JOC Note
pubs.acs.org/joc

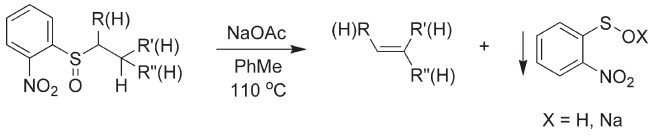
o-Nitrophenyl Sulfoxides: Efficient Precursors for the Mild Preparation of Alkenes

Xiao Lu[†] and Timothy E. Long*[,†,‡]

[†]*Department of Pharmaceutical and Biomedical Sciences and* [‡]*Center for Drug Discovery, University of Georgia, Athens, Georgia 30602-2352*

tlong@rx.uga.edu

Received October 19, 2009

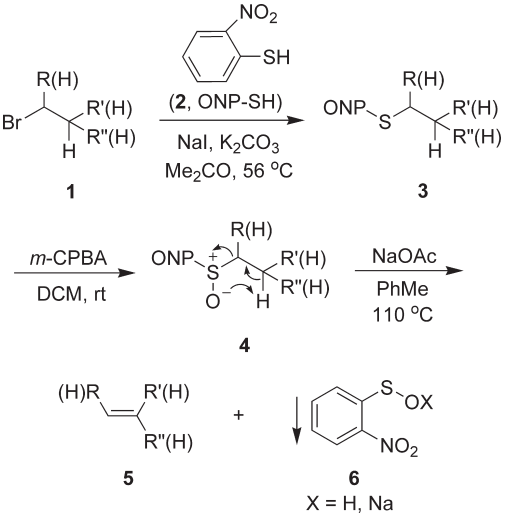


o-Nitrophenyl sulfoxides were found to be efficient synthetic precursors of various alkene types. The elimination occurs in toluene and NaOAc to generate substituted and terminal alkenes. Alkene products were easily obtained in high purity due to the simultaneous precipitation of the *o*-nitrophenyl sulfenic acid byproduct. The methods described have practical applications for the preparation of unsaturated compounds under mild, thermolytic conditions.

A common method to introduce double bonds into molecules is by thermal β-elimination. Although a range of precursors (i.e., amine oxides,[1] 4° ammonium iodides,[2] tosylhydrazones,[3] xanthate esters,[4] selenoxides,[5,6] sulfoxides[7]) may be employed, the reaction can have limited utility for compounds sensitive to harsh temperatures or bases. A recent survey evaluating the efficacy of conversion of sulfoxides to vinylglycines discovered that *o*-nitrophenyl (ONP) analogues underwent synperiplanar β-elimination at temperatures as low as 100 °C.[8] Their unique reactivity gave a reason to explore the practical application of ONP sulfoxides for generating alkenes under mild, thermolytic conditions.

The ONP sulfoxides (**4**) used for the study were synthesized from alkyl halides and *o*-nitrothiophenol (**2**) under conventional alkaline Finkelstein[9] conditions by the general route depicted in Scheme 1. Subsequent oxidation of sulfides **3** with *m*-CPBA afforded sulfoxides **4** in good overall yields. The β-elimination reactions were then performed under toluene reflux with an inorganic base to neutralize the ONP sulfenic acid **6** byproduct. Although not required, the base supplement prevented decomposition of the acid into toluene-soluble impurities thereby yielding the alkenes in high purity based on NMR analysis. K_2CO_3, Na_2CO_3, and $NaHCO_3$ were each found to be effective sulfenic acid scavengers; however, NaOAc was preferred as it did not induce isomerization of the double bond in sensitive molecules.

SCHEME 1. Synthesis of Alkenes from Alkyl Halides via ONP Sulfoxides 4 by Thermal β-Elimination



Upon reflux over NaOAc, the toluene solutions of the sulfoxides faded slowly from bright yellow due to precipitation of sulfenic acid **6**. As thermolysis of this byproduct continued, the solvent turned pale or colorless and the solid NaOAc darkened by the acid being absorbed. After the reactions were complete, the salt impurities were removed by simple vacuum filtration through Celite. Concentration of the filtrate yielded the alkenes in high purity as illustrated by the crude ^{1}H NMR in Figure 1 of ester **5a**.

The practical use of ONP sulfoxides was first evaluated for the synthesis of terminal alkenes **5a** and **5b** (Scheme 2a). Under the thermolytic conditions described, the alkenes were successfully generated with no detectable side products such as deoxygenated sulfoxide (e.g., sulfides **3a** and **3b**; not shown) and isomerized alkene.

Obtained likewise in high yield and purity were substituted alkenes **5c** and **5d** demonstrating the ONP sulfoxides as capable precursors of α,β-unsaturated esters in hindered

(1) (a) Cope, A. C.; Foster, T. T.; Towle, P. H. *J. Am. Chem. Soc.* **1949**, *71*, 3929–3934. (b) DePuy, C. H.; King, R. W. *Chem. Rev.* **1960**, *60*, 431–457.
(2) (a) Hofmann, A. W. *Ber. Dtsch. Chem. Ges.* **1881**, *14*, 494–496. (b) Hofmann, A. W. *Ber. Dtsch. Chem. Ges.* **1881**, *14*, 659–669. (c) Cope, A. C.; Trumbell, E. R. *Org. React.* **1960**, *11*, 317–493.
(3) (a) Bamford, W. R.; Stevens, T. S. *J. Chem. Soc.* **1952**, 4735–4750. (b) Shapiro, R. H..; et al. *Org. React.* **1976**, *23*, 405–507. (c) Adlington, R. M.; Barrett, A. G. M. *Acc. Chem. Res.* **1983**, *16*, 55–59.
(4) (a) Chugaev, L. *Ber. Dtsch. Chem. Ges.* **1899**, *32*, 3332–3335. (b) Nace, H. R. *Org. React.* **1962**, *12*, 57–100.
(5) Grieco, P. A.; Sydney, G.; Mugio, N. *J. Org. Chem.* **1976**, *41*, 1485–1486.
(6) Sharpless, K. B.; Young, M. W. *J. Org. Chem.* **1975**, *40*, 947–949.
(7) (a) Field, L. *Synthesis* **1972**, 101–133. (b) Field, L. *Synthesis* **1978**, 713–740. (c) Trost, B. M.; Salzman, T. N.; Hiroi, K. *J. Am. Chem. Soc.* **1976**, *98*, 4887–4902. (d) Trost, B. M. *Acc. Chem. Res.* **1978**, *11*, 453–461. (e) Trost, B. M. *Chem. Rev.* **1978**, *78*, 363–382.
(8) Patel, S. K.; Long, T. E. *Tetrahedron Lett.* **2009**, *50*, 5067–5070.
(9) Finkelstein, H. *Ber. Dtsch. Chem. Ges.* **1910**, *43*, 1528–1532.

DOI: 10.1021/jo902248z Published on Web 12/04/2009

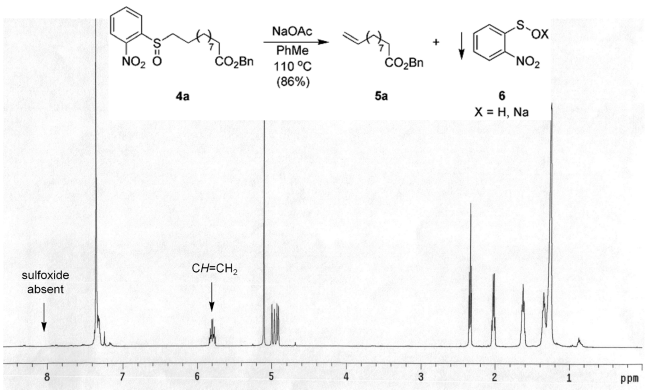
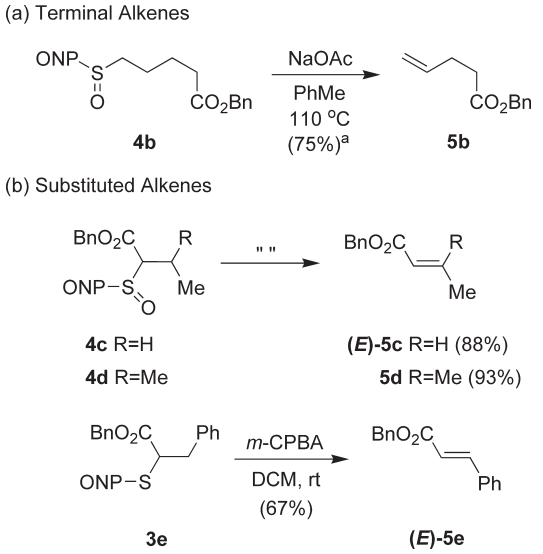


FIGURE 1. ^{1}H NMR of filtered reaction product **5a** prior to chromatographic purification.

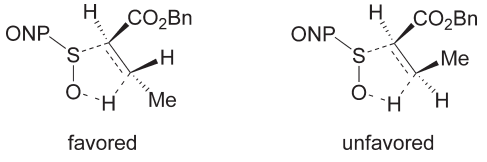
SCHEME 2. Preparation of Terminal and Substituted Alkenes from ONP Sulfoxides



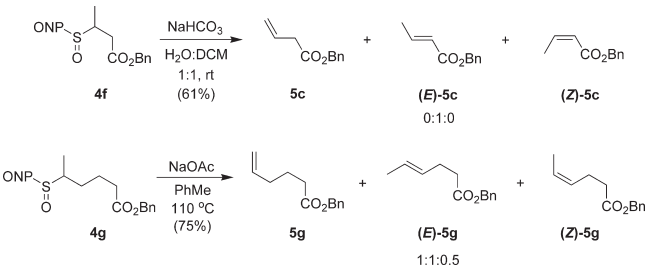
[a]Calculated from isolated crude yield.

substrates (Scheme 2b). In the case of sulfoxide **4c**, only trans product **5c** was observed,[10] and surprisingly, a trace amount of the alkene was isolated during the preceding S-oxidation reaction. This suggested that the activation energy to generate terminal alkenes is higher and the reaction temperature could be reduced for substituted alkene syntheses. Phenyl was shortly after identified as a substituent that prompted expulsion of acid **6** during the oxidation of sulfide **3e**, providing (*E*)-benzyl cinnamate (*E*)-**5e** in situ at rt. In addition, workup with 5% $NaHCO_3$ was found to catalyze the elimination of other branched ONP sulfoxides as

(10) The trans selectivity for ester (*E*)-**5c** was believed to be due to an unfavorable interaction between the benzyl ester and methyl in the transition state of the cis product.



SCHEME 3. Terminal vs. Substituted Alkene Generation



detected by a transient blue tinting of the aqueous layer. This further revealed that the pK_a of the β-hydrogen atom was perhaps more influential on the sulfoxides' ability to convert to alkenes.[11a]

Correspondingly, the eliminations were effected in the absence of heat for esters positioned β to the ONP sulfoxide. The conversion of ester **4f** occurred within minutes under reflux giving ester (*E*)-**5c** exclusively, and when performed at rt using biphasic alkaline conditions, the trans alkene was the only isomer isolated from the organic layer (Scheme 3). The relevance of β-hydrogen acidities was further probed by evaluating directional preferences in ONP sulfoxide **4g**, which possessed negligible differences in the pK_a values. The reaction afforded a mixture of alkenes **5g**, (*E*)-**5g**, and (*Z*)-**5g**, thus revealing a lack of influence in the degree of carbon substitution and the significance of β-proton acidity on product outcome.

Attention was next turned to evaluating the relative efficiency of ONP sulfoxides in comparison with aryl sulfoxide groups (Scheme 4) that were employed in reported preparations[11−14] of alkenes. The study was performed by screening disulfoxides **4h**−**m** under the mild thermolysis conditions established for the ONP sulfoxides. Phenyl sulfoxides[7] which are often used as alkene precursors was found to be an ineffective substrate in disulfoxides **4h** and **4i** as only ONP eliminated products **5h** and **5i** were generated after 18 h of reflux. This was not unexpected as temperatures ≥140 °C are typically needed to effectively catalyze the elimination of phenyl sulfoxides bound to *n*-alkyl chains in molecules.[12] *p*-Tolyl[13] and *p*-chlorophenyl[14] sulfoxides **5j** and **5k**, respectively, were similarly obtained in high yield thereby demonstrating that harsher conditions are also required to prompt their reaction.

A final comparison was performed to establish the effect of nitro group positioning (Scheme 4d). It was discovered with *p*-nitrophenyl sulfoxides that partial thermolysis under toluene reflux can occur. Although a minor amount of bis-eliminated alkene was generated during the reaction,

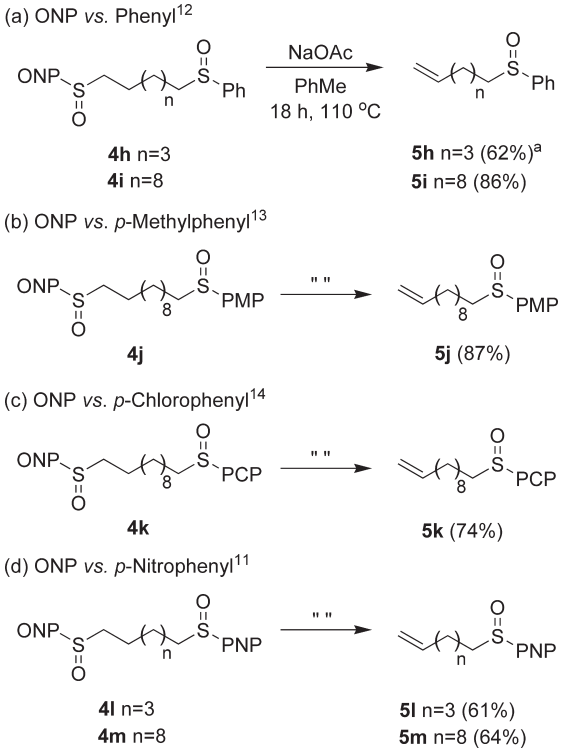
(11) (a) Yoshimura, T.; Tsukurimichi, E.; Iizuka, K.; Mizuno, H.; Isaji, H.; Shimasaki, C. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 1891–1899. (b) Emerson, D. W.; Korniski, T. J. *J. Org. Chem.* **1969**, *34*, 4115–4118.

(12) (a) Catozzi, N.; Edwards, M. G.; Raw, S. A.; Wasnaire, P.; Taylor, R. J. K. *J. Org. Chem.* **2009**, *74*, 8343–8354. (b) Matsuo, J.; Kawano, M.; Takeuchi, K.; Tanaka, H.; Ishibashi, H. *Tetrahedron Lett.* **2009**, *50*, 1917–1919. (c) Simila, S. T. M.; Martin, S. F. *Tetrahedron Lett.* **2008**, *49*, 4501–4504. (d) Ishibashi, H.; Kato, I.; Takeda, Y.; Kogure, M.; Tamura, O. *Chem. Commun.* **2000**, *16*, 1527–1528. (e) Mash, E. A.; Gregg, T. M. *J. Org. Chem.* **1995**, *60*, 6180–6182. (f) Zonjee, J. N.; De Koning, H.; Speckamp, W. *Tetrahedron* **1989**, *45*, 7553–7564.

(13) Cinquini, M.; Cozzi, F.; Raimondi, L.; Restelli, A. *Gazz. Chim. Ital.* **1985**, *115*, 347–350.

(14) (a) Ishibashi, H.; Komatsu, H.; Maruyama, K.; Ikeda, M. *Tetrahedron Lett.* **1985**, *26*, 5791–5794. (b) Ishibashi, H.; Komatsu, H.; Ikeda, M. *J. Chem. Res., Synop.* **1987**, *9*, 296–297.

SCHEME 4. Comparisons of ONP Sulfoxide Efficacy with Reported Aryl Sulfoxide Groups[a]



[a]Calculated from the theoretical yield.

the absence of ONP sulfoxide in the crude product indicated that the ortho position maximizes the effect of the nitro group to promote the β-elimination. Such electronic influences were similarly observed by Sharpless[6] and Sayama[15] in their evaluation of aryl selenoxides. It was therefore reasoned that the enhanced reactivity of ONP sulfoxides is due to an increase in β-proton acidity conferred by the electron-withdrawing nitro group and that ortho positioning may further accelerate the elimination at the congested pyramidal sulfur center to relieve steric strain.

In summary, the results of this study revealed that *o*-nitrophenyl sulfoxides can serve as effective precursors of different alkene types. Their ability to convert under mild reflux and essentially neutral conditions makes them useful substrates for generating unsaturation in molecules. As noted, β-eliminations typically require harsh conditions that may include strong bases and prolong heating at 140 °C or above. Phenyl selenides are often utilized in place of aryl sulfides in thermal or base sensitive molecules; however, the higher cost and toxicity associated with selenoxide use may limit reaction scales. The readily available *o*-nitrothiophenol is price efficient and its bright yellow sulfoxides can be easily visualized on silica gel allowing for their simple purification. Likewise, the ONP chromophore is beneficial as a colorimetric indicator providing an efficient means to conduct and monitor β-elimination reactions.

Experimental Section

Preparation of *o*-Nitrothiophenol (2). To a suspension of *o*-nitrophenyl disulfide (0.805 g, 2.61 mmol) in 20 mL of degassed THF was added PPh_3 (1.03 g, 3.92 mmol), 2-mercaptoethanol (184 μL, 2.61 mmol), and 470 μL of H_2O (26.1 mmol). The solution was stirred at 50 °C for 6 h then cooled to rt, concentrated, redissolved in DCM, washed with brine, dried over Na_2SO_4, and evaporated. The resulting orange oil was subjected to flash chromatography (9:1 hexanes:EtOAc) and *o*-nitrothiophenol[16] (653 mg, 4.21 mmol) was isolated in 80.5% yield from the bright yellow band fractions: mp 40−42 °C.

Preparation of Sulfides 3: General Procedure. To a suspension of NaI (0.4 mmol), K_2CO_3 (1 mmol), and bromide **1** (1 mmol) in dry acetone (10 mL) was added 1.05 mmol equiv of *o*-nitrothiophenol (**2**). The mixture was refluxed with stirring until the reaction was complete. The solution was then filtered, evaporated, redissolved in DCM, washed with brine, dried over Na_2SO_4, and concentrated. The sulfides were purified by flash chromatography in accordance to product R_f values.

Benzyl 11-(2-nitrophenylthio)undecanoate (3a): yellow oil (670 mg, 88%); TLC (SiO_2) R_f 0.48 (6:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (dd, 1H, J = 7.0, 1.5 Hz), 7.52 (dt, 1H, J = 8.0, 1.5 Hz), 7.38 (d, 1H, J = 8.0 Hz), 7.34−7.29 (m, 5H), 7.21 (dt, 1H, J = 8.0, 1.0 Hz), 5.09 (s, 2H), 2.92 (t, 2H, J = 7.5 Hz), 2.33 (t, 2H, J = 7.5 Hz), 1.71 (qnt, 2H, J = 7.5 Hz), 1.62 (qnt, 2H, J = 7.5 Hz), 1.45 (qnt, 2H, J = 7.5 Hz), 1.30−1.26 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.7, 146.0, 138.4, 136.2, 133.5, 128.6, 128.2, 126.7, 126.2, 124.3, 66.1, 34.4, 32.4, 29.4, 29.3, 29.2, 27.9, 25.0; ESI-HRMS calcd for $C_{24}H_{31}NO_4S$ $[M + H]^+$ 430.2052, found 430.2041.

S-Oxidation of Sulfides 3: General Procedure. To a stirring solution of sulfides **3a**−**g** (1 mmol) in DCM (10 mL) was added *m*-CPBA (1.25 mmol equiv) in 5 mL of DCM or in the case of disulfoxides **4h**−**m**, 2.50 equiv of peroxide was used. After 2.5 h, the reactions were quenched with 5% $NaHCO_3$ (20 mL) and extracted twice with DCM. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated. The crude sulfoxides were purified by flash chromatography in accordance to product R_f values.

Benzyl 11-(2-nitrophenylsulfinyl)undecanoate (4a): yellow solid (532 mg, 74%); mp 37−38 °C; TLC (SiO_2) R_f 0.43 (3:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31−8.28 (m, 2H), 7.93 (t, 1H, J = 7.5 Hz), 7.68 (t, 1H, J = 7.5 Hz), 7.32−7.28 (m, 5H), 5.09 (s, 2H), 3.15 (ddd, 1H, J = 13.0, 9.5, 7.0 Hz), 2.72 (ddd, 1H, J = 13.0, 9.5, 4.5 Hz), 2.32 (t, 2H, J = 7.5 Hz), 2.02−1.95 (m, 1H), 1.63−1.58 (qnt, 2H, J = 7.5 Hz), 1.51−1.46 (m, 1H), 1.41−1.35 (m, 1H), 1.30−1.24 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.8, 144.8, 144.0, 136.3, 135.5, 131.4, 128.7, 128.3, 126.9, 125.3, 66.2, 57.2, 34.4, 29.4, 29.4, 29.3, 29.2, 28.6, 25.2, 23.3; ESI-HRMS calcd for $C_{24}H_{32}NO_5S$ $[M + H]^+$ 446.1996, found 446.2004.

***β*-Elimination of ONP Sulfoxides (4): General Procedure.** Sulfoxide **4** (1 mmol equiv) and NaOAc (10 mmol equiv) were heated with stirring in PhMe (10 mL) at 110 °C for 1−18 h. The solution was then cooled to rt and the precipitate removed by vacuum filtration through Celite. The flask was rinsed with toluene then filtered, and the solvent was evaporated to provide alkene **5**. Decolorization of the concentrated product can be achieved by vacuum filtration of the oil through a plug of silica with 3:1 hexanes:EtOAc, or for instances when starting material is still present, the mixture can be reheated in toluene with a fresh 10 equiv of NaOAc until the reaction is complete.

Benzyl undec-10-enoate (5a): colorless oil (28.2 mg, 86%); TLC (SiO_2) R_f 0.40 (20:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34−7.30 (m, 5H), 5.79 (ddt, 1H, AB*M*, J_{BM} = 16.5 Hz, J_{AM} = 10.5, 6.5 Hz), 5.10 (s, 2H), 4.98 (dd, 1H, A*B*M, J_{BM} = 16.5 Hz, J_{AB} = 1.5 Hz), 4.92 (dd, 1H, *A*BM, J_{AM} = 10.5 Hz, J_{AB} = 1.5 Hz), 2.34 (t, 2H, J = 7.5 Hz), 2.02 (m, 2H), 1.63

(15) Sayama, S.; Onami, O. *Tetrahedron Lett.* **2000**, *41*, 5557–5560.

(16) Sopchik, A. E.; Kingsbury, C. A. *J. Chem. Soc., Perkin Trans. 2* **1979**, *8*, 1058–1063.

(qnt, 2H, $J = 7.0$ Hz), 1.36 (qnt, 2H, $J = 7.0$ Hz), 1.28−1.25 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.7, 139.2, 136.2, 128.6, 128.2, 128.2, 114.2, 66.1, 34.4, 33.8, 29.3, 29.2, 29.1, 28.9, 24.0; ESI-HRMS calcd for $C_{18}H_{26}O_2$ $[M + Na]^+$ 297.1825, found 297.1826.

Acknowledgment. Generous financial support of this research was provided by the American Foundation for Pharmaceutical Education. Special thanks are also given to the Department of Pharmaceutical and Biomedical Sciences and Dr. Dennis Phillips for mass spectroscopy analyses.

Supporting Information Available: Experimental procedures and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.