H_{eq}-2), 7.25 (*d*, 2H, J_{ortho} = 8.0 Hz, aromatic Hs), 7.53 (*d*, 2H, J_{ortho} = 8.0 Hz, aromatic Hs).
3d	76	20:80	δ 1.16 (*s*, 3H, Me), 2.42 (*s*, 3H, aromatic Me), 7.15 (*d*, 2H, J_{ortho} = 8.0 Hz, aromatic Hs), 7.48 (*d*, 2H, J_{ortho} = 8.0 Hz, aromatic Hs).
3e	78	-----	δ 2.40 (*s*, 3H, aromatic Me), 3.65 (*m*, 1H, H-4), 7.25 (*d*, 2H, J_{ortho} = 8.0 Hz, aromatic Hs), 7.42 (*d*, 2H, J_{ortho} = 8.0 Hz, aromatic Hs).

toluenesulfinyl *p*-tolylsulfone (2) in anhydrous chloroform, at 0° C for few minutes, in the presence of tris(dimethylamino)sulfur trimethylsilyldifluoride (TAS-F). Under these conditions, the rather hard sulfonium enolate anion that is expected[4] to result from the reaction of fluoride ion with the silyl enol ether can attack efficiently the sulfinyl sulfur of **2**, with loss of its sulfonyl moiety as a stable sulfinate anion. The sulfinylating agent, *p*-toluenesulfinyl *p*-tolylsulfone (2), is readily prepared[5] by reaction of sodium *p*-toluenesulfinate and *p*-toluenesulfinyl chloride in anhydrous ethyl ether under nitrogen atmosphere. It is a crystalline product m.p. 77-79° C that can be safely stored in the refrigerator for weeks or even months.

The procedure turns out to be of quite general application, leading in all cases (see Table) to the desired products in satisfactory yields. Its most interesting feature is regioselectivity that is in fact assured by the use of silylenolethers (which can be generated with the desired regiochemistry, isolated, and purified[3] before the reaction if it is considered necessary). Indeed, the only previously reported[6] direct sulfinylation of ketones, utilizing *O*-methyl benzenesulfinate and sodium hydride, does suffer from the equilibration of the enolates when the starting ketone shows two non-equivalent enolizable positions. Under our mild conditions (ice bath for few minutes) the equilibration *in situ* of any intermediate enolate anions appears quite unlikely.

Trimethylsilyldienolethers, coming from α,β-unsaturated ketones, in principle exhibit an analogous behaviour: indeed it is noteworthy that in this case only their corresponding γ-sulfinyl derivatives can be obtained, in spite of the higher hardness of the dienolate anions α-position[7] which, as a consequence, should be expected to undergo a preferential substitution. This can be tentatively accounted for by considering the cooccurrence in the reaction mixture of a second product



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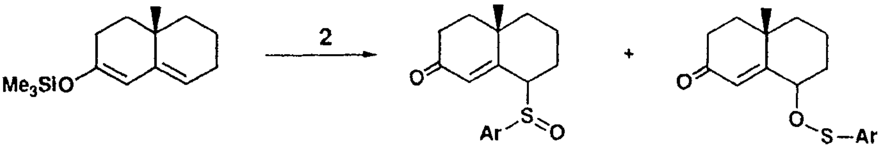

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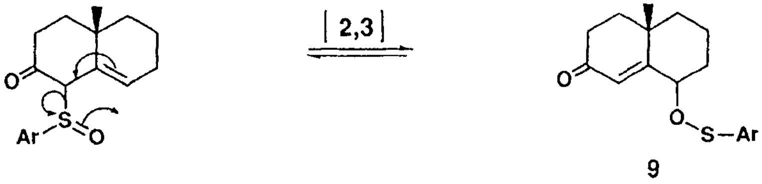
recognized as an allylic sulfenic ester, like in (9). In fact, the latter is known[8] to be an equilibrium species deriving from an allyl sulfoxide through a sigmatropic [2,3] rearrangement, as is shown in the scheme below. At least in the cases we have tested, it is possible that the α-sulfinyl derivatives are formed and eventually converted to their corresponding allylic sulfenic esters, more stable owing to the conjugation of the double bond and the carbonyl group.

Considering the high yields, the mild conditions, and the ease of performance and work-up, this method can be very well considered as the first reliable one-pot procedure for the preparation of β-ketosulfoxides, thus finding rather broad application in synthesis.

Tris(dimethylamino)sulfur trimethylsilyldifluoride (TAS-F) was purchased from Aldrich Chemical Co. Anhydrous tetrahydrofuran (reagent grade, Carlo Erba) was distilled from $LiAlH_4$. Silica gel (70-230 mesh) was purchased from Carlo Erba. ^1H NMR spectra were recorded on a Bruker WH (270 MHz) instrument in $CDCl_3$ solutions.



Scheme - Sigmatropic [2,3] Rearrangement of Allylic β-Ketosulfoxides.

2-(*p*-Toluenesulfinyl)-cyclohexanone (3a). Typical procedure. To a mixture of specially prepared (or stored) *p*-toluenesulfinyl *p*-tolylsulfone (0.38 g; 1.30 mmol) and trimethylsilylenolether (**1a**) (0.18 g; 1.08 mmol) in anhydrous chloroform (10 mL), a solution of tris(dimethylamino)sulfur trimethylsilyldifluoride (TAS-F) (0.37 g; 1.30 mmol) in few milliliters of the same solvent is added dropwise over 5 min, at 0° C, under magnetic stirring and argon (or nitrogen) atmosphere. The reaction mixture is then quenched and extracted with H_2O (3 x 10 mL). The organic layer, dried (Na_2SO_4) and evaporated *in vacuo*, yields a crude product which after chromatography on silica gel (9:1 benzene:Et_2O) affords **3a** (0.22 g; 0.92 mmol; 86% yield); *ax*:*eq* = 24:76; ^1H NMR (see Table).

Sulfinylation of silyldienolethers (4) and (7). When the silyldienolethers (4) and (7) were treated with *p*-toluenesulfinyl *p*-tolylsulfone (2) under the experimental conditions reported in the typical procedure above, the following products were isolated respectively:

From (**4**): i) (**5**) (50% yield); oil; ^1H NMR: δ 2.30 (*s*, 3H, aromatic Me), 3.70 (*m*, 1H, H-4), 6.03 (*d*, 1H, $J_{2\text{-}3}$ = 9.8 Hz, H-2), 6.95 (*m*, 1H, H-3), 7.28 (*d*, 2H, J_{ortho} = 8.0 Hz, aromatic Hs), 7.57 (*d*, 2H, J_{ortho}= 8.0 Hz, aromatic Hs); IR:1665 cm^{-1}; m/e = 234 (M^+).

ii) **6** (20% yield); oil; ^{1}H NMR: δ 2.28 (*s*, 3H, aromatic Me), 4.82 (*m*, 1H, H-4), 6.20 (*d*, 1H, $J_{2\text{-}3}$ = 9.0 Hz, H-2), 6.95 (*m*, 1H, H-3), 7.30 (*d*, 2H, J_{ortho} = 8.0 Hz, aromatic Hs), 7.61 (*d*, 2H, J_{ortho} = 8.0 Hz, aromatic Hs); IR: 1655, 1050 cm^{-1}; m/e = 234 (M$^+$).

From (7): i) **8** (55% yield); oil; ^{1}H NMR: δ 1.42 (*s*, 3H, angular Me), 2.42 (*s*, 3H, aromatic Me), 3.29 (*t*, 1H, $J_{6eq\text{-}7ax}$ = $J_{6eq\text{-}7eq}$ = 3.0 Hz, H-6), 5.85 (*s*, 1H, H-4), 7.32 (*d*, 2H, J_{ortho} = 8.0 Hz, aromatic Hs), 7.59 (*d*, 2H, J_{ortho} = 8Hz, aromatic Hs); IR: 1670 cm^{-1}; m/e = 302 (M$^+$).

ii) (**9**) (35% yield); oil; ^{1}H NMR: δ 1.30 (*s*, 3H, angular Me), 2.41 (*s*, 3H, aromatic Me), 4.87 (*m*, 1H, H-6), 5.98 (*s*, 1H, H-4), 7.30 (*d*, 2H, J_{ortho} = 8.0 Hz, aromatic Hs), 7.60 (*d*, 2H, J_{ortho} = 8.0 Hz, aromatic Hs); IR: 1669, 1042 cm^{-1}; m/e = 302 (M$^+$).

ACKNOWLEDGEMENT: Financial support was provided by CNR "Progetto Finalizzato Chimica Fine e Secondaria" (Roma) to R.C.

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(Received in UK 04 December 1992)