Reinheckel Protocol Revisited: Synthesis of (*E*)-α,β-Unsaturated Sulfoxides

Giovanni Signore, Simona Samaritani, Corrado Malanga, Rita Menicagli*

Dipartimento di Chimica e Chimica Industriale, Università di Pisa, Via Risorgimento 35, 56126 Pisa, Italy
Fax +39(050)2219260; E-mail: rime@dcci.unipi.it

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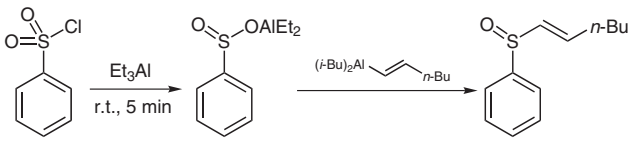
Abstract: A new synthetic approach to aryl and alkyl α,β-unsaturated sulfoxides is reported. The reaction has been optimized with respect to solvent, temperature, and ratio of reagents. The described procedure allows the synthesis of the title compounds in good yields (71–82%) starting from readily available reagents, in a cost-effective procedure.

Key words: sulfoxides, organometallic reagents, alk-1-enyl alanes, aluminum, Reinheckel reaction

Alkenyl sulfoxides are useful intermediates in organic synthesis.[1] Despite the interest in this class of compounds, their preparation is rather complicated, and usually requires the use of multi-step procedures, or of expensive reagents. Among the various approaches to α,β-unsaturated sulfoxides, which have been extensively reviewed,[2] the most general ones are: oxidation of the corresponding sulfides,[3] condensation starting from carbonyl compounds,[4] hydrogenation of alkynyl sulfoxides employing organozirconium derivatives,[5] and reaction of alkyl sulfinates with Grignard reagents.[6] Symmetrical alanes were used in the 1960s by Reinheckel,[7] who synthesized many arylalkyl and diaryl sulfoxides using aluminum sulfinates. On the basis of those reports we examined the possibility of using dialkyl alkenyl alanes in the second step of this approach (Scheme 1). In a preliminary experiment the aluminum sulfinate was reacted with (*E*)-hex-1-enyldiisobutylaluminum at room temperature.



Scheme 1

As shown in Table 1, entry 1, a 35% yield was obtained after a reaction time of five hours, however, prolonging the reaction time to 15 hours and heating at reflux did not increase the yield. In order to increase the yield, the ratio between the alane and the sulfinate was increased up to 1.5:1. When the reaction was performed at room temperature the yield was once again 37% (Table 1, entry 2). A subsequent reaction was carried out at reflux (Table 1, entry 3) and the yield increased to 50%. Considering the solvent has often a remarkable effect on the outcome of the reactions, different solvents were tried in order to increase the yield. Upon formation of the aluminum sulfinate, dichloromethane was removed and replaced by hexane. After the addition of the alkenyl alane, the reaction mixture was refluxed and the unsaturated sulfoxide was obtained in 72% yield (Table 1, entry 4).

Considering the effect of the temperature on the reaction outcome, we performed the reaction with isooctane as the solvent; there was not a trace of products detected, due to the thermal decomposition of the organoalane. As shown in Table 1, entry 6, when coordinating THF was used, no trace of the desired sulfoxide was detected even under forcing conditions (60 hours at reflux). These data suggested that the Lewis acidity of the organometallic reagent promoted the formation of the product. It was thus interesting to verify if the addition of a Lewis acid, such as diethylaluminum chloride, could enhance the yield of the sulfoxide, avoiding the addition of the extra half-equivalent of alkenyl alane.

When the reaction was carried out with a stoichiometric amount of dialkyl alkenyl alane after the addition of increased amounts (0.5–2 equivalents) of diethylaluminum chloride, the yield did not exceed 50% (Table 1, entries 7–9).

Table 1 Optimization of the Reaction Conditions

Entry	Solvent	Temperature (°C)	Yield (%)
1[a]	CH_2Cl_2–hexane, 1:1	25	35
2[b]	CH_2Cl_2–hexane, 1:1	25	37
3[a]	CH_2Cl_2–hexane, 1:1	40	50
4[b]	Hexane	68	72
5[a]	Isooctane	100	0
6[b]	THF	68	0
7[a,c]	Hexane	68	50
8[a,d]	Hexane	68	50
9[a,e]	Hexane	68	50

[a] Ratio $PhSO_2Cl$/diisobutyl(hex-1-enyl)alane, 1:1.
[b] Ratio $PhSO_2Cl$/diisobutyl(hex-1-enyl)alane, 1:1.5.
[c] Ratio $Et_2AlCl/PhSO_2Cl$, 0.5:1.
[d] Ratio $Et_2AlCl/PhSO_2Cl$, 1:1.
[e] Ratio $Et_2AlCl/PhSO_2Cl$, 2:1.

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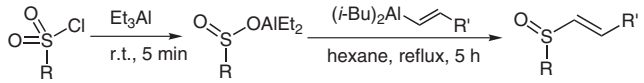
In order to verify the applicability of the method, a range of alkenyl alanes and sulfonyl chlorides were employed using the same protocol described in Table 1, entry 4 (Scheme 2).



Scheme 2

The results reported in Table 2 indicate that the presence of only one substituent β to the alkenyl moiety does not appreciably affect the reaction time and yield (Table 2, entries 1–3). On the contrary, when (*E*)-diisobutyl(hex-3-en-3-yl)alane was used, the reaction failed.

Table 2 Synthesis of α,β-Unsaturated Sulfoxides

Entry[a]	R	R′	Yield (%)[b]
1	Ph	*n*-Hex	71
2	Ph	c-Hex	75
3	Ph	*t*-Bu	71
4	*p*-MeC_6H_4	*n*-Bu	82
5	Me	*n*-Bu	75

[a] Ratio sulfonyl chloride/diisobutyl(alk-1-enyl)alane, 1.5:1, hexane, 68 °C.
[b] Calculated for the isolated, chemically pure product after 5 h.

It must be underlined that the protocol described allows the synthesis of (*E*)-methyl hex-1-enyl sulfoxide, which was previously not possible under the experimental conditions reported by Reinheckel.[7b]

Noteworthy, no trace of the isobutyl sulfoxide was detected in the reaction mixtures. Considering the interest in acetylenic sulfoxides, the same protocol was also applied to the readily available alkynyl alanes (Table 2, entry 7), but no trace of the desired product was obtained, and the use of drastic conditions afforded only small amounts (5–10%) of isobutyl phenyl sulfoxide. Interestingly, the more reactive corresponding acetylenic Grignard reagent failed to afford the desired product.

In conclusion, our procedure extends the scope of the Reinheckel protocol, previously limited to the synthesis of diaryl and aryl alkyl sulfoxides. We prepared the title compounds by the Reinheckel protocol which was for the first time applied to unsymmetrical alanes, and at the same time provided an efficient access to α,β-unsaturated sulfoxides completely free of the isobutyl sulfoxide. This simple procedure can be easily scaled up and can thus provide a convenient access to this class of compounds.

All the reactions were performed in dry apparatus under an inert atmosphere (N_2). Solvents were dried and reagents purified by standard procedures.[8] DIBAL-H was prepared from Al(*i*-Bu)$_3$. $AlEt_3$ (Schering©) was distilled (bp 51 °C/0.1 mmHg). GLC analyses were performed on a Perkin-Elmer 8500 instrument [ZB1 column (15 m × 0.25 mm), film 0.25 μm] equipped with a flame ionization detector and a split-splitless injector, with He as the carrier gas. TLC analyses were performed on silica gel 60 plates (Fluka) and chromatographic purifications were carried out with silica gel 60 (Fluka, 230–440 mesh) with EtOAc as the eluent. ^1H and ^{13}C NMR (200 and 50 MHz, respectively) spectra were recorded on a Varian Gemini 200 spectrometer; all NMR data were obtained using $CDCl_3$ solutions. TMS was used as the internal reference for ^1H NMR, while ^{13}C NMR peaks were referenced to $CDCl_3$. MS were taken on an 5980 Hewlett-Packard GC instrument, equipped with an HP-5MS column (30 m × 0.25 mm, film 0.25 μm) interfaced with an Hewlett-Packard 5995A instrument, with He as carrier gas.

Aluminum Sulfinates; General Procedure
A solution of Et_3Al (1 mmol) in CH_2Cl_2 (3 mL) was slowly added at r.t. to a solution of sulfonyl chloride (1 mmol) in CH_2Cl_2 (3 mL). After the exothermic reaction was complete, the mixture was cooled to r.t., stirred for 1 h, and used in the subsequent reaction.

Hydroalumination of Alkynes; General Procedure
DIBAL-H (hexane; 10 mL, 1.5 mmol) was slowly added to a cooled (0 °C) hexane solution (15 mL) of the alkyne (1.6 mmol). The mixture was then refluxed for 5 h.

Unsolvated Dialkyl Alk-1-ynyl Alanes; Typical Procedure[9]
Et_3N (0.075 mmol) and 1-hexyne (1 mmol) in hexane (10 mL) were added to a cooled (0 °C) solution of DIBAL-H (hexane; 10 mL, 1 mmol). After stirring for 2 h at 0 °C the mixture was allowed to warm to r.t. and used without further purification.

Reaction of Aluminium Sulfinates with Organoalanes; General Procedure
Organoalane (1.5 mmol) in hexane (10 mL) was added at r.t. a solution of aluminum sulfinate (1 mmol) in hexane (10 mL). The mixture was refluxed for 5 h, cooled, and passed through a short column (5 cm) of silica gel (EtOAc, 200 mL) in an inert atmosphere to afford the chemically pure sulfoxide.

(*E*)-Phenyl Hex-1-enyl Sulfoxide[10]
Yellow oil.

^1H NMR: δ = 0.89 (t, *J* = 7.2 Hz, 3 H), 1.25–1.50 (m, 4 H), 2.23 (dtd, *J* = 7.0, 6.5, 1.4 Hz, 2 H), 6.23 (dt, *J* = 15.0, 1.4 Hz, 1 H), 6.62 (dt, *J* = 15.0, 7.2 Hz, 1 H), 7.45–7.65 (m, 5 H).

^{13}C NMR: δ = 13.4, 21.7, 29.7, 31.3, 124.0, 128.9, 130.4, 134.5, 141.2, 143.8.

GC-MS: *m*/*z* (%) = 208 ($M^{+\cdot}$, 14), 192 (36), 160 (60), 149 (52) 117 (100), 111 (66) 104 (57) 91 (21), 78 (36).

(*E*)-Phenyl Oct-1-enyl Sulfoxide[11]
Yellow oil.

^1H NMR: δ = 0.87 (t, *J* = 6.6 Hz, 3 H), 1.20–1.60 (m, 8 H), 2.22 (dtd, *J* = 6.6, 7.0, 1.1 Hz, 2 H), 6.23 (dt, *J* = 15.3, 1.5 Hz, 1 H), 6.62 (dt, *J* = 15.3, 6.6 Hz, 1 H), 7.45–7.65 (m, 5 H).

^{13}C NMR: δ = 13.8, 22.3, 27.8, 28.5, 31.3, 31.8, 124.2, 129.0, 130.6, 134.7, 141.3, 144.0.

GC-MS: *m*/*z* (%) = 236 ($M^{+\cdot}$, 10), 219 (28), 188 (47), 149 (18), 117 (96), 110 (50), 91 (27), 78 (31), 77 (23).

(*E*)-Phenyl 3,3-Dimethylbut-1-enyl Sulfoxide[12]
Yellow oil.

^1H NMR: δ = 1.09 (s, 9 H), 6.14 (d, *J* = 15.3 Hz, 1 H), 6.62 (d, *J* = 15.3 Hz, 1 H), 7.45–7.65 (m, 5 H).

^{13}C NMR: δ = 21.8, 25.8, 26.0, 31.5, 127.8, 128.9, 130.1, 138.2, 144.3, 151.4.

GC-MS: *m*/*z* (%) = 208 ($M^{+\cdot}$, 19), 177 (17), 160 (41), 145 (100), 110 (31), 77 (24).

(*E*)-Phenyl 2-Cyclohexylethenyl Sulfoxide[13]
Yellowish oil.

^{1}H NMR: δ = 1.0–1.2 (m, 5 H), 1.5–1.8 (m, 5 H), 2.10 (m, 1 H), 6.10 (dd, *J* = 15.4, 1.1 Hz, 1 H), 6.51 (dd, *J* = 15.4, 6.2 Hz, 1 H), 7.4–7.6 (m, 5 H).

^{13}C NMR: δ = 25.5, 25.7, 31.55, 31.65, 40.25, 124.4, 129.2, 130.7, 132.8, 144.15, 146.4.

GC-MS: *m*/*z* (%) = 234 ($M^{+\cdot}$, 5), 219 (18), 218 (100), 186 (18), 136 (36), 109 (71), 67 (63).

(*E*)-4′-Methylphenyl Hex-1-enyl Sulfoxide[14]
Yellow oil.

^{1}H NMR: δ = 0.88 (t, *J* = 7.0 Hz, 3 H), 1.2–1.5 (m, 4 H), 2.22 (dtd, *J* = 7.0, 6.6, 1.5 Hz, 2 H), 2.40 (s, 3 H), 6.20 (dt, *J* = 15.0, 1.5 Hz, 1 H), 6.59 (dt, *J* = 15.0, 7.0 Hz, 1 H), 7.3–7.5 (m, 4 H).

^{13}C NMR: δ = 14.0, 21.6, 22.3, 30.4, 31.9, 124.8, 130.2, 135.3, 135.3, 141.2, 141.4, 141.5.

GC-MS: *m*/*z* (%) = 222 ($M^{+\cdot}$, 5), 206 (11), 174 (67), 131 (100), 123 (29), 91 (29).

(*E*)-Methyl Hex-1-enyl Sulfoxide[12]
Yellow oil.

^{1}H NMR: δ = 0.91 (t, *J* = 7 Hz, 3 H), 1.25–1.55 (m, 4 H), 2.24 (dtd, *J* = 7.0, 6.4, 1.5 Hz, 2 H), 2.60 (s, 3 H), 6.27 (dt, *J* = 15.0, 1.5 Hz, 1 H), 6.49 (dt, *J* = 15.0, 6.6 Hz, 1 H).

^{13}C NMR: δ = 14.0, 22.4, 30.4, 31.9, 41.0, 134.2, 141.2.

GC-MS: *m*/*z* (%) = 146 ($M^{+\cdot}$, 49), 129 (11), 117 (12), 103 (10), 81 (51), 55 (100), 41 (72).

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References

(1) (a) Westwell, A. D.; Rayner, C. M. In *Organosulfur Chemistry*; Academic Press: New York, **1998**, 198. (b) De Lucchi, O.; Pasquato, L. *Tetrahedron* **1988**, *44*, 6755. (c) Forristal, I.; Rayner, C. M. In *Advances in Sulfur Chemistry*, Vol. 2; JAI Press: New York, **2000**, 155. (d) Posner, G. H.; Asirvatham, E.; Ali, S. F. *J. Chem. Soc., Chem. Commun.* **1985**, 542. (e) Carreno, M. C. *Chem. Rev.* **1995**, *95*, 1717.

(2) (a) Procter, D. J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 335; and references therein. (b) Drabowicz, J.; Kielbasinski, P.; Mikolajczyk, M. In *The Chemistry of Sulphones and Sulphoxides*; Patai, S.; Rappoport, Z.; Stirling, C. J. M., Eds.; John Wiley & Sons: Chichester UK, **1988**, 233.

(3) (a) Baciocchi, E.; Gerini, M. F.; Lapi, A. *J. Org. Chem.* **2004**, *69*, 3586. (b) Russel, G. A.; Ochrymowycz, L. A. *J. Org. Chem.* **1960**, *35*, 2016. (c) Mikolajczyk, M.; Grzejszczak, S.; Midura, W.; Zatorski, A. *Synthesis* **1976**, 396. (d) Craig, D.; Daniels, K.; Marsh, A.; Rainford, D.; Smith, A. M. *Synlett* **1990**, 531. (e) Mikolajczyk, M.; Perlikowska, W. O.; Melanczuk, J.; Crzstau, H. J.; Perraudarcy, A. *Synlett* **1991**, 913.

(4) Mikolajczyk, M.; Perlikowska, W.; Omelanczuk, J.; Cristau, H. J.; Perraud-Darcy, A. *J. Org. Chem.* **1998**, *63*, 9716.

(5) (a) Huang, X.; Duan, D.; Zheng, W. *J. Org. Chem.* **2003**, *68*, 1958. (b) Zhong, P.; Guo, M.-P.; Huang, X. *J. Chem. Res., Synop.* **2000**, 588. (c) Zhong, P.; Huang, X.; Guo, M.-P. *Tetrahedron* **2000**, *56*, 8921. (d) Zhong, P.; Huang, X.; Guo, M.-P. *Synth. Commun.* **2001**, *31*, 615.

(6) (a) Hogg, D. R. In *The Chemistry of Sulfenic Acids and their Derivatives*; Patai, S., Ed.; John Wiley & Sons: Chichester, UK, **1990**, 361. (b) Van den Breok, L. A. G. M.; Delbressine, L. P. C.; Ottenheijm, J. C. J. In *The Chemistry of Sulfenic Acids and their Derivatives*; Patai, S., Ed.; John Wiley & Sons: Chichester, UK, **1990**, 701. (c) Kosugi, H.; Kitaoka, M.; Tagami, K.; Takahashi, A.; Uda, H. *J. Org. Chem.* **1987**, *52*, 1078. (d) Posner, G. H.; Tang, P. W. *J. Org. Chem.* **1978**, *43*, 4131. (e) Cardellicchio, C.; Fiandanese, V.; Naso, F. *J. Org. Chem.* **1992**, *57*, 1718.

(7) (a) Jahnke, D.; Reinheckel, H. *Organomet. Chem. Synth.* **1970**, *1*, 31. (b) Reinheckel, H.; Jahnke, D. *Chem. Ber.* **1966**, *99*, 1718. (c) Reinheckel, H.; Haage, K.; Jahnke, D. *Organomet. Chem. Rev., Sect. A* **1969**, *4*, 47. (d) Janke, D.; Reinheckel, H. Ger Patent 1248656, **1967**; *Chem. Abstr.* **1967**, *66*, 49731. (e) Reinheckel, H.; Jahnke, D. *Abhandlungen der Deutschen Akademie der Wissenschaften zu Berlin Klasse fuer Chemie Geologie und Biologie*; Akademie Verlag: Berlin, **1967**, 67. (f) Reinheckel, H.; Jahnke, D. Gb Patent 1062405, **1967**; *Chem. Abstr.* **1967**, *67*, 473356. (g) Reinheckel, H.; Jahnke, D. Dd Patent 51311, **1967**; *Chem. Abstr.* **1967**, *66*, 104821. (h) Reinheckel, H.; Jahnke, D. Dd Patent 50599, **1966**; *Chem. Abstr.* **1967**, *66*, 75814.

(8) Perrin, D. D.; Armarego, W. L. F.; Perrin, D. R. *Purification of Laboratory Chemicals*; Pergamon: New York, **1983**.

(9) Feuvrie, C.; Blanchet, J.; Bonin, M.; Micouin, L. *Org. Lett.* **2004**, *6*, 2333.

(10) Tsuyoshi, S.; Hanaki, N.; Kuramochi, Y.; Yujiro, I.; Hosoya, K.; Sakai, K. *Tetrahedron* **2002**, *58*, 2533.

(11) Posner, G. H.; Tang, P.-W. *J. Org. Chem.* **1978**, *43*, 4131.

(12) van Steenis, J. H.; van Es, J. J. G. S.; van der Gen, A. *Eur. J. Org. Chem.* **2000**, 2787.

(13) Furuta, K.; Ikeda, Y.; Meguriya, N.; Ikeda, N.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2781.

(14) Huang, X.; Duan, D.; Zheng, W. *J. Org. Chem.* **2003**, *68*, 1958.