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A PRACTICAL SYNTHESIS OF 1,3-OXAZOLE

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Abstract—A short synthesis of oxazole (1,3-oxazole, **1**) is described.

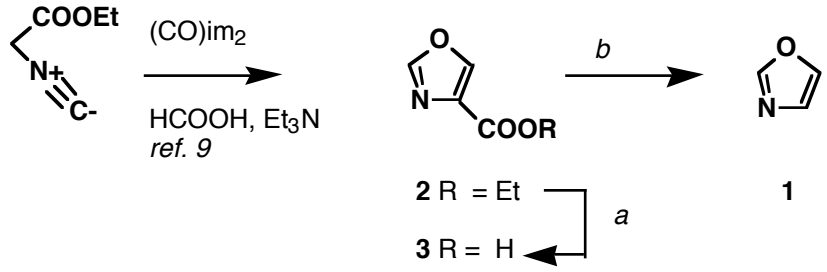
1,3-Oxazole, also known simply as oxazole (**1**), is a low-boiling (69-70° C) member of the π-rich aromatic five-membered heterocycles with a characteristic 'pyridine-like' odor.[1] Oxazole is not found in nature in the free state, but the ring is usually encountered as 2,4-disubstituted oxazoles within the structures of complex biologically active natural products produced by certain bacteria and marine invertebrates. The latter include the exceedingly cytostatic agents, phorboxazoles A and B (IC_{50}'s ~10^{-10}M),[2] and antifungal alkaloids, bengazoles.[3] It has been shown that 2,4-disubstituted oxazoles are formally biosynthesized from acylserine precursors by enzyme catalyzed cyclodehydration-oxidation.[4]

1 *1,3-oxazole*

Most synthetic methods for generation of 2,4-disubstituted oxazoles are biomimetic variations on the latter sequence. We have described recently an alternative strategy to the synthesis of 2,4-disubstituted oxazole natural products that takes advantage of a directed two-step lithiation-electrophilic addition procedure by 'grafting' the substituents directly onto the parent heterocycle **1**.[5] The utility of the grafting approach in synthesis of biologically active oxazole-containing natural products opens new vistas for substituted oxazole synthesis and has made **1** a timely commodity. Unfortunately, **1** is no longer commercially available and, because the literature syntheses of **1** are not trivial undertakings, a practical synthesis of **1** is now of contemporary interest.

The classic Cornforth synthesis of **1**[6] describes a five-step sequence beginning with glycine ethyl ester hydrochloride and *O*-isopropyl formimidate and proceeds through ethyl oxazole-4-carboxylate (**2**) to afford

1 in 9.4% overall yield. An improved synthesis of **1** by Bredereck and Bangert[7] involves condensation of formamide with diethyl dihydroxyfumarate (obtained by Fischer esterification of the corresponding acid), and saponification of the resultant diester, followed by decarboxylation of the derived dibasic oxazole-4,5-dicarboxylate salt to provide **1** in four steps and an overall yield of 22-42%. The main drawback of the latter synthesis is the use of dihydroxyfumaric acid as starting material, which is difficult to prepare. Moreover, the overall yields in both preparations are low. A patented process for recovery of trace levels of **1** (0.03-0.2%), found in aqueous waste-stream of industrial acrylonitrile manufacture, involves complexation with salts of mercury and other transition metals and subsequent liberation of **1** by steam-distillation.[8] Clearly this is impractical on a laboratory scale. We describe here a short synthesis that meets our needs for multigram quantities of **1** in a minimum number of steps (three). The procedure is a combination of the Schöllkopf ethyl isocyanoacetate-based preparation of ethyl oxazole-4-carboxylate (**2**)[9] followed by saponification/ion-exchange recovery of **3** and decarboxylation. The method is amenable to scale-up, provides **1** in fewer steps and comparable yield and obviates problems attendant to millimole-scale recovery and handling of polar intermediates, such as **3**, and the volatile **1**.



a, (i) KOH, THF-H_2O, 25° C, 5 h, (ii) Amberlyst® 15 (H^+); *b*, quinoline, CuO (catalytic), 190-200° C.

Commercially available ethyl isocyanoacetate was treated with formic acid and carbonyl diimidazole in the presence of Et_3N according to Schöllkopf and coworkers[9] to provide ethyl oxazole-4-carboxylate (**2**, 52%[10]). Saponification of **2** (KOH,aq THF,25° C,5 h) followed by acidification gave oxazole-4-carboxylic acid (**3**), but efficient recovery of this polar carboxylic acid at millimole-scale was capricious. Optimal recovery of **3** was achieved after neutralization of the saponified solution by addition of ion exchange resin (Amberlyst® 15,H^+ form). Removal of the resin by filtration and evaporation of the solvent from the filtrate gave **3** (78-85%).

Decarboxylation of **3** was accomplished using Cornforth's procedure[6] (quinoline, catalytic CuO, 190-200° C). The distillation and recovery of **1** from the hot quinoline mixture was aided by use of a short-path 'U' tube between the still pot and receiver and immersion of the receiver in a dry ice-acetone bath. Bulb-to-bulb redistillation of the condensate gave pure **1** (59-74%). The product was shown by ^1H NMR and ^{13}C NMR to be **1** in >95% purity. Thus, **1** was prepared from ethyl isocyanoacetate in three steps in an overall yield of 24-33%.

Practical access to **1** alleviates an impediment to development of metalation-addition chemistry of the title compound for preparation of new oxazole derivatives.

ACKNOWLEDGMENTS

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EXPERIMENTAL

General Experimental Procedures. ^{1}H NMR and ^{13}C NMR spectra were recorded on a General Electric QE300 instrument, FTIR spectra were recorded on a Mattson Galaxy 3000 FTIR spectrometer. Other experimental procedures can be found elsewhere.[11]

Ethyl oxazole-4-carboxylate (2)[6] The title compound was prepared from freshly prepared ethyl isocyanoacetate,[12] carbonyl diimidazole and formic acid according to Schöllkopf (52%)[9] . ^{1}H NMR ($CDCl_3$) 8.28 (s, 1H), 7.94 (s, 1H), 4.40 (q, 2H, J = 6.7 Hz), 1.40 (t, 3H, J = 6.7 Hz).

Oxazole-4-carboxylic acid (3)[6] Aqueous KOH (4M, 11.4 mL) was added to a stirred solution of **2** (5.37 g, 38.1 mmol) in THF (20 mL). Additional THF (20 mL) was added to bring the two-phases to homogeneity and the mixture stirred for 5 h after which no starting material could be detected (TLC). The solution was 'titrated' by addition of strong cation exchange resin (Amberlyst® 15) until the supernatant reached pH~4 at which point the mixture became turbid. The mixture was filtered and the resin washed with THF then water. The combined filtrates were concentrated using an efficient rotary evaporator and the light brown solid residue of **3** dried overnight in a vacuum dessicator over P_2O_5 (3.68 g, 85%). ^{1}H NMR ($CDCl_3$-1% $(CD_3)_2SO$) 11.4 (bs, 1H), 8.23 (d, 1H, J = 0.9 Hz), 7.94 (d, 1H, J = 0.9 Hz). ^{13}C NMR ($CDCl_3$-1% $(CD_3)_2SO$) 162.0 (C=O), 151.0 (d), 143.5 (d), 133.0 (s).

Oxazole (1)[6]

Oxazole-4-carboxylic acid (3.57 g, 31.6 mmol) was dissolved in redistilled quinoline (XX mL) contained in a round bottom still flask. Copper (II) oxide (~10 mg) was added to the mixture and the flask equipped with a 'U-tube' adapter with ground glass joints, vacuum port and a receiver flask. The apparatus was flushed with dry N_2, the receiver immersed in a dry ice-acetone bath and the still flask was heated in an oil bath with continuous stirring. When the bath temperature reached 190-200° a clear liquid began to distill. After ~10 min no additional liquid was observed to pass over and the 'U tube' was heated with a heated air gun to drive over the remaining 'hold-up'. The product was shown to be **1** (1.69 g, 77%) contaminated with a small amount of quinoline. Redistillation of the product in a Kugelrohr (80-100° C oven temperature) gave pure **1**[6] (1.28 g, 59%), >95% pure by ^{1}H NMR. ^{1}H NMR ($CDCl_3$) 7.90 (s), 7.68 (s), 7.15 (s). When the reaction was repeated on a larger scale (10 g of **2**) the yield of **1** was 4.54 g (74%).

Oxazole (**1**) was divided into aliquots and sealed in glass ampoules for storage at 4° C until required.[13]

REFERENCES AND NOTES

1. The name 'oxazole' was coined by Hantzsch (*Ber*., 1876, **9,** 1525) in the context of substituted oxazole derivatives; however, the first described synthesis of **1** is credited to Cornforth and Cornforth (see reference 6). Oxazole is appreciably less basic than pyridine, pKa $[\mathbf{1}\bullet H]^+$ 0.8±0.2 (D. Brown and P. B. Ghosh, *J. Chem. Soc. B.*, 1969, 270). Density: ρ 1.050 $g.cm^{-3}$.
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9. K.-W. Henneke, U. Schöllkopf, and T. Neudecker, *Liebigs. Ann. Chem*., 1979, 1370.
10. The yield of **2** was not optimized.
11. P. A. Searle and T. F. Molinski, *J. Org. Chem*., 1994, **59**, 6600.
12. G. D. Hartman and L. M. Weinstock in 'Organic Syntheses'; Vol. 6, ed. by W. E. Noland, Wiley, New York, 1988, p. 620. The commercial isocyanide is also suitable for use after redistillation.
13. Storage of **1** at room temperature, in light, resulted in some discoloration after a few months, but this did not seem to affect the reactivity towards metallation (see reference 5). The product was dried before use by storage over 3Å molecular sieves or solid KOH.