Pergamon

Tetrahedron Letters, Vol. 36, No. 39, pp. 7051-7054, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)01461-6

Unsaturation of Ketones, Nitriles and Lactams with Methyl Phenylsulfinate

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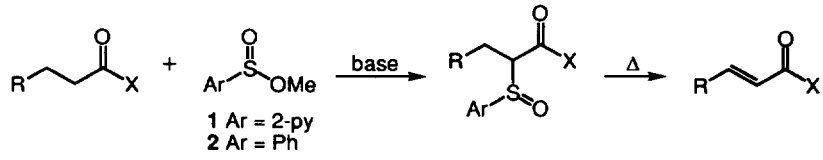
Abstract: *An improved synthesis of methyl phenylsulfinate **2** by treatment of diphenyl disulfide with bromine in the presence of methanol has been developed. Use of this reagent in the preparation of α,β-unsaturated ketones, nitriles and lactams is described.*

The preparation of α,β-unsaturated carbonyl compounds and nitriles from the corresponding saturated compounds is among the most useful and important transformations in organic chemistry.[1] This process is most commonly carried out through the well known and efficient syn elimination of appropriate selenoxides developed by Reich.[2] Although this chemistry has wide scope, we have for some time sought an unsaturation method which does not involve selenium, owing to cost and toxicity considerations. These considerations become increasingly important in research projects that demand multi-gram quantities of the unsaturated compound, as is the case in our exploratory studies[3] of chiral non-racemic bicyclic lactams (see Table). We thus chose to re-examine the analogous sulfur chemistry, much of which has been elucidated in classic studies by Trost and coworkers.[4] The latter recently described their use of methyl 2-pyridylsulfinate[5] **1** to install the sulfur moiety in the correct oxidation state for the elimination, thus avoiding the oxidation step of what has become the standard sequence (sulfenylation/oxidation/elimination). The overall transformation is shown in equation 1. The α-sulfoxide substituent is installed directly by reaction of the enolate with a sulfinate ester and elimination follows thermally to provide the unsaturated product.

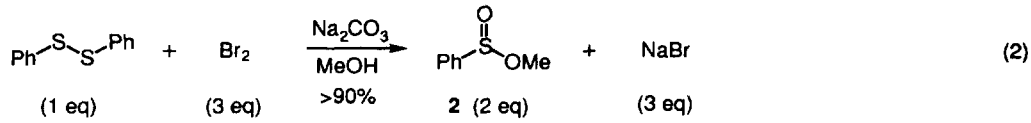


(1)

We have now examined the use of the simpler analog, methyl phenylsulfinate **2** in this sequence and although we developed this procedure for use in our bicyclic lactam chemistry, we found that it is also useful for the dehydrogenation of ketones and nitriles. As this approach to

unsaturation has been largely overlooked until recently, we wish to report our findings in this area.[6]

Preparation of methyl phenylsulfinate. It is likely that the reaction sequence outlined in equation 1 has not been employed more frequently because of the difficulties associated with the preparation of methyl phenylsulfinate **2**. In the past, the best method for the synthesis of **2** involved the oxidation of diphenyl disulfide with lead tetraacetate in the presence of methanol.[7] With the recent disclosure that **2** can be prepared by treatment of diphenyl disulfide with *N*-bromosuccinimide in methanol[8], the present route to unsaturation became much more attractive. Although we were able to obtain 70% yields of **2** by the reported procedure, the concomitant formation of dimethyl succinate as a by-product required somewhat laborious purification procedures when the reaction was conducted on a large scale. To circumvent this problem, elemental bromine was employed as the oxidant, and found to be an excellent reagent for this transformation. Thus, treatment of diphenyl disulfide with bromine in the presence of sodium carbonate and methanol furnished **2** in greater than 90% yield after distillation (eq. 2).[9] The sulfinate ester **2** showed no signs of decomposition upon storage at room temperature over a period of three months.



(2)

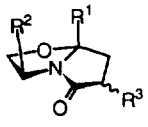
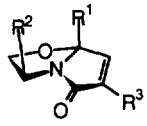
Unsaturations. The initial procedure utilized to introduce the α,β-unsaturation involved treatment of a THF solution of the compound to be unsaturated and methyl phenylsulfinate **1** with potassium hydride (2.5 eq). Ketones were found to form the α-sulfinyl ketones in *ca.* 5 min at room temperature, while nitriles and lactams reacted more slowly.[10] It was found that sulfinylation of nitriles required heating of the THF solution to reflux for 6-12 h, while lactams reacted within 6 h at room temperature or 30 min at reflux temperature. Once the starting material was consumed (TLC), the solution was subjected to an aqueous workup and the crude product was taken up in toluene. Anhydrous sodium carbonate was added to prevent undesired side reactions associated with the sulfur by-products, and the mixture was heated to reflux. In the case of ketones and nitriles, the elimination to the unsaturated derivative was complete within 5 min, while lactams required 3-6 h. The Table (Method A) shows that yields were typically above 80% in this reaction. As has been observed previously, ketones (entry 3) are unsaturated with high *E/Z* selectivity[4], while nitriles gave much lower geometric selectivity (entries 7,9). It is noteworthy that more sterically encumbered enolates, such as those in 2,6-dimethylcyclohexenone (entry 6) and an α-methyllactam (entry 16) did not react with **2**. Furthermore, esters and lactones failed to yield unsaturated derivatives, presumably due to the low reactivity of **2** as an electrophile and the relatively low thermal stability of ester enolates.

It seemed advantageous to effect this procedure in a single experimental step, and indeed this turned out to be the case. In this variation, the sulfinylation was performed as described above, but rather than isolating the intermediate sulfoxide, acetic acid (2.5 eq) was added to neutralize the THF solution. Heating to reflux provided the desired unsaturated compounds in overall yields which were generally comparable to the two-step sequence (Table, Method B).[11]

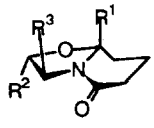
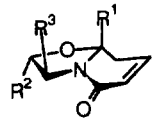
This experimentally simple and cost effective method for the preparation of α,β-unsaturated compounds can now be added to the selenium-based eliminations although the mildness of the latter may still offer some advantages when thermally sensitive molecules are involved.

Table 1. Methyl Phenylsulfinate Unsaturations

Entry	Substrate[a]	Product	Method[b]	% Yield (*E*:*Z*)[c,d]
1	4-*t*-butylcyclohexanone	4-*t*-butylcyclohexenone	A	88
2	"	"	B	82
3	valerophenone	phenyl butenyl ketone	A	90[e]
4	"	"	B	81[e]
5	α-tetralone	α-napthol	A	80
6	2,6-dimethylcyclohexanone		A	0
7	hydrocinnamonitrile	cinnamonitrile	A	80 (2:1)
8	"	"	B	80 (4:1)
9	hexanonitrile	2-hexenonitrile	A	50 (1.5:1)

	R^1	R^2	R^3		
10	Me	Ph	H	A	80
11	Ph	Ph	H	A	93
12	CH_2OBn	Ph	H	A	85
13	$CH_2CH_2C{=}CMe_2$	Ph	H	A	80
14	$CH_2CH_2C{=}CMe_2$	*i*-Pr	H	A	88
15	Me	*t*-Bu	H	A	74
16	Me	Ph	Me	A	0

	R^1	R^2	R^3		
17	Me	H	Ph	A	88
18	Me	Ph	CH_2OMe	A	86

[a]Ketones and nitriles were obtained from commercial sources, saturated bicyclic lactams were prepared as described previously (ref.3). [b]Method A: Two-step procedure, Method B: one-pot procedure. [c]Isolated yields. [d]All products had spectral data consistent with the given structures, and were judged to be >96% pure by ^1H NMR. [e]Only the *E* isomer was formed.

ACKNOWLEDGEMENT

We are grateful to the National Institutes of Health for financial support of this work.

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(6) See also: Magnus, P. D.; Pappalardo, P. *J. Am. Chem. Soc.* **1983**, *105*, 6525, Trost, B. M.; Latimer, L. H. *J. Org. Chem.* **1978**, *43*, 1131-1140.

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(9) To a solution of diphenyl disulfide (5.03 g, 23.0 mmol) in methanol (500 mL) was added sodium carbonate (12.2 g, 115 mmol), followed by bromine (11.05 g, 3.56 mL, 69.1 mmol). The yellow solution was stirred for 3 h, during which time the suspension became colorless. The reaction mixture was concentrated and the residue was partitioned between CH_2Cl_2 (300 mL) and water (200 mL). The layers were separated and the aqueous portion was extracted with CH_2Cl_2 (2 x 100 mL). The combined organics were washed with sat. $NaHCO_3$ (100 mL) and brine (100 mL), dried (Na_2SO_4) and concentrated. The residue was distilled under reduced pressure (79-83 °C, 0.3 mm Hg) to give methyl phenylsulfinate (6.5 g, 90%) as a colorless liquid (*STENCH!*).

(10) Sulfinylations of ketones by treatment with sulfinate esters and NaH have been reported: Coates, R. M.; Pigott, H. D. *Synthesis*, **1975**, 319-320, Monteiro, H. J.; De Souza, J. P. *Tetrahedron Lett.* **1975**, 921-924.

(11) General procedures: **Method A**. To a solution of the substrate in THF (*ca.* 0.3 M) and **2** was added oil-free KH (2.5 eq). The resulting solution was treated as follows for different substrates: ketones, rt, 5 min; nitriles, reflux, 6-12 h; lactams, rt, 3-6 h or reflux, 30 min. The solution was concentrated and the residue was partitioned between 0.5 M H_3PO_4 and CH_2Cl_2. The aqueous portion was extracted with additional CH_2Cl_2 (2x), the combined organics were dried (Na_2SO_4), and concentrated. The residue was taken up in toluene (*ca.* 0.1 M) and solid Na_2CO_3 (5 eq), and the mixture was heated at reflux until TLC indicated the reaction was complete (5 min-6 h). The reaction mixture was filtered through a pad of Celite, concentrated and the product was purified by flash chromatography followed by bulb-to-bulb distillation. **Method B**. The sulfinylation was performed as in Method A, and AcOH (2.5 eq) was added directly to the solution. The solution was then heated to reflux until TLC indicated the reaction was complete (6-24 h). The volume of the solution was increased fourfold by addition of diethyl ether, and the mixture was washed with sat. $NaHCO_3$. The dried (Na_2SO_4) organics were concentrated and purified as described in Method A.

(*Received in USA* 16 *June* 1995; *revised* 24 *July* 1995; *accepted* 28 *July* 1995)