Methyl 2-Pyridinesulfinate. A Convenient Reagent for Sulfinylation–Dehydrosulfinylation

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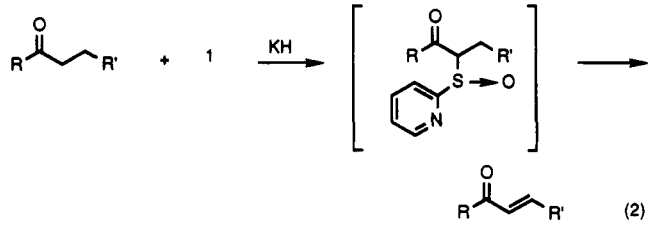
In conjunction with a program involving the development of new strategies for the synthesis of cyclooctyl natural products,[1] our attention was drawn to the problem of introducing double bonds α to a carbonyl group in medium-sized rings. Elimination of the β-keto selenoxide of cyclooctanone and cycloheptanone is reported to fail unless the oxidation of the selenide and the elimination are performed under very exacting conditions.[2] In considering a more satisfactory solution, we wanted to avoid an oxidation step as some of our targets possessed an easily oxidizable functionality.[3]

Our previous experiences with sulfoxide-based eliminations suggested that their elimination in medium-sized rings are less prone to the serious side reactions that plagued the selenoxide elimination.[4] Conjecturing that the acidic byproducts of the elimination were responsible for the complications, we chose to explore sulfinylation[5]–dehydrosulfinylation using methyl 2-pyridinesulfinate (1). Our choice was driven by (1) the internal buffering by the basic pyridine, (2) the propensity of 2-pyridinesulfenic acid to decompose to innocuous byproducts,[6] (3) the prospect for enhancing the rate of elimination by coordination to the pyridine nitrogen,[7] and (4) the potential for more effective removal of sulfur byproducts by metal coordination.[8]

Exposure of 2-mercaptopyridine to NBS in methanol (eq 1) provides a very simple route to the sulfinate 1.

(1)



(2)

Sulfinylation proceeds at room temperature in THF using potassium hydride, whereas elevated temperatures are required using sodium hydride. The intermediate β-keto sulfoxide is directly thermolyzed to the enone (eq 2).[9]

Table I summarizes the examples of this simplified protocol. The stated yield refers to the two-step protocol of converting the saturated ketone into the enone (or phenol).

Several points are noteworthy. A sulfenic acid trap is generally not required. A tetralone is smoothly aromatized to the napthol without complications of further electrophilic substitution by the sulfur elimination products (entry 1). With unsymmetrical ketones, the order of sulfinylation is $CH_2 > CH_3$ (entries 4 and 6) and $CH_2 >$ CH (entries 3 and 11).[10] Even esters can be dehydrogenated by this protocol although the sulfinylation with potassium hydride required refluxing THF (entry 5). The rate differences of sulfinylation between esters and ketones suggest dehydrogenation of ketones in the presence of esters (entry 6). The modest isolated yield in this case is surprising considering the TLC of the crude reaction shows only one spot. High selectivity for the *E*-olefin is observed in all acyclic cases as well as that of cyclododecanone.

The case of the seven-, eight-, and 12-membered ring substrates (entries 7–11) are most interesting. While decomposition of the sulfoxide of cyclooctanone by FVT (in the injection port of a GC) appear to proceed well, its thermolysis in solution leads to an overall 33% yield. Adding excess dihydropyran enhances the overall yield to 66%. Alternatively, addition of metal salts proves efficaceous. Of the various copper and palladium salts explored, copper sulfate and palladium chloride prove most effective, the latter giving a quantitative yield as determined by gas chromatography. For preparative purposes, the use of the copper salt is preferred.

The most stringent test for the efficacy of this procedure is the dehydrogenation of the cyclooctanone thioketal of entry 11. The presence of the thioketal precludes sequences requiring an oxidation step. Selenoxide eliminations fails. Sulfinylation–dehydrosulfinylation with methyl benzenesulfinate proceeds in low yields. On the other hand, the protocol using methyl 2-pyridinesulfinate with cupric sulfate for the elimination gives a very satisfactory 74% yield of the desired product after reacylation of the small amount of alcohol produced during the sequence.

Thus, sulfinylation–dehydrosulfinylation with methyl 2-pyridinesulfinate is a convenient chemo- and regioselective sequence for dehydrogenation of ketones and esters. The applicability for other active methylene compounds has not been explored but would be promising based upon the related sulfenylation–dehydrosulfenylation sequences. The higher electrophilicity of this sulfinylating agent compared to simple arylsulfinates enhances its utility. The role of metal salts in promoting the elimination may be due either to speeding up the elimination or removing sulfenic acid remnants by coordination.

(1) For a review of synthetic approaches, see: Petasis, N. A.; Patane, M. A. *Tetrahedron* **1992**, *48*, 5757.
(2) Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434.
(3) For a seleninylation–dehydroseleninylation approach, see: Barton, D. H. R.; Lester, D. J.; Ley, S. V. *Chem. Commun.* **1978**, 131.
(4) Trost, B. M.; Salzmann, T. N.; Hiroi, K. *J. Am. Chem. Soc.* **1976**, *98*, 4887.
(5) Coates, R. M.; Pigott, H. *Synthesis* **1975**, 319. Monteiro, H. J.; De Souza, J. P. *Tetrahedron Lett.* **1975**, 921.
(6) Walter, W.; Matthias, P. M. *Annalen* **1969**, *727*, 35.
(7) For activation of a pyridyl sulfonate to effect dehydration of an alcohol by $PdCl_2$, see: Hanessian, S.; Kagotani, M.; Komaglow, K. *Heterocycles* **1989**, *28*, 1115.
(8) For a report of elimination of pyridyl sulfoxides, see: Dubs, P.; Stussi, R. *Helv. Chim. Acta* **1978**, *61*, 998.
(9) Cf. Barton, D. H. R.; Sas, W. *Tetrahedron* **1990**, *46*, 3419 and earlier references therein.
(10) For an interesting example of regioselective sulfinylation–dehydrosulfinylation with methyl *p*-toluenesulfinate, see: Trost, B. M.; Latimer, L. H. *J. Org. Chem.* **1978**, *43*, 1031.
(11) Kasturi, T. R.; Arunachalam, T. *Can. J. Chem.* **1968**, *46*, 3625. Byrde, R. J. W.; Downing, D. F.; Woodcock, D. *Biochem. J.* **1959**, *72*, 344.
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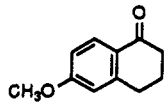
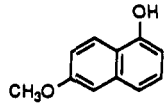
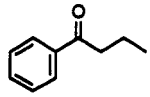
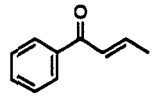
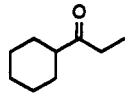
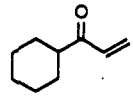
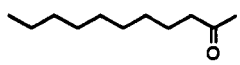
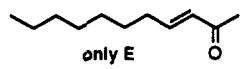
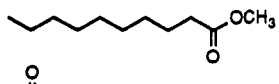
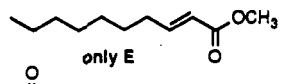
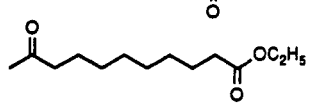
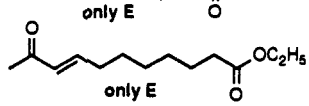
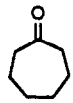
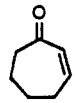
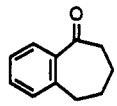
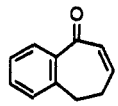
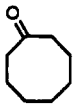
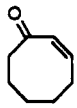
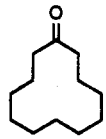
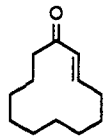
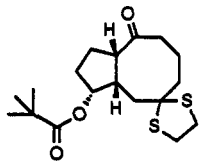
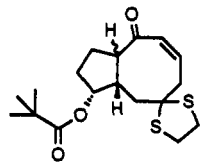
0022-3263/93/1958-1579$04.00/0

Table I. Dehydrogenations with Methyl 2-Pyridinesulfinate[a]

entry	carbonyl compd	olefin	elimination method[b]	yield (%)
1			A	79
2			A	97
3			A	86
4		 only E	A	90
5[c]		 only E	A	57
6		 only E	B	28
7			B	53
8			B	27
9			A B C	33 62 66
10		 94% E	B	95
11[d]			B	74[e]

[a] In each case sulfinylation was performed at 0.2 M in THF at rt with 3 equiv KH and 1.5 equiv of 1 unless otherwise noted. [b] In all cases, elimination was performed at 0.1 M in toluene. Method A: at 110 °C. Method B: 2 equiv of $CuSO_4$ at 110 °C. Method C: 5 equiv of DHP at 110 °C. [c] Sulfinylation performed with 3 equiv of KH, 3 equiv of 1 in THF at 66 °C. [d] Ring fusion isomeric ratio of 4.8:1 *Z*:*E*. [e] Yield after reacylation of small amount of secondary alcohol with $tC_4H_9COCl/(C_2H_5)_3N$.

Experimental Section

Methyl 2-Pyridinesulfinate. NBS (35.4 g, 0.20 mol) was added in one portion to 2-mercaptopyridine (11.1 g, 0.10 mol) dissolved in 500 mL of 1:1 CH_3OH/CH_2Cl_2 at 0 °C. After being stirred for 15 min, the mixture was poured into 300 mL of saturated aqueous $NaHCO_3$ solution. The phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (6 × 200 mL). The combined organic layers were washed with saturated aqueous NaCl, dried ($MgSO_4$), and concentrated in vacuo to an orange oil. The oil was distilled through a 10-cm Vigreux column (bp 90–95 °C (0.06 mmHg)) affording the sulfinate (8.7 g, 55%) as a clear oil, R_f = 0.47 (50% ethyl acetate/hexane), ρ = 1.29 g/mL. IR ($CDCl_3$): δ 3050, 2944, 2251, 1753, 1721(s), 1578, 1564, 1452, 1426, 1134(vs), 1079, 1041 cm^{-1}. ^1H-NMR (200 MHz, $CDCl_3$): δ = 8.72 (ddd, J = 4.73, 1.6, 1.0 Hz, 1 H), 7.9–8.15 (m, 2 H), 7.47 (ddd, J = 6.93, 4.74, 2.36 Hz, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 150.39, 137.98, 126.42, 120.35, 51.25. Anal. Calcd for $C_6H_7O_2SN$: 157.0209. Found: 157.0198.

General Procedure. Sulfinylation. To a suspension of KH (3 equiv, 35% dispersion in oil, washed with pentane under nitrogen) in THF at rt was added the ketone (1 equiv) in sufficient THF to result in a 0.2 M solution. Methyl 2-pyridinesulfinate, (1.1–1.5 equiv) was introduced dropwise via syringe causing the solution to foam and turn red-orange. After the indicated time (typically 5–30 min), the reaction was poured into a sulfate buffer (pH = 2). The aqueous phase was then adjusted to pH 6–7 with solid $NaHCO_3$ and extracted into ethyl acetate. The combined organics layers were washed with saturated aqueous NaCl solution, dried ($MgSO_4$), and concentrated in vacuo to a yellow oil which was thermolyzed without further purification.

Elimination. Method A. A 0.1 M solution of the 2-pyridylsulfinyl ketone in toluene was heated to 110 °C. After being stirred for the indicated time, the mixture was concentrated and submitted directly to chromatography on silica gel or distilled.

Method B. As above except that for 1 equiv of sulfinyl ketone, 2 equiv of powdered cupric sulfate was added. Upon completion

Table II. Experimental Details

compd (mg, mmol)	sulfinylation: sulfinate (wt, mmol)	KH (mg, mmol)	time (min.)	R_f, C_2H_5OAc/hexane (ratio)	elimination: additive (wt, mmol)	time	product mg (yield, %)	R_f, C_2H_5OAc/hexane (ratio)	ref
7-methoxytetralone (176.2, 1.0)	235 mg, 1.5	123, 3.0	5	0.25 (1:1)	none	10 min	45[a] (79)	0.70 (1:1)	11[h]
butyrophenone (148, 1.0)	235 mg, 1.5	123, 3.0	5	0.22, 0.29 (1:1)	none	15 min	142 (97)	0.38 (1:4)	3[c]
cyclohexyl ethyl ketone (40, 0.29)	68 mg, 0.44	35, 0.86	30	0.18 (1:1)	none	1 h	34 (86)	0.83 (1:1)	expl[d]
methyl nonyl ketone (170, 1.0)	235 mg, 1.5	123, 3.0	20	0.32 (1:1)	none	15 min	151 (90)	0.78 (1:1)	expl[d]
methyl decanoate (186.3, 1.0)	2 × (235 mg, 1.5)	123, 3.0	60[e]	0.40, 0.46 (1:1)	none	45 min	158 (57)[f]	0.70 (1:1)	expl[d]
ethyl 10-oxoundecanoate (228, 1.0)	172 mg, 1.1	123, 3.0	5	0.34 (1:1)	$CuSO_4$ (320 mg, 2.0)	30 min	64 (28)	0.62 (1:1)	expl[d]
cycloheptanone (560, 5.0)	1.17 g, 7.5	615, 15	1	0.20 (1:1)	$CuSO_4$ (1.6 g, 10.0)	1 h	290 (53)[g]	0.43 (1:4)	12[h]
benzo[a]suberone (480.6, 3.0)	706 mg, 4.5	369, 9.0	5	0.23 (1:1)	$CuSO_4$ (320 mg, 2.0)	1 h	42[i] (27)	0.50 (1:1)	expl[d]
cyclooctanone (126, 1.0)	235 mg, 1.5	123, 3.0	1	0.25 (1:1)	none	9 h	40 (33)	0.59 (1:1)	12[h]
	235 mg, 1.5	123, 3.0	1		$CuSO_4$ (320 mg, 2.0)	1 h	77 (62)		
	235 mg, 1.5	123, 3.0	1		2,3-dihydropyran (430 mg, 5.0)	1 h	82 (66)		
(500, 3.96)	677 mg, 4.35	388, 4.35	5		$PdCl_2$ (35 mg, 0.2)	20 min	12.3[j] (quant)		
cyclododecanone (200, 1.1)	207 mg, 1.32	135 mg, 3.29	5	0.04 $PdCl_2$	$CuSO_4$ (35.2, 0.22)	100 °C, 20 min	19.0 mg, 0.1 (95)	0.55 (1:4)	4b
1β*H*, 8β*H*, 2-oxo-6-(2,5-dithiaspirocyclopentyl)-9-(trimethylacetoxy)bicyclo[6.3.0]undecane (43, 0.12)	28.3 mg, 0.180	15.5, 0.38	5	0.04, 0.1 (1:4)	$CuSO_4$ (40.3, 0.25)	2 h	26 (61)	0.70 (1:2)	exp[d]

[a] The sulfoxide was prepared on a 1 mmol scale and then divided into three portions (0.33 mmol each) and submitted to the thermolysis in the crude form. [b] Mp 80–82 °C (lit.[11] mp 85 °C). [c] Compared to authentic sample, see ref 3. [d] For characterization, see text in Experimental Section. [e] Reaction performed at 66 °C. [f] brsm = based upon recovered starting material. The yield was determined by NMR spectroscopy since thermolyzing the crude product of sulfinylation gives an inseparable mixture of unsaturated and saturated enoate. To obtain pure enoate, the sulfoxide was purified and thermolyzed to give a 54% yield. [g] Purified by bulb-to-bulb distillation. [h] Compared to authentic sample, see ref 12. [i] The sulfoxide was prepared on a 3 mmol scale and then divided into three portions (1 mmol each) and submitted to the thermolysis in the crude form. [j] The reaction was divided in 40 portions and submitted to thermolysis. The yield of enone determined by GC (tridecane internal standard) was obtained from only one of these portions.

of the reaction, filtering, and concentration, the product was directly chromatographed or distilled.

Method C. As above except 5 equiv of dihydropyran was added. Table II summarizes the experimental details.

Characterization Data. Cyclohexyl Vinyl Ketone. IR ($CDCl_3$): 1693, 1671, 1451, 1405 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.43 (dd, *J* = 17.50, 10.5 Hz, 1 H), 6.25 (dd, *J* = 17.5, 1.4 Hz, 1 H), 5.75 (dd, *J* = 10.5, 1.5 Hz, 1 H), 2.6 (m, 1 H), 1.6–1.8 (bm, 4 H), 1.2–1.4 (bm, 4 H), 0.8–0.9 (bm, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.0, 127.7, 48.15, 28.6, 28.5, 25.8, 25.7, 25.6 (C=O not observed). Anal. Calcd for $C_9H_{14}O$: 138.1045. Found: 138.1036.

(*E*)-Undec-3-en-2-one. IR ($CDCl_3$): 1670, 1624, 1466, 1362 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.8 (dt, *J* = 16.0, 6.8 Hz, 1 H), 6.06 (dt, *J* = 16.0, 1.5 Hz, 1 H), 2.24 (s, 3 H), 2.20 (m, 2 H), 1.45 (m, 2 H), 1.3 (bm, 10 H), 0.9 (m, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.74, 148.65, 131.20, 32.4, 31.7, 29.2, 29.0, 28.0, 26.8, 22.6, 14.0. Anal. Calcd for $C_{11}H_{20}O_2$: 168.1515. Found: 168.1521.

Methyl (*E*)-Dec-2-enoate. IR ($CDCl_3$): 1728, 1658, 1436, 1270, 1197, 1170 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.97 (dt, *J* = 16.0, 7.0 Hz, 1 H), 5.81 (dt, *J* = 15.7, 1.6 Hz, 1 H), 3.72 (s, 3 H), 2.20 (qd, *J* = 7.15, 1.6 Hz, 2 H), 1.45 (m, 2 H), 1.3 (m, 8 H), 0.89 (m, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.2, 150.0, 120.8, 51.5, 32.5, 32.0, 29.1, 28.2, 22.5, 14.0 (one signal overlapped). Anal. Calcd for $C_{11}H_{20}O_2$: 184.1464. Found: 184.1466.

Ethyl (*E*)-10-Oxoundec-8-enoate. IR ($CDCl_3$): 1734, 1698, 1676, 1627, 1253, 1181 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.77 (dt, *J* = 16.0, 7.0 Hz, 1 H), 6.04 (dt, *J* = 16.0, 1.4 Hz, 1 H), 4.10 (q, *J* = 7.2 Hz, 2 H), 2.27 (t, *J* = 7.5 Hz, 2 H), 2.22 (s, 3 H), 2.20 (qd, *J* = 6.4, 1.5 Hz, 2 H), 1.6 (m, 2 H), 1.45 (m, 2 H), 1.32 (m, 4 H), 1.23 (t, *J* = 7.1, Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.7, 173.7, 148.3, 131.3, 60.2, 34.2, 32.3, 28.8, 28.7, 27.8, 26.8, 24.7, 14.2. Anal. Calcd for $C_{13}H_{22}O_3$: 226.1570. Found: 226.1573.

Benzo[*a*]cyclohept-2-en-1-one. IR ($CDCl_3$): 1646, 1621, 1598, 1307 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.74 (dd, *J* = 7.7, 1.4 Hz, 1 H), 7.42 (td, *J* = 7.4, 1.5 Hz, 1 H), 7.30 (td, *J* = 7.5, 1.2 Hz, 1 H), 7.19 (bd, *J* = 7.1 Hz, 1 H), 6.75 (dt, *J* = 12.0, 4.9 Hz, 1 H), 6.28 (dt, *J* = 12.1, 1.9 Hz, 1 H), 3.07 (m, 2 H), 2.6 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.0, 147.0, 139.9, 139.7, 132.4, 132.1, 129.6, 128.9, 126.7, 34.4, 29.7. Anal. Calcd for $C_{11}H_{10}O$: 158.0732. Found: 158.0742.

(1β*H*,8β*H*)-2-Oxo-6,6-(ethylenedithio)-9-(pivaloyloxy)-bicyclo[6.3.0]-3-undecen-3-one (4.8:1 *Z*/*E* Mixture). IR ($CDCl_3$): 1722, 1665, 1479, 1281, 1162 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.45 (dt, *J* = 12.2, 8.7 Hz, 0.2 H, diast. B), 6.31 (dd, *J* = 12.2, 1.4 Hz, 0.2 H, diast. B), 6.20 (bm, 0.8 H, diast. A), 6.04 (d, *J* = 12.3 Hz, 0.8 H, diast. A), 5.24 (t, *J* = 4.3 Hz, 0.8 H, diast. A), 5.11 (t, *J* = 4.3 Hz, 0.2 H, diast. B), 3.52 (m, 0.2 H, diast. B), 3.2–3.4 (m, 2.8 H), 3.1 (m, 2 H), 2.86 (dd, *J* = 13.4, 9.2 Hz, 0.8 H, diast. A), 2.78 (m, 2 H), 2.25–2.5 (m, 4 H), 1.75–1.9 (m, 2 H), 1.68 (bs, 2 H), 1.11 (s, 7.2 H), 0.62 (s, 1.8 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.3, 178.3, 139.4, 137.5, 79.6, 67.9, 51.4, 46.2, 42.2, 39.9, 39.2, 38.8, 38.6, 30.7, 26.9, 26.8, 26.7, 23.0. Anal. Calcd for $C_{18}H_{26}O_3S_2$: 354.1328. Found: 354.1313.

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Supplementary Material Available: ^{13}C NMR spectra for the olefin products of entries 1, 3, 4, 5, 6, 8, and 11 (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.