Sulfonylisoxazolines: Reliable Intermediates for the Preparation of β-Hydroxy Nitriles

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A series of six sulfonylisoxazolines, which were readily prepared via cycloaddition of benzenesulfonylcarbonitrile oxide to alkenes, were cleaved in 86–94% yield to β-hydroxy nitriles by the action of excess 2% Na–Hg^0. The stereochemistry present at the isoxazoline C-4 and C-5 positions was retained during cleavage; since nitrile oxide cycloaddition to alkenes is a stereospecific process, the overall sequence permitted high diastereoselection. Under standard conditions the sulfonylisoxazolines derived from (*E*)- and (*Z*)-stilbene gave a mixture of benzyl alcohol and phenylacetonitrile rather than β-hydroxy nitriles; when the reactions were buffered, however, the β-hydroxy nitriles could be obtained in 88–91% yield. The β-hydroxy nitriles obtained from (*E*)- and (*Z*)-stilbene rapidly underwent a retro-aldol reaction in the presence of aqueous base at room temperature. The β-hydroxy nitrile obtained from 1-methylcyclopentene was epimerized by base and, at or above 80 °C, was cleaved to 6-oxoheptanenitrile.

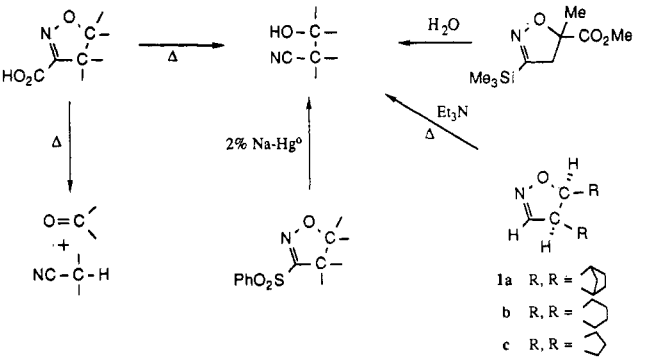
Highly stereoselective procedures for the preparation of β-hydroxy nitriles are potentially useful reactions for the assemblage of complex synthetic targets. From the literature it is clear that a variety of isoxazolines differing in functionalization at the 3-position can serve in the synthesis of β-hydroxy nitriles (Scheme I). The most widely studied method[1] involves thermal decarboxylation of isoxazoline-3-carboxylic acids, obtained by hydrolysis of the corresponding ethyl esters. This method is not universally successful. For example, the isoxazoline-3-carboxylic acid derived from *trans*-stilbene[1c] fails to give any hydroxy nitrile: isoxazoline C_4–C_5 bond rupture occurs, affording benzaldehyde and phenylacetonitrile. In another approach, Huisgen and Christl[2] were able to convert the fulminic acid cycloadduct **1a** to the corresponding β-hydroxy nitrile using triethylamine. We were similarly able to obtain hydroxy nitriles from **1b,c** but only with difficulty: after heating **1c** for 17 h in refluxing triethylamine, the crude products consisted of two-thirds unchanged **1c** and only one-third the corresponding β-hydroxy nitrile. In yet another approach, De Sarlo et al.[3] hydrolyzed a 3-(trimethylsilyl)isoxazoline to the corresponding β-hydroxy nitrile under very mild conditions.

The reaction of 3-(phenylsulfonyl)isoxazolines with 2% Na–Hg^0 also affords β-hydroxy nitriles.[4] The sulfonyl isoxazolines **2–7**, which include cyclic and open-chain examples, gave β-hydroxy nitriles in yields ranging from 86% to 94% (Table I). Standard conditions involved reaction with 5–10 molar equiv of 2% Na–Hg^0 added in two portions to wet THF at 20 °C over 2 h. The β-hydroxy nitriles **10–12** and **15a** were obtained as single diastereomers in agreement with the expected retention of stereochemistry during rupture of the isoxazoline ring. β-Hydroxy nitrile **11**, derived from cyclohexene, was isomeric with a sample of *trans*-2-hydroxycyclohexanecarbonitrile, prepared by a known route.

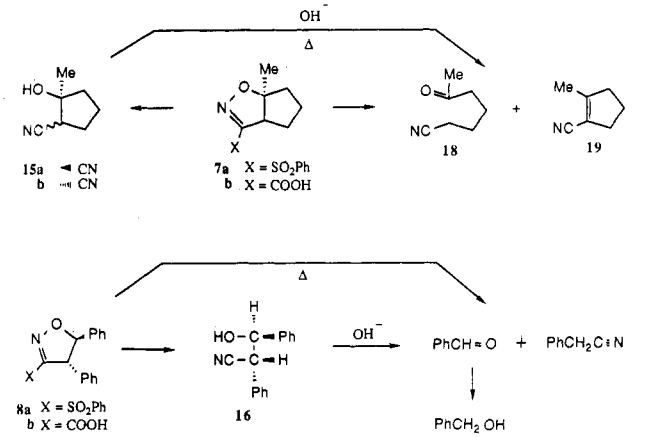
Conversion of the sulfonylisoxazoline **7a** to β-hydroxy nitrile **15a** is especially noteworthy (Scheme II). The corresponding approach involving decarboxylation of the isoxazoline-3-carboxylic acid **7b** was reported[1a] to give only the C_4–C_5 bond cleavage product **18**. Thus, in at least one case a sulfonylisoxazoline is the clearly preferred precursor to a β-hydroxy nitrile. Apparently the C_4–C_5 cleavage reaction always competes with β-hydroxy nitrile formation from decarboxylation of isoxazoline-3-carboxylic acids, although only to a minor extent in most cases.[1a]

When either the sulfonylisoxazoline **8a** or **9** was treated with 2% Na–Hg^0, the products obtained were benzyl alcohol and phenylacetonitrile. These results are strongly reminiscent of Kalvoda and Kaufmann's[1c] observations for the decarboxylation of the corresponding isoxazoline-3-carboxylic acid **8b**. In the present case, however, benzaldehyde must have been reduced by the sodium amalgam.

Scheme I



Scheme II



(1) (a) Kozikowski, A. P.; Adamczyk, M. *J. Org. Chem.* **1983**, *48*, 366. (b) Moersch, G. W.; Wittle, E. L.; Neuklis, W. A. *J. Org. Chem.* **1967**, *32*, 1387 and references cited therein. (c) Kalvoda, J.; Kaufmann, H. *J. Chem. Soc., Chem. Commun.* **1976**, 209.

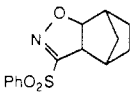
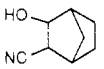
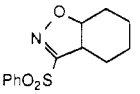
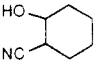
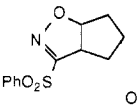
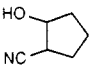
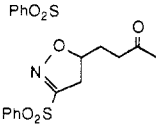
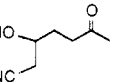
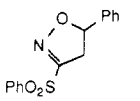
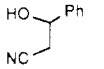
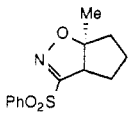
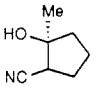
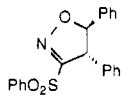
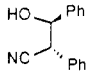
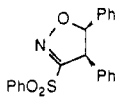
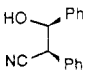
(2) Huisgen, R.; Christl, M. *Chem. Ber.* **1973**, *106*, 3291 and references cited therein.

(3) Brandi, A.; De Sarlo, F.; Guarna, A.; Speroni, G. *Synthesis* **1982**, 719.

(4) (a) For a preliminary account, see: Wade, P. A.; Hinney, H. R. *J. Am. Chem. Soc.* **1979**, *101*, 1319. (b) Wade, P. A.; Pillay, M. K. *J. Org. Chem.* **1981**, *46*, 5425.

0022-3263/87/1952-2973$01.50/0

Table I. β-Hydroxy Nitriles Obtained from Sulfonylisoxazolines

sulfonylisoxazoline		β-hydroxy nitrile		yield[a]
	2		10	91%
	3		11	94%
	4		12	89%
	5		13	86%
	6		14	88%
	7a		15a	93%
	8a		16	0% 88%[b]
	9		17	0% 91%[b]

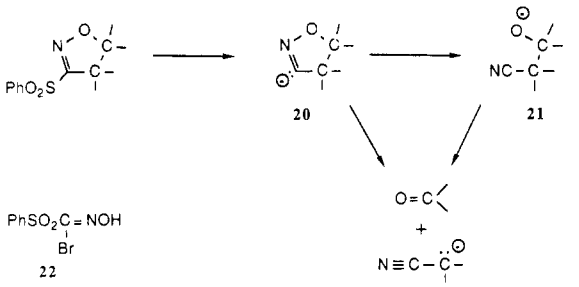
[a] In wet THF, unless otherwise noted. [b] In CH_2Cl_2 layered with aqueous HPO_4^{2-}–$H_2PO_4^-$ buffer.

This was confirmed by the ^1H NMR observation that small amounts of benzaldehyde were present during incomplete reaction and by the demonstration that benzaldehyde could be converted to benzyl alcohol under the reaction conditions.

Repetition of the reaction of sulfonylisoxazoline **8a** with 2% Na–Hg[0] in the presence of aqueous phosphate buffer led to formation of a mixture of β-hydroxy nitrile **16**,[5] benzyl alcohol, and phenylacetonitrile. One problem encountered here was the destruction of the sodium amalgam by the buffer, necessitating a very large excess and periodic replenishment. Another problem was the critical pH dependence of the results: at a pH > 10 largely C_4–C_5 bond cleavage was observed whereas at pH <9 mainly β-hydroxy nitrile was obtained (but with a substantial portion of unreacted starting material). These difficulties were overcome by using methylene chloride in contact with aqueous phosphate buffer as the reaction medium. Under these conditions, an 88% yield of β-hydroxy nitrile **16** could be obtained along with only a trace (<3%) of the C_4–C_5 bond-cleavage products. Similarly, the diastereomeric β-hydroxy nitrile **17**[5] was obtained in 91% yield from sulfonylisoxazoline **9**.

From the above results it seemed highly likely that formation of the C_4–C_5 cleavage products from **8a** and **9** was due to a retro-aldol reaction of the β-hydroxy nitriles **16** and **17**, respectively. This was easily confirmed: THF–5% aqueous sodium hydroxide mixtures containing either **16** or **17** afforded complete conversion to benzaldehyde and phenylacetonitrile in less than 5 min at room temperature.

Scheme III



The β-hydroxy nitrile **15a** also proved to be base-sensitive, although more than one reaction was observed. Heating a mixture of benzene, 5% aqueous sodium hydroxide, and **15a** at reflux gave conversion of the reactant to mainly cyano ketone **18** (40% isolated yield) after 3 h. Also present at the end of the reaction was a small amount of a more volatile product, identified as 2-methyl-1-cyclopentenecarbonitrile (**19**) on the basis of NMR and IR data. During the reaction an additional species, the epimer **15b**, was apparent. After refluxing for 40 min, GC analysis indicated a 42:56:02 mixture of cyano ketone **18**, β-hydroxy nitrile **15** (67:33, **15a**/**15b**), and nitrile **19**, respectively. The epimers **15a** and **15b** could be partially separated by preparative TLC: a fraction enriched in **15b** (27:73, **15a**/**15b**) was obtained and examined by ^1H NMR, IR, and GC. When this mixture was heated with base for 25 min, the amount of **15b** decreased until a 67:33 ratio was attained and a small amount of cyano ketone **18** (ca. 10%) was formed. At room temperature, stirring a benzene solution of pure **15a** in contact with 5% aqueous base for 24 h led to a 65:35 mixture of **15a** and **15b** with no significant formation of **18** or **19**.

The formation of **15b** was shown to occur via a simple deprotonation–reprotonation sequence. Using 5% sodium hydroxide in deuterium oxide, rapid deuterium exchange was observed simultaneous with epimerization. Use of 5% potassium hydroxide in methanol again resulted in epimerization and no ether formation, ruling out an elimination–conjugate addition mechanism.

Discussion and Conclusions

The syn-cyanohydroxylation procedure based on sulfonylisoxazoline intermediates is a versatile synthetic approach to β-hydroxy nitriles. The starting isoxazolines are preparable by any of four published procedures.[4,6,7] One of these,[4b] reaction of bromo oxime **22** and silver nitrate, is particularly effective with alkenes recalcitrant to other means of nitrile oxide cycloaddition. The stereochemistry of the cycloaddition products has proven unambiguous for each case examined: alkene stereochemistry is retained. That ring-opening occurs without loss of stereointegrity is clearly demonstrated by formation of β-hydroxy nitrile **16** from sulfonylisoxazoline **8a** and **17** from **9**, free in each case of contamination by the other diastereomer.

The other[1] major method for syn-cyanohydroxylation, based on decarboxylation of isoxazoline-3-carboxylic acids,

(5) The diastereomers **16** and **17** have previously been reported only as a mixture: (a) Sagasawa, T.; Toyoda, T. *Synth. Commun.* **1979**, *9*, 553. (b) Hamana, H.; Sugasawa, T. *Chem. Lett.* **1982**, 1401.

(6) (a) Wade, P. A.; Amin, N. V.; Yen, H.-K.; Price, D. T.; Huhn, G. F. *J. Org. Chem.* **1984**, *49*, 4595. (b) Wade, P. A.; Yen, H.-K.; Hardinger, S. A.; Pillay, M. K.; Amin, N. V.; Vail, P. D.; Morrow, S. D. *J. Org. Chem.* **1983**, *48*, 1796. (c) Whitney, R. A.; Nicholas, E. S. *Tetrahedron Lett.* **1981**, *22*, 3371.

(7) 3-(Phenylthio)isoxazolines, available from (phenylthio)nitromethane cycloaddition to alkenes following the Mukaiyama procedure, can be oxidized to 3-(phenylsulfonyl)isoxazolines: private communication, D. P. Curran [University of Pittsburgh].

involves an additional ester hydrolysis step and is reported to give lower yield in several cases where a comparison can be made. Relatively high temperatures (>150 °C) are needed for the decarboxylation. However, this approach would be advantageous for construction of complex molecules possessing aldehyde functionality, since 2% Na–Hg[0] reduces aldehyde carbonyl groups. The commercial availability of ethyl chlorooximinoacetate, the necessary precursor to isoxazoline-3-carboxylic acids, is another advantage of the decarboxylation route.

It seems likely that cleavage of sulfonylisoxazolines to β-hydroxy nitriles involves one-electron transfer to the sulfonyl group[8] (Scheme III). Subsequent C–S bond cleavage would afford first the free radical, and hence the anion **20**; alternatively, the anion might be formed directly. The anion **20** has been postulated in the ring cleavage of isoxazoline-3-carboxylic acids[1c] and might also be present in cleavage of 3-unsubstituted-[2] and 3-(trimethylsilyl)-isoxazolines,[3] although direct evidence is lacking in all cases. Rapid ring-opening of this anion has been postulated to afford the open-chain alkoxide **21**.[1c] Those cases of decarboxylation where C_4–C_5 bond cleavage occurs have also been postulated to go through alkoxide **21**; in at least one case the β-hydroxy nitrile itself did not undergo thermal cleavage under reaction conditions.[1c] Another apparently more favored mechanism[1a,c] suggested for C_4–C_5 bond cleavage is a concerted $[{}_\sigma 2_a + {}_\sigma 2_a + {}_\omega 2_s]$ cycloreversion of the carbanion **20**.

In view of the observed instability of β-hydroxy nitriles **15–17** to base, particularly of **15** at elevated temperature, we favor a mechanism for isoxazoline C_4–C_5 bond rupture that involves fragmentation of the alkoxide **21** rather than a synchronous process. Except for isoxazolines derived from stilbene, all of the observed "problem isoxazolines" leading to C_4–C_5 bond rupture have 5,5-disubstituted structures. That may well reflect an alkoxide stability problem: the more basic 3° alkoxides are more prone to cleavage than 1° or 2° alkoxides. Of course, cleavage of the alkoxide must be very fast in the decarboxylation route, since it must occur competitively with protonation. We have observed conversion of the β-hydroxy nitrile **15a** to cyano ketone **18** at 170 °C on the base-treated injection block of a gas chromatograph. This observation is consistent with rapid C–C bond cleavage of the alkoxide. It is also possible that alkoxide **21** is initially produced in an excited vibrational state when formed via the decarboxylation route. The vibrationally excited **21** might be much more highly prone to fragmentation than a ground-state molecule of **21**: indeed, fragmentation might be virtually concerted with the excited-state alkoxide formation.

Experimental Section

General. Gas chromatography (GC) was carried out on a Varian 1420 instrument equipped with a 5% SE-30 preparative column (2 m × 0.64 cm) and a 10% SE-30 analytical column (1 m × 0.32 cm). Thin-layer chromatography (TLC) was carried out on 0.25-mm analytical and 1.00-mm preparative silica gel GF plates (Analtech). NMR spectra were taken in $CDCl_3$ (Me_4Si internal standard) on a JEOL FX-90Q instrument. Infrared (IR) spectra were recorded on a Perkin-Elmer 457 spectrometer. Mass spectra (MS) were recorded on a Finnegan 4023 GC–MS instrument. Procedures for the preparation of sulfonylisoxazolines **4**, **8a**, and **9** have been previously described.[6a,b] Reactions were worked up, unless otherwise stated, by drying the organic layer over anhydrous Na_2SO_4 and concentrating at reduced pressure. Stock pH 7 buffer solution was purchased from Fisher Scientific Company (Catalog No. SO-B-108): the vendor states that 1 L of the solution contains KH_2PO_4 (0.054 mol) reacted with NaOH (0.032 mol). Concentrated buffer solution (pH 7.15) was prepared by mixing 2.0 M NaOH (59 mL) with 2.0 M KH_2PO_4 (100 mL).

Preparation of Bromo Oxime 22. To a stirred ice-cold mixture of sodium acetate (41 g), (phenylsulfonyl)nitromethane (23.32 g, 0.116 mol), and CH_2Cl_2 (400 mL) was added dropwise over 30 min a solution of Br_2 (18.54 g, 0.116 mol) in CH_2Cl_2 (200 mL). After 10 min, the reaction mixture was washed with water, dried, and concentrated to 33.51 g of a pale yellow oil: TLC (CH_2Cl_2–HOAc, 99:1) indicated three products having R_f 0.5, 0.6 (major), and 0.7. NMR indicated a 7:86:7 mixture of non-, mono-, and α,α-dibromo-*N*-nitrosulfones: δ 7.5–8.1 (m, aryl H), 6.79 (s, 1 H, $PhSO_2CHBrNO_2$), and 5.64 (s, 2 H, $PhSO_2CH_2NO_2$).

A cold (−10 °C) solution of the crude bromination product in diethyl ether (350 mL) was treated over 20 min with 0.3 M etheral diazomethane (four 100-mL portions) and after 10 min the resulting solution was *partially* stripped at reduced pressure to remove excess CH_2N_2 (*caution: complete stripping in one preparation led to vigorous decomposition of the nitronic ester*). The residue (50 mL) was taken up in CH_2Cl_2 (200 mL) and the stirred solution was refluxed for 15 min. The solvents were removed at reduced pressure and the resulting oil was treated with CH_2Cl_2 (5 mL) and then hexane (5 mL). This solution was allowed to crystallize[9] at −20 °C overnight. The resulting white solid was recrystallized from CH_2Cl_2–hexane. Depending on the efficiency of crystallization, typical runs gave from 6.6 to 9.4 g (22–31% yield) of bromo oxime **22**: mp 101–102 °C; IR (KBr) 3330 (br, OH), 1610, 1580 (C=C, C=N), 1330, and 1160 cm^{-1} (SO_2); NMR δ 9.84 (variable position, s, 1 H) and 7.5–8.1 (m, 5 H).

Anal. Calcd for $C_7H_6BrNO_3S$: C, 31.83; H, 2.29; N, 5.30. Found: C, 32.10; H, 2.30; N, 5.59.

Preparation of Sulfonylisoxazoline 5. A solution containing bromo oxime **22** (1.32 g, 5.0 mmol), 5-hexen-2-one (8 mL), and CH_2Cl_2 (8 mL) was added dropwise over 2 h to a well-stirred mixture of 1 M aqueous Na_2CO_3 (8 mL) and 5-hexen-2-one (8 mL). Water (20 mL) and CH_2Cl_2 (50 mL) were added and the layers separated. The organic layer was washed with water, dried, and concentrated to an oil. Column chromatography (CH_2Cl_2 elution) gave 1.14 g (81% yield) of pure **5**. Distillation (Kugelrohr) gave the analytical sample: bp 160–170 °C (0.02 mm); IR (film) 1710 (C=O), 1330, and 1160 cm^{-1} (SO_2); NMR δ 7.4–8.1 (m, 5 H), 4.5–5.1 (m, 1 H), 3.38 (dd, 1 H, J = 11, 18 Hz), 2.95 (dd, 1 H, J = 9, 18 Hz), 2.53 (t, 2 H, J = 7 Hz), 2.11 (s, 3 H), and 1.6–2.2 (m, 2 H).

Anal. Calcd for $C_{13}H_{15}NO_4S$: C, 55.51; H, 5.38; N, 4.98. Found: C, 55.22; H, 5.42; N, 5.03.

Preparation of Sulfonylisoxazoline 2. **2** was prepared from norbornylene (0.71 g, 7.5 mmol) in 90% yield similarly to **5**. Recrystallization from 95% ethanol gave the analytical sample: mp 84–85 °C; IR (film) 1300 and 1160 cm^{-1} (SO_2); NMR δ 7.4–8.1 (m, 5 H), 4.70 (d, 1 H, J = 8.5 Hz), 3.42 (d, 1 H, J = 8.5 Hz), 2.75 (br s, 1 H), 2.58 (br s, 1 H), and 0.9–1.8 (m, 6 H).

Anal. Calcd for $C_{14}H_{15}NO_3S$: C, 60.63; H, 5.45; N, 5.05. Found: C, 60.32; H, 5.44; N, 4.90.

Preparation of Sulfonylisoxazoline 3. **3** was prepared from cyclohexene in 76% yield similarly to **5**. Distillation (Kugelrohr) gave the analytical sample: bp 135–145 °C (0.08 mm); IR (film) 1320 and 1160 cm^{-1} (SO_2); NMR δ 7.5–8.1 (m, 5 H), 4.4–4.8 (m, 1 H), 3.42 (br dd, 1 H), and 1.1–2.3 (m, 8 H).

Anal. Calcd for $C_{13}H_{15}NO_3S$: C, 58.86; H, 5.70; N, 5.28. Found: C, 58.83; H, 5.74; N, 5.41.

Preparation of Sulfonylisoxazoline 6. **6** was prepared from styrene (8.4 g, 80 mmol) in 82% yield similarly to **5**. Recrystallization from 95% ethanol gave the analytical sample:[10] mp 83.5–84 °C; IR (KBr) 1330 and 1160 cm^{-1} (SO_2); NMR δ 7.5–8.1 (m, 5 H), 7.32 (m, 5 H), 5.78 (dd, 1 H, J = 9, 10.5 Hz), 3.72 (dd, 1 H, J = 10.5, 17 Hz), 3.32 (dd, 1 H, J = 9, 17 Hz).

(8) Sulfone groups are well-known one-electron acceptors, although normally, 6% Na–Hg^0 is needed for desulfonation: (a) Posner, G. H; Brunelle, D. J. *Tetrahedron Lett.* **1973**, 935. (b) Trost, B. M.; Arndt, H. C.; Strege, P. E.; Verhoeven, T. R. *Ibid.* **1976**, 3477. (c) Chang, Y.-H.; Pinnick, H. W. *J. Org. Chem.* **1978**, *43*, 373. Ring cleavage of 3-phenylisoxazolines to 1,3-aminols with 6% Na–Hg^0 has also been observed: Jäger, V.; Buss, V. *Liebigs Ann. Chem.* **1980**, 101.

(9) Attempts to chromatograph impure **22** invariably lead to partial formation of 3,4-bis(phenylsulfonyl)furoxan.

(10) Compound **6** has previously been reported as an oil: ref 6c.

Anal. Calcd for $C_{15}H_{13}NO_3S$: C, 62.72; H, 4.56; N, 4.88. Found: C, 62.97; H, 4.73; N, 4.72.

Preparation of Sulfonylisoxazoline 7a. An 0.3 M etheral diazomethane solution (three 15-mL portions) was added over 10 min to a cold (0–5 °C) solution of (phenylsulfonyl)nitromethane (2.14 g, 10.6 mmol) in CH_2Cl_2 (20 mL). After 10 min of additional stirring, excess diazomethane was removed by *partial* concentration (*caution: there is one report of an explosion involving a concentrated sample of the same nitronic ester present here*[11]). The residue (ca. 20 mL) was diluted with CH_2Cl_2 (30 mL), partially concentrated (to ca. 20 mL), and again diluted with CH_2Cl_2 (30 mL). 1-Methylcyclopentene (6.44 g, 84.8 mmol) and boron trifluoride etherate (2.6 mL) were added and the solution was refluxed for 40 min under Ar. After cooling, the reaction mixture was washed with 5% NaOH (40 mL) followed by water (40 mL), dried, and concentrated to an oil. Column chromatography (hexane–EtOAc, from 98.5:1.5 to 80:20 gradient) gave 1.46 g (52% yield) of **7a**. Distillation (Kugelrohr) gave the analytical sample: bp 160–165 °C (0.05 mm); IR (film) 1340 and 1160 cm^{-1} (SO_2); NMR δ 7.5–8.1 (m, 5 H), 3.50 (dd, 1 H, J = 2, 8.8 Hz), and 1.46 (s) on 1.2–2.5 (m, 9 H total).

Anal. Calcd for $C_{13}H_{15}NO_3S$: C, 58.87; H, 5.66. Found: C, 58.52; H, 5.56.

General Procedure for Cleavage of Sulfonylisoxazolines 2–7. A mixture of sulfonylisoxazoline (2 mmol), THF (15 mL), water (0.5 mL), and freshly prepared 2% Na–Hg[0][12] (6.5 g, 5.7 mmol of Na^0) was stirred for 1 h. More water (0.25 mL) and 2% Na–Hg[0] (3.3 g, 2.9 mmol of Na^0) were added and stirring was continued for an additional 1 h. Methylene chloride (15 mL) and anhydrous Na_2SO_4 were added; the resulting mixture was filtered after 10 min and concentrated. The crude products were purified by vacuum distillation (Kugelrohr).

***exo,exo*-3-Hydroxybicyclo[2.2.1]heptane-2-carbonitrile (10).** The distilled product (>98% pure, GC) was obtained as an oil: bp 90–100 °C (0.025 mm) [lit. bp 110 °C (0.001 mm)]. Spectra were identical with published spectra[2] for **10**.

***cis*-2-Hydroxycyclopentanecarbonitrile (12).** The distilled product (98% pure, GC) was obtained as an oil: bp 95–110 °C (1.9 mm). An analytical sample was obtained by preparative GC; spectra matched those reported in the literature[1a] for **12**.

Anal. Calcd for C_6H_9NO: C, 64.84; H, 8.16; N, 12.60. Found: C, 64.77; H, 8.26; N, 12.59.

***cis*-2-Hydroxycyclohexanecarbonitrile (11).** The distilled product was obtained as an oil: bp 130–140 °C (0.1 mm). It slowly crystallized: mp 32.5–34 °C; IR (melt) 3450 (OH) and 2250 cm^{-1} (CN); NMR δ 3.75 (m, 1 H), 3.03 (m, 1 H), 2.6 (s, 1 H, exchanges with D_2O), 1.3–2.2 (m, 8 H).

Anal. Calcd for $C_7H_{11}NO$: C, 67.17; H, 8.86; N, 11.19. Found: C, 67.37; H, 9.00; N, 11.01.

3-Hydroxy-6-oxoheptanenitrile (13). The distilled product (>98% pure, GC) was obtained as an oil: bp 95–105 °C (0.11 mm); IR (film) 3460 (OH) and 2260 cm^{-1} (CN); NMR δ 4.00 (quin, 1 H, J = 6 Hz), 3.7 (br s, 1 H, exchanges with D_2O), 2.72 (t, J = 7 Hz), on 2.56 (d, J = 6 Hz, 4 H total), 2.22 (s, 3 H), and 1.4–2.2 (m, 2 H).

Anal. Calcd for $C_7H_{11}NO_2$: C, 59.56; H, 7.85; N, 9.74. Found: C, 59.46; H, 7.93; N, 9.92.

3-Hydroxy-3-phenylpropanenitrile (14). The distilled product (>95% pure, GC) was obtained as an oil: bp 140–150 °C (0.12 mm). Spectra were identical with published spectra[13] of **14**.

***cis*-2-Hydroxy-2-methylcyclopentanecarbonitrile (15a).** The distilled product (>96% pure, GC) was obtained as an oil: bp 50–60 °C (0.03 mm); IR (film) 3460 (OH) and 2240 cm^{-1} (CN); NMR δ 2.58 (m, 1 H), 1.97 (s, 1 H, exchanges with D_2O) on 1.5–2.4 (m, 7 H total), and 1.49 (s, 3 H); MS, m/e 125 (M^+), 108 (M^+ – OH).

Several attempts to obtain a satisfactory analytical sample by preparative GC were unsuccessful: Anal. Calcd for $C_7H_{11}NO$: C, 67.17; H, 8.86. Found: C, 66.60; H, 9.02.

***trans*-2-Hydroxycyclohexanecarbonitrile.**[14] A mixture of cyclohexene oxide (1.46 g, 14.9 mmol), $MgSO_4$ (2.94 g, 24.5 mmol), KCN (1.81 g, 23.8 mmol), and water (70 mL) was stirred for 20 h. Water and CH_2Cl_2 were added; the organic layer was separated, washed with water, dried, and concentrated. The residue was distilled (Kugelrohr; bp 75–85 °C [0.05 mm]) to give 1.01 g (54% yield) of a solid: mp 46–47 °C [lit.[14] mp 46–47 °C]; NMR δ 3.60 (m, 1 H), 3.18 (s, 1 H, exchanges with D_2O), 1.2–2.5 (m, 9 H).

Cleavage of Sulfonylisoxazoline 8a: Nonbuffered Conditions. The standard procedure for preparing β-hydroxy nitriles was repeated on **8a** (724 mg, 2 mmol). NMR analysis of the crude product showed none of the β-hydroxy nitrile **16**. Purification by preparative TLC (CH_2Cl_2 elution) gave phenylacetonitrile (139 mg, 60% yield) as the less polar fraction and benzyl alcohol (116 mg, 54% yield) as the more polar fraction. Products were identified on the basis of spectra (NMR, IR and MS) and comparison to authentic samples.

Cleavage of Sulfonylisoxazoline 8a: Buffered Conditions. To a slowly stirred mixture of **8a** (145 mg, 0.4 mmol), CH_2Cl_2 (40 mL), and stock pH 7 buffer solution (9 mL) was added in one portion 2.5% Na–Hg[0][12] (12.6 g, 13.7 mmol of Na^0). During the next 30 min the pH of the water layer was tested at 1–2-min intervals; concentrated buffer solution was added at such a rate (typically 10–12 drops every 3 min after a more rapid initial rate) so as to maintain pH <10. More 2.5% Na–Hg[0] (6.5 g, 7.1 mmol of Na^0) was added, and again pH <10 was maintained by adding concentrated buffer solution (total volume ca. 10 mL). After 30 min the mixture was decanted from spent amalgam; CH_2Cl_2 (two 10-mL portions) was added and decanted from the amalgam. The combined decanted layers were separated and the organic layer was dried and concentrated. The residue (91.7 mg) was purified by preparative TLC (CH_2Cl_2) to give starting **8a** (6.8 mg, 5% recovery) and pure **16** (78 mg, 88% yield) as a solid: mp 104–105 °C; IR (KBr) 3430 (OH) and 2250 cm^{-1} (CN); NMR δ 7.28 (m, 10 H), 4.96 (d, 1 H, J = 5.7 Hz), 4.04 (d, 1 H, J = 5.7 Hz), and 2.84 (s, 1 H, OH); MS, m/e 223 (M^+), 206 (M^+ – OH), 107 (base, $PhCHOH^+$).

Anal. Calcd for $C_{15}H_{13}NO$: C, 80.72; H, 5.83. Found: C, 80.30; H, 5.89.

From an early run using buffered aqueous THF as the reaction media, an NMR spectrum of the crude products indicated a mixture containing benzaldehyde (15%), starting sulfonylisoxazoline **8a** (30%), β-hydroxy nitrile **16** (30%), benzyl alcohol (25%), and phenylacetonitrile.

Cleavage of Sulfonylisoxazoline 9. The procedure employing buffered CH_2Cl_2 developed for the trans isomer, sulfonylisoxazoline **8a**, was repeated using **9** (145 mg, 0.4 mmol). An NMR spectrum of the crude products showed **17**; a trace (<3%) of C_4–C_5 bond cleavage occurred in the reaction. The pure product (81 mg, 91% yield) obtained from preparative TLC was recrystallized from CCl_4–hexane to obtain an analytical sample: mp 91–92 °C; IR (KBr) 3525 (OH) and 2240 cm^{-1} (CN); NMR δ 7.32 (m, 1 H), 5.00 (dd, 1 H, J = 3.3, 6.6 Hz), 4.14 (d, 1 H, J = 6.6 Hz), and 2.35 (d, 1 H, J = 3.3 Hz, OH); MS, m/e 223 (M^+), 206 (M^+ – OH), 107 (base, $PhCHOH^+$).

Base Stability of β-Hydroxy Nitriles 16 and 17. A THF (4 mL) solution of **16** (10 mg) was treated with 5% NaOH (0.16 mL) and the resulting mixture stirred for 5 min. Excess 0.6 N HCl and CH_2Cl_2 were added. The layers were separated and the organic layer was washed with water, dried, and concentrated to give an oil: TLC and NMR indicated complete conversion to a 50:50 mixture of benzaldehyde and phenylacetonitrile.

Compound **17** gave identical results under similar treatment.

Base Stability of β-Hydroxy Nitrile 15a. A mixture of **15a** (97 mg), benzene (5 mL), and aqueous 5% NaOH (5 mL) was heated at reflux for 3 h. GC analysis indicated in order of increasing t_R: **19** (8%), **15a,b** (16%, 61:39 **15a**/**15b**), and **18** (76%). Water and CH_2Cl_2 were added to the reaction and the layers were separated. The organic layer was washed, dried, and concentrated to give the crude product. Preparative TLC (CH_2Cl_2–MeOH, 99:1) gave 38.6 mg of **18** (40% yield) as an oil: NMR and IR spectra were consistent with the literature.[15]

(11) Nordmann, R.; Graff, P.; Maurer, R.; Gahwiler, B. H. *J. Med. Chem.* **1985**, *28*, 1109.

(12) Prepared by the procedure outlined in: Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*; Wiley: New York, 1967; Vol. 1, p 1030.

(13) Kaiser, E. M.; Hauser, C. R. *J. Org. Chem.* **1968**, *33*, 3402.

(14) Mousseron, M.; Winternitz, F.; Joullien, J. *C.R. Acad. Sci.* **1948**, *226*, 91.

(15) Pirkle, W. H.; Adams, P. E. *J. Org. Chem.* **1979**, *44*, 2169.

A sample of **19** was obtained by repeating the reaction for 16 h. Concentration of the organic layer during workup was carried out at atmospheric pressure and the crude product was purified by preparative GC: IR ($CHCl_3$) 1630 (C=C) and 2200 cm^{-1} (CN); NMR 2.3–2.8 (m, 4 H), 1.99 (s) on 1.75–2.2 (m, total 5 H).

The reaction was repeated for 40 min to obtain a 56:42:02 mixture of **15** (67:33 **15a**/**15b**), **18**, and **19**, respectively. Preparative TLC (CH_2Cl_2–MeOH, 99:1) of the crude products gave in low yield a fraction enriched in **15b** (27:73 **15a**/**15b**) as the lower third of the alcohol band: IR (film) 3450 (OH) and 2240 cm^{-1} (CN); NMR δ 1.55 (s, 70%) and 1.49 (s, 30%) on 1.3–2.9 (m). This enriched material was subjected to refluxing benzene–5% aqueous NaOH for 25 min and at that time the isomer ratio was measured by GC: (67:33 **15a**/**15b**).

β-Hydroxy nitrile **15a** (40 mg), benzene (2.5 mL), and aqueous 5% NaOH (2.5 mL) were mixed and stirred at room temperature for 24 h. Workup as in the above procedure gave 30 mg (75% recovery) of an oil which by GC and NMR was a mixture of diastereomers (65:35 **15a**/**15b**); no **19** could be detected and only a trace (<5%) of **18** was apparent.

Registry No. **2**, 70367-26-9; **3**, 108470-80-0; **4**, 108470-81-1; **5**, 70367-30-5; **6**, 70367-29-2; **7a**, 108470-82-2; **8a**, 85355-68-6; **9**, 85355-67-5; **10**, 15166-77-5; **11**, 70367-35-0; *trans*-**11**, 63301-31-5; **12**, 70367-34-9; **13**, 70367-36-1; **14**, 17190-29-3; **15a**, 108470-83-3; **15b**, 108470-86-6; **16**, 71312-66-8; **17**, 71312-73-7; **18**, 18458-15-6; **19**, 765-76-4; **22**, 70367-23-6; $PhSO_2CH_2NO_2$, 21272-85-5; $PhSO_2CHBrNO_2$, 108470-84-4; $PhSO_2CBr_2NO_2$, 108470-85-5; $CH_3CO(CH_2)_2CH{=}CH_2$, 109-49-9; $PhCH{=}CH_2$, 100-45-2; Na–Hg, 11146-94-4; $PhCH_2CN$, 140-29-4; $PhCH_2OH$, 100-51-6; PhCHO, 100-52-7; norbornylene, 498-66-8; cyclohexene, 110-83-8; 1-methylcyclopentene, 693-89-0; cyclohexene oxide, 286-20-4.

A New Synthesis of 4- and 5-Imidazolethiols

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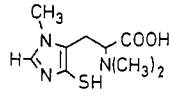
Several examples of a new, mild, and regiocontrolled multistep synthesis of multiply substituted 4- and 5-imidazolethiols are reported. The key step involves a dehydration/cyclization promoted by trimethylsilyl triflate and triethylamine.

The discovery in marine invertebrate oocytes of multiply alkylated histidinethiols[1] (of which **1**, ovothiol C, is exemplary), which appear to be important during embryogenesis,[2] prompted us to study methods for the synthesis of 4-histidinethiols. In the course of this study, we devised a new method for the preparation of substituted 4-imidazolethiols. This procedure made possible the synthesis of L-ovothiol A[3] and, furthermore, appears to be general. Additional examples and details of this process are described herein. Furthermore, a variant of this process has been used for the synthesis of 5-imidazolethiols.



1

Although 4(5)-imidazolethiols are a relatively little studied class, a few methods for their construction have appeared. Introduction of a sulfur substituent onto a preformed imidazole ring has been achieved by direct deprotonation and subsequent thiation of the resulting C-lithioimidazole.[4] Alternatively, a halide at C-4(5) activated by an electron-withdrawing substituent at C-5(4) may be displaced by a sulfur nucleophile.[5] Direct construction of an imidazole ring bearing a 4-thiol group has been accomplished by the condensation of imines with α-oxo thionoamides.[6,7] Given the substitution pattern and functionality of the ovothiols, it was not obvious that any of these methods were directly applicable to ovothiol synthesis. Accordingly, we devised an alternate approach.

Scheme I summarizes the new 4-imidazolethiol synthesis. Conversion, under standard conditions, of an aldehyde and primary amine to the corresponding cyano amine **2** followed by acylation[8] gave the nitrile amide **3**. Addition of hydrogen sulfide[9] to the nitrile took place under mild conditions to afford cyclization substrate **4**. Cyclization of **4** was accomplished with trimethylsilyl triflate[10,11] and triethylamine in methylene chloride to yield **5**. The imi-

Scheme I

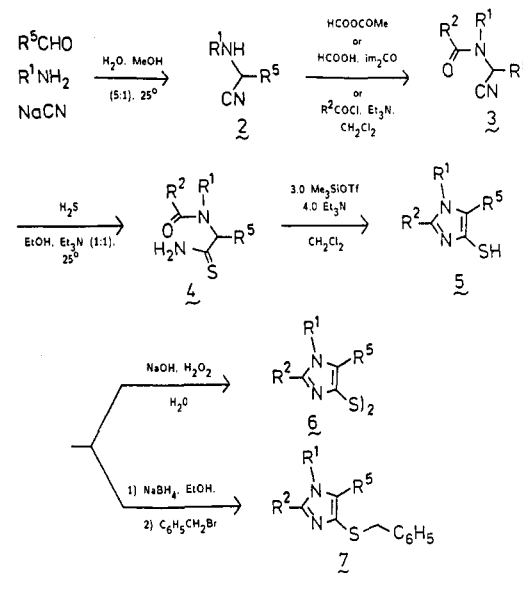


Table I. Yields for the Synthesis of 4-Imidazolethiols

entry	substituents R^1	R^2	R^5	4, % (overall)	heterocycle,[a] % (formula)
1	CH_3	H	H	36	60 (**6a**)
2	n-C_4H_9	i-C_3H_7	i-C_3H_7	... (70)[b]	57 (**6b**)
3	n-C_4H_9	C_6H_5	i-C_3H_7	... (86)[b]	46 (**6c**)
4	CH_3	H	CH_2OTHP	52 (30)[b]	69 (**7a**)
5	CH_3	H	$CH_2OCH_2C_6H_5$	64 (52)[b]	42[c] (**5a**)
6	CH_3	H	$CH_2CH_2OCH_2C_6H_5$	50 (35)[b]	84 (**7b**)
7	CH_3	H	$CH_2CH{=}C(CH_3)_2$	26	84 (**7c**)

[a] Yield from **4**. [b] Reflects yield of **4** without intermediate purification of **2** or **3**. [c] *tert*-Butyldimethylsilyl triflate substituted for trimethylsilyl triflate.

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