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α-Sulfenylalkylation of Carbonyl Compounds at the α-Position via Magnesium Amide–Induced Enamine Sulfenylalkylation with Sulfoxides

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Abstract: The reactions of enamines with sulfoxides bearing α-hydrogens in the presence of a magnesium amide, generated *in situ* from the reaction of ethylmagnesium bromide with diisopropylamine, afforded the corresponding α-sulfenylalkylated ketones and aldehydes in isolated yields ranging from 39 to 76%. This procedure was successfully extended to the bis(methylthio)methylation with methyl (methylthio)methyl sulfoxide. © 1998 Elsevier Science Ltd. All rights reserved.

INTRODUCTION

A number of interesting methods have been reported[1] for preparing α-(α-sulfenyl)alkylated carbonyl compounds because of their efficiency in organic synthesis.[1,2] Most of these methods rely upon the sulfenylalkylation of carbonyl compounds.[1a-f] The methods reported by Paterson and Fleming[1a,b,d,f] involve reactions of ketone silyl enol ethers with α-chloro thioethers. Hosomi and Sakurai[1e] have used monothioacetals in their approach similar to that of Paterson and Fleming. α-(*N,N*-Dialkylamino)thioethers have been used in the method utilizing enamines reported by Sekiya et al.[1c] These methods are convenient, but the use of rather unstable sulfenylalkylation reagents may somewhat lower their efficiency. Among the various α-sulfenylalkylation reagents, sulfoxides bearing α-hydrogens seem to be the most convenient with respect to their handling and availability.[3] Thus, the Lewis acid–promoted Pummerer-type reactions of silyl enol ethers with α-activated sulfoxides, such as α-sulfinyl ketones[4] or allyl sulfoxides,[5] have been reported to give the corresponding α-sulfenylalkylated ketones by Mukaiyama et al. or Hunter et al., respectively. Moreover, Kita et al. have reported that the zinc iodide–induced reaction of ketene silyl enol ethers with a simple sulfoxide, such as phenyl 2-phenylethyl sulfoxide, gave the corresponding α-sulfenylalkylated carboxylates.[6] However, to the best of our knowledge, there has been no report on the preparation of α-(α-sulfenyl)alkylated ketones or aldehydes utilizing simple sulfoxides. On the other hand, we have recently reported the transformations of sulfoxides carrying α-hydrogen(s) into symmetrical[7a,b] and unsymmetrical dithioacetals,[7d] and thioethers[7c] including vinyl thioethers,[7b] through formation of the sulfur-stabilized carbonium ion intermediates induced by magnesium amides. So, we were interested in investigating the possibility of developing a procedure for the α-sulfenylalkylation of carbonyl compounds using simple sulfoxides as an extension of these magnesium amide-induced transformations. In this paper, we wish to describe the results of our investigation, which offer a simple

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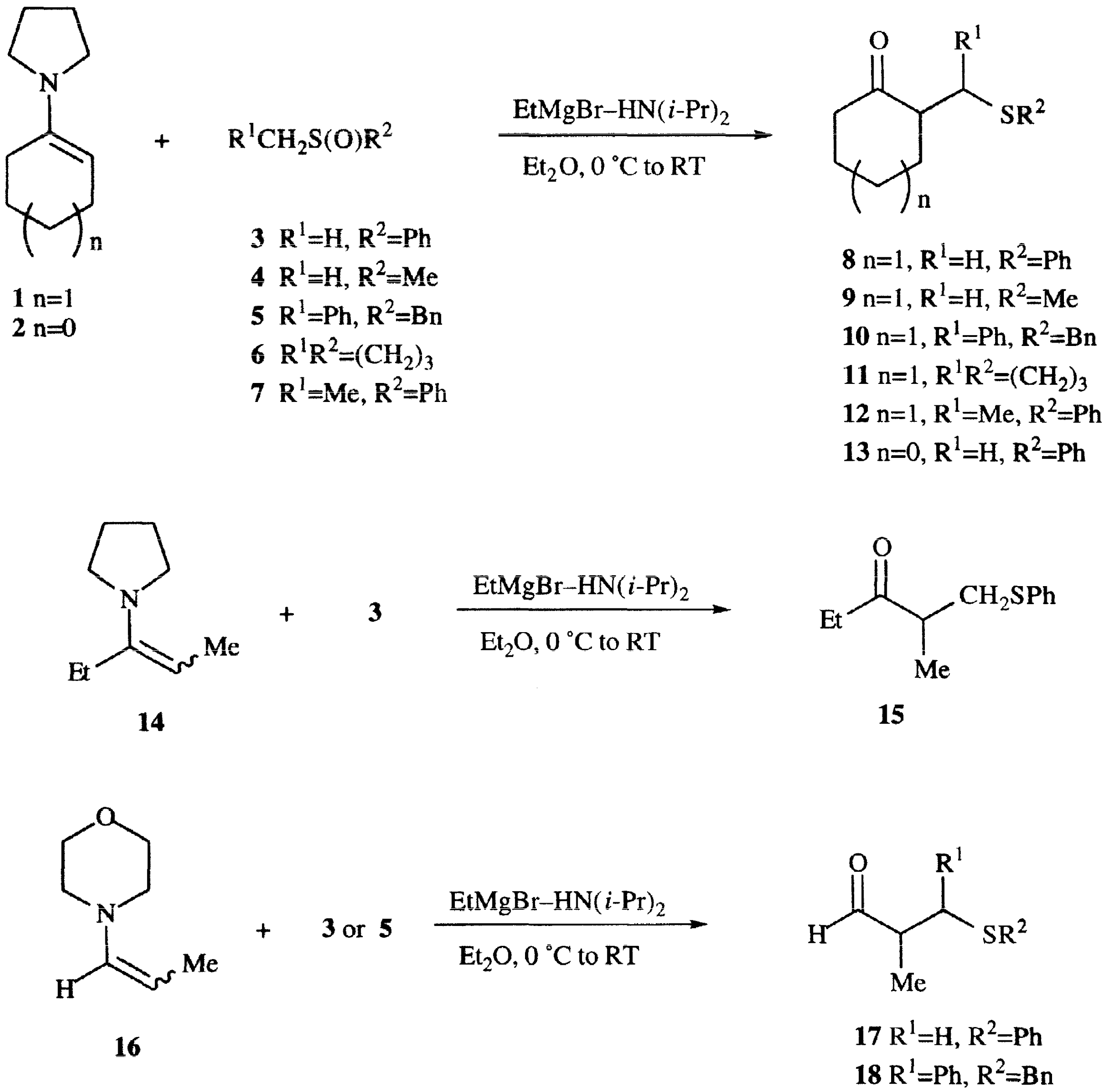
and general route to α-(α-sulfenyl)alkylated ketones and aldehydes from enamines and sulfoxides, as outlined in Scheme 1.

RESULTS AND DISCUSSION

We selected 1-pyrrolidinocyclohexene (**1**) and methyl phenyl sulfoxide (**3**) as the model substrates, and carried out several experiments on reaction conditions for the satisfactory production of the desired product, 2-(phenylthiomethyl)cyclohexanone (**8**). It was found that when the enamine **1** was treated with equimolar amounts of the sulfoxides **3** in Et_2O containing the (diisopropylamino)magnesium reagent, generated *in situ* from 3 molar amounts each of EtMgBr and diisopropylamine, at room temperature, the α-



Scheme 1

Table 1. Preparation of α-(α-alkylthio)alkylated ketones and aldehydes from enamines and sulfoxides

Entry	Enamine	Sulfoxide	Product (yield/%)[a]
1	**1**	**3**	**8** (76)
2	**1**	**4**	**9** (39)
3	**1**	**5**	**10** (71)[b,e]
4	**1**	**6**	**11** (55)[c,e]
5	**1**	**7**	**12** (42)[d,e]
6	**2**	**3**	**13** (62)
7	**14**	**3**	**15** (63)
8	**16**	**3**	**17** (47)
9	**16**	**5**	**18** (55)[d,e]

[a] Isolated yields based on enamines. [b] A mixture of diastereomers (ca. 7:3). [c] A mixture of diastereomers (ca. 8:2). [d] A mixture of diastereomers (ca. 1:1). [e] The stereochemistry of each diastereomer was not determined.

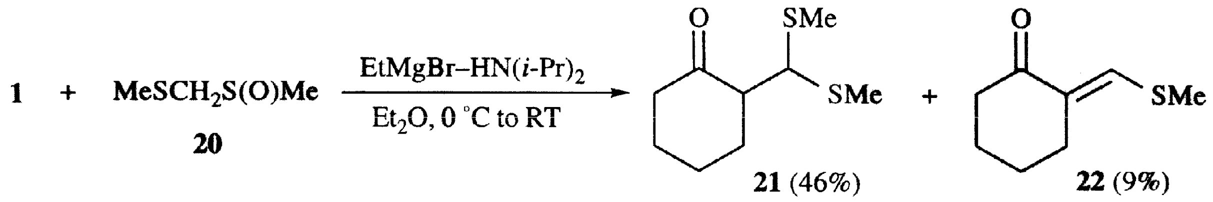
sulfenylalkylated ketone **8** was obtained in an acceptable yield. In order to examine the generality of the present procedure, reactions using ranges of sulfoxides and enamines under the above-mentioned conditions were carried out. The results obtained are summarized in Table 1, which indicates that several sulfoxides, including a cyclic sulfoxide such as tetrahydrothiophene 1-oxide (**6**), gave similar results (Entries 2–5), and that an enamine derived from propanal **16**, also smoothly underwent the reaction with **3** and **5** to afford the corresponding α-sulfenylalkylated aldehydes **17** and **18** in reasonable yields (Entries 8 and 9, respectively). Each of these products could be isolated by preparative TLC on silica gel in a pure form. It should be noted that the attempted reaction of **3** with isopropyl phenyl sulfoxide did not give the expected α-sulfenylalkylated ketone and that no detectable amount of **8** was observed in the reaction mixture of 1-(trimethylsiloxy)cyclohexene with **3**.

The pathway depicted in Scheme 2, which involves the nucleophilic attack of an enamine on the sulfur-stabilized carbonium ion intermediate **19**, is proposed for the formation of the α-sulfenylated ketones.

$$\mathbf{3\text{–}7} \xrightarrow{i\text{-}Pr_2NMgX} \underset{\mathbf{19}}{\left[R^1CH{=}\overset{+}{S}R^2 \longleftrightarrow R^1\overset{+}{C}H{-}SR^2\right]} \xrightarrow{\mathbf{1, 2, 14}\text{, or }\mathbf{16}} \xrightarrow{H_3O^+} \mathbf{8\text{–}13, 15, 17}\text{, or }\mathbf{18}$$

Scheme 2

Subsequently, we investigated the possibility of an application of the present procedure to α-[bis(methylthio)]methylation with methyl (methylthio)methyl sulfoxide (**20**), and found that treatment of the enamine **1** with **20** in the presence of the magnesium amide under conditions similar to those described above afforded 2-bis(methylthio)methylcyclohexanone (**21**)[8e] in moderate yield, along with a small quantity of 2-(*E*)-(methylthiomethylene)cyclohexanone (**22**),[9] arising from a loss of methanethiol from **21**, as shown in Scheme 2.[8] The *E* geometry of **22** was confirmed by a comparison of its spectral data (IR and ^{1}H NMR) with those previously reported by Ila and Junjappa.[9]



Scheme 3

It can thus be seen that the present magnesium amide-induced reaction between enamines and sulfoxides allows general access to α-(α-sulfenyl)alkylated carbonyl compounds. Although the yields of the products were not very high, the method has advantages of simple manipulations as well as readily available starting materials. It is also possible that the α-bis(alkylthio)alkylation could generally be achieved by this method.

EXPERIMENTAL

The mps were recorded with a Laboratory Devices MEL-TEMP II melting point apparatus and are uncorrected. The IR spectra were determined with a Perkin-Elmer 1600 Series FT IR spectrometer. The ^{1}H (operating at 270 MHz) and ^{13}C (operating at 67.8 Hz) NMR spectra were obtained using $SiMe_4$ as the internal reference with a JEOL JNM-GX270 FT NMR spectrometer in $CDCl_3$. The coupling constants (J) are given in Hz. Low-resolution mass spectra were recorded on a JEOL AUTOMASS 20 spectrometer (Centre for Cooperative Research and Development, this University). Thin layer chromatography (TLC) was carried out on Merck Kieselgel 60 PF_{254}. All of the solvents used were dried over appropriate drying agents and distilled under argon prior to use. 3-Pyrrolidino-2-pentene (**14**)[10] and 1-morpholino-1-propene (**16**)[11] were prepared according to the appropriate reported procedures. All other chemicals except for **14** and **16** were obtained commercially, and purified by distillation prior to use.

2-(Phenylthiomethyl)cyclohexanone 8.[1c] The following preparation of **8** illustrates the general procedure for the α-sulfenylalkylation of enamines. To a stirred solution of EtMgBr (3.0 mmol) in Et_2O (4.5 ml) at 0 °C was added i-Pr_2NH (0.30 g, 3.0 mmol). The mixture was stirred for 1h at the same temperature and then at room temperature for 15 min. The resulting turbid solution was cooled to 0 °C and treated successively with the enamine **1** (0.15 g, 1.0 mmol) and the sulfoxide **3** (0.14 g, 1.0 mmol). The resulting reaction mixture was allowed to warm to room temperature, and stirring was continued overnight, after which time it was quenched with saturated aqueous NH_4Cl and extracted with Et_2O (3 × 20 ml). The combined extracts were washed with brine and dried ($MgSO_4$). After evaporation of the solvent, the residue was purified by preparative TLC on silica gel to afford **8** (0.16 g, 76%) as a pale-yellow oil: R_f 0.63 (1:3 EtOAc–hexane); ν_{max} (neat)/cm^{-1} 1710; δ_H 1.35–1.7 (4H, m), 1.85–1.9 (1H, m), 2.0–2.1 (1H, m), 2.35–2.6 (3H, m), 2.73 (1H, dd, J 13.2 and 3.2), 3.48 (1H, dd, J 13.2 and 4.9), 7.15–7.35 (5H, m); δ_C 25.0, 27.8, 33.4, 33.9, 42.0, 50.4, 125.9, 128.9, 129.0, 131.9, 211.2.

2-(Methylthiomethyl)cyclohexanone 9:[1c,e] R_f 0.39 (1:5 EtOAc–hexane); ν_{max} (neat)/cm^{-1} 1708; δ_H 1.35-1.9 (6H, m), 2.10 (3H, s), 2.3–2.55 (4H, m), 2.97 (1H, dd, J 13.1 and 5.1).

2-[α-(Benzylthio)benzyl]cyclohexanone 10: a mixture of diastereomers (*ca.* 7:3); R_f 0.49 (1:5 EtOAc–hexane) (Found: C, 77.55; H, 7.37; S, 10.24. $C_{20}H_{22}OS$ requires C, 77.38; H, 7.14; S, 10.33); ν_{max} (neat)/cm^{-1} 1712; δ_H 1.25–1.95 (6H, m), 2.15–2.35 (2H, m), 2.7–2.8 (1H, m), 3.4–3.7 (2H, m), 4.13 (0.7H, d, *J* 8.7), 4.26 (0.3H, d, *J* 1.3 Hz), 7.15–7.35 (10H, m); *m/z* 310 (M+, 0.60%), 219 (19), 121 (25), 91 (100).

2-(2-Tetrahydrothienyl)cyclohexanone 11: a mixture of diastereomers (*ca.* 8:2); R_f 0.63 (1:5 EtOAc–hexane) (Found: C, 65.28; H, 8.68; S, 17.29. $C_{10}H_{16}OS$ requires C, 65.17; H, 8.75; S, 17.40); ν_{max} (neat)/cm^{-1} 1707; δ_H 1.35–2.6 (13H, m), 2.7–2.95 (2H, m), 3.52 (0.2H, q, *J* 7.7), 3.64 (0.8H, q, *J* 7.7); *m/z* 184 (M+, 60%), 87 (100).

2-(1-Phenylthioethyl)cyclohexanone 12:[1b,f] a mixture of diastereomers (*ca.* 1:1); R_f 0.15 (1:40 EtOAc–hexane); identified by a comparison of its IR and ^{1}H NMR data with those reported in ref. 1f.

2-(Phenylthiomethyl)cyclopentanone 13:[1a,c,f] R_f 0.50 (1:3 EtOAc–hexane); identified by a comparison of its IR and ^{1}H NMR data with those reported in ref. 1f.

2-Methyl-1-phenylthio-3-pentanone 15: R_f 0.66 (1:3 EtOAc–hexane) (Found: C, 69.48; H, 7.56; S, 15.13. $C_{12}H_{16}OS$ requires C, 69.19; H, 7.74; S, 15.39); ν_{max} (neat)/cm^{-1} 1713; δ_H 1.04 (3H, t, *J* 7.3), 1.19 (3H, d, *J* 6.9), 2.3–2.6 (2H, m), 2.7–2.95 (2H, m), 3.24 (1H, dd, *J* 12.9 and 6.9), 7.1–7.4 (5H, m); δ_C 7.5, 16.7, 35.0, 36.5, 45.5, 126.2, 128.9, 129.6, 132.7, 213.1; *m/z* 208 (M+, 80%), 123 (92), 110 (100).

2-Methyl-3-(phenylthio)propanal 17: R_f 0.67 (1:3 EtOAc–hexane) (Found: C, 66.93; H, 6.65; S, 17.55. $C_{10}H_{12}OS$ requires C, 66.63; H, 6.71; S, 17.79); ν_{max} (neat)/cm^{-1} 1723; δ_H 1.16 (3H, d, *J* 6.9 Hz), 2.4–2.65 (1H, m), 2.85 (1H, dd, *J* 13.5 and 7.1), 3.23 (1H, dd, *J* 13.5 and 6.4), 7.1–7.5 (5H, m), 9.61 (1H, s); *m/z* 180 (M+, 11%), and 110 (100).

3-Benzylthio-2-methyl-3-phenylpropanal 18: a mixture of diastereomers (ca. 1:1); R_f 0.47 (1:7 EtOAc-hexane) (Found: C, 75.45; H, 6.62; S, 11.64. $C_{17}H_{18}OS$ requires C,75.51; H, 6.71; S, 11.86); ν_{max} (neat)/cm^{-1} 1723; δ_H 0.87 (1.5H, d, *J* 6.9), 1.14 (1.5H, d, *J* 6.9), 2.6-2.85 (1H, m), 3.41 and 3.42 (combined 1H, 2d, *J* 13.4 each), 3.56 and 3.57 (combined 1H, 2d, *J* 13.4 each), 3.75 (0.5H, d, *J* 10.2), 4.00 (0.5H, d, *J* 6.9), 7.1–7.5 (10H, m), 9.50 (0.5 H, d, *J* 1.8), 9.56 (0.5H, d, *J* 3.3); *m/z* 270 (M+, 0.45), 213 (2.6), 145 (7.4), 118 (54), 91 (100).

2-Bis(methylthio)methylcyclohexanone 21:[8e] R_f 0.59 (1:3 EtOAc–hexane); identified by a comparison of its IR and ^{1}H NMR data with those reported in ref. 8e.

(*E*)-2-Methylthiomethylenecyclohexanone 22:[9] 0.40 (1:3 EtOAc–hexane); identified by a comparison of its IR and ^{1}H NMR data with those reported in ref. 9.

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