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Practical Synthesis of 3-Amino-4,5-dimethylisoxazole from 2-Methyl-2-butenenitrile and Acetohydroxamic Acid

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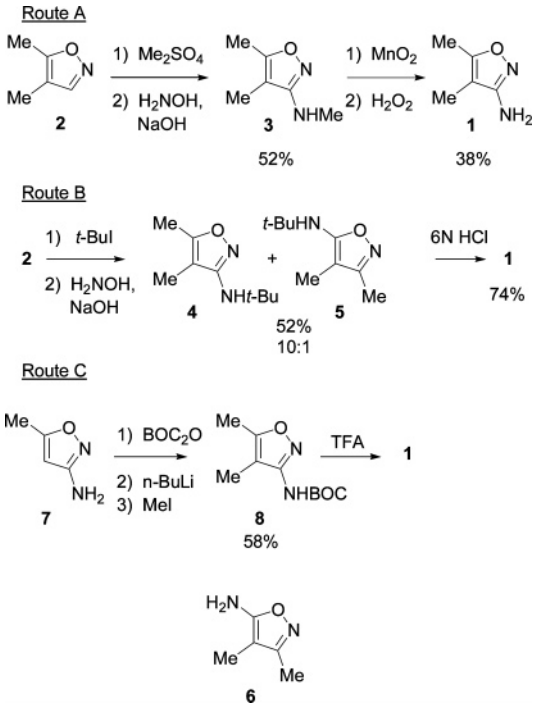
Abstract:

3-Amino-4,5-dimethylisoxazole was prepared from technical-grade 2-methyl-2-butenenitrile and acetohydroxamic acid in a 62% overall yield on a multimole scale. The key features of this synthesis are (1) DBU treatment of the technical-grade nitrile mixture to provide a starting material of acceptable purity and (2) use of acetohydroxamic acid as an N-protected hydroxylamine equivalent. This operationally simple method provides the title compound in reasonable overall yield and free of contamination from the isomeric 5-amino-3,4-dimethylisoxazole.

Introduction

In connection with a drug discovery program aimed at the synthesis of endothelin receptor antagonists,[1] we needed a convenient, unambiguous mole-scale preparation of 3-amino-4,5-dimethylisoxazole **1**. Three different syntheses of **1** had been reported, all of which functionalize a preformed isoxazole core (Scheme 1). The first Hoffmann−La Roche route (Scheme 1, route A) proceeds via condensation of an isoxazolium salt with hydroxylamine.[2] The subsequent oxidative removal of the N-methyl substituent from **3** requires a two-step oxidation−hydrolysis sequence. A variation on this route[3] (Scheme 1, route B) proceeds via the *tert*-butylamino derivative **4**, which is dealkylated more conveniently by treatment with 6 N hydrochloric acid. However, in this variation the isomeric 3,4-dimethyl-5-(*tert*-butylamino)isoxazole **5** is also produced, and care is required to avoid contamination of the final product by the isomeric aminoisoxazole **6**. The starting material for both of these routes, 4,5-dimethylisoxazole **2**,[4] is not readily available. Workers at Shionogi[5] (Scheme 1, route C) have prepared **1** via the metalation and methylation of BOC-protected 3-amino-5-methylisoxazole **8**. The starting material **7** is readily available, and there is no possibility for production of the regioisomeric 5-aminoisoxazole **6**. For these reasons we used route C in our initial work and were able to prepare multigram lots of **1** in this manner. The route suffers from several drawbacks for large-scale work, however. It requires relatively large reactors and careful cryogenic temperature control to avoid over-methylation, and it requires the use of iodomethane. For these reasons we sought a more convenient, scalable preparation of **1**.[6]

Scheme 1. **Reported syntheses of 3-amino-4,5-dimethylisoxazole 1**



De novo synthesis of an isoxazole ring bearing a 3-amino substituent is usually performed by condensing hydroxylamine with a doubly electrophilic nitrile such as a β-ketonitrile or a β-bromoacrylonitrile.[7] Preparations of 3-amino-4,5-dialkylisoxazoles are in fact quite rare, and typically these

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(4) Justoni, R. *Rend., Ist. Lomb. Sci.* **1938**, *71*, 407−424; *Chem. Abstr*. **1940**, *34*, 21257.

(5) Konoike, T.; Kanda, Y.; Araki, Y. *Tetrahedron Lett.* **1996**, *37*, 3339−3342.

(6) During preparation of this manuscript, workers from Ube Industries described a four-step process for preparation of **1** starting from propionitrile, *tert*-butyl acetate, and hydroxylamine, yielding **1** (free base) in an approximately 50% overall yield. The key steps are condensation of 3,3-diethoxy-2-methylbutanenitrile with hydroxylamine to form the corresponding amidoxime, followed by cyclization with sulfuric acid. See: Matsushita, A.; Yoshii, K.; Ogami, M.; Nakamura, T; Yamada, S. (a) JP2002363171, 2002; (b) JP2002332269, 2002.

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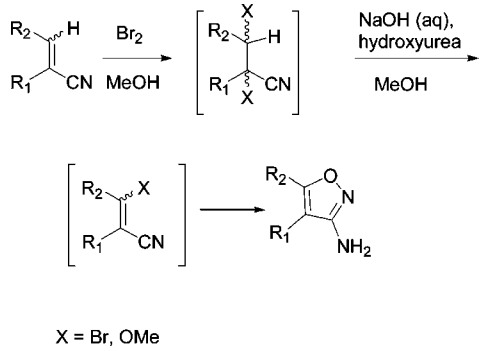
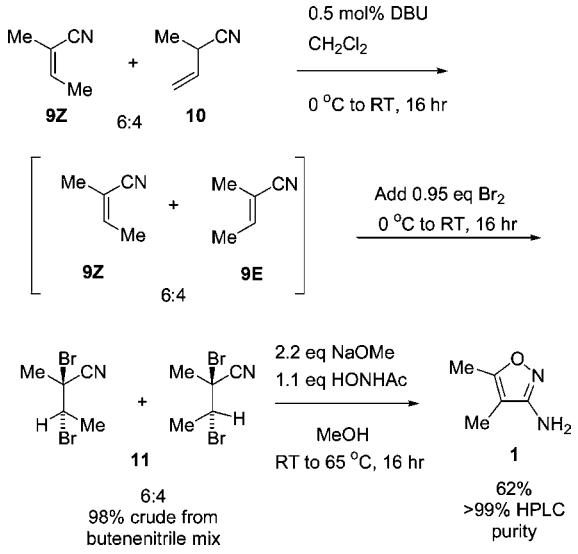
Scheme 2. **Kloetzer route to 4- or 5-alkyl-3-aminoisoxazoles**



preparations are complicated by competing formation of the isomeric 5-aminoisoxazole.[8] In the case of isomers **1** and **6**, separation is difficult. A more attractive strategy, typically applied to the synthesis of 3-amino-1,2-benzisoxazoles,[9] is the use of an N-protected hydroxylamine equivalent. Kloetzer and co-workers[10] have investigated the reaction of β-bromoacrylonitriles with hydroxyurea to prepare simple monocyclic isoxazoles and have developed a convenient preparation of either 4- or 5-monoalkyl 3-aminoisoxazoles (Scheme 2). The β-bromoacrylonitriles (or their synthetic equivalents) can be generated in situ via base-promoted elimination of HBr from a 2,3-dibromoproprionitrile. Hydroxyurea functions as an N-protected hydroxylamine equivalent, allowing for generation of the desired 3-aminoisoxazole product free of regioisomeric impurities. Although Kloetzer and coworkers did not prepare **1** using this method, the route has been applied to the synthesis of 4,5-diphenyl-5-aminoisoxazole.[11] We now report the successful adaptation of this route to the convenient multimole production of **1** (Scheme 3).

Adapting Kloetzer's method to the preparation of **1** required identifying a source of 2-methyl-2-butenenitrile **9**. **9** has been prepared on a laboratory scale by dehydration of 2-butanone cyanohydrin, as an *E*/*Z* mixture contaminated with 2-ethylacrylonitrile.[12] **9** is a byproduct from the industrial hydrocyanation of 1,3-butadiene and is commercially available[13] in a technical grade. Technical grade **9** contains 50−70% **9Z**; the remainder is primarily isomer **10** (^{1}H NMR analysis). An additional terminal olefin component (presumably 4-pentenenitrile, ca. 5%) is also present, along with a trace of another species. After some experimentation, we discovered that technical-grade **9** could be converted cleanly into a mixture consisting predominantly of **9Z** and **9E** by treatment with 0.5 mol % DBU in

Scheme 3. **Preparation of 1**



dichloromethane solution at rt. The rearrangement of **10** to **9E** appears to be stereospecific, since the ratio of **9Z** to **9E** in the product appears to reflect the ratio of **9Z** to **10** in the starting material.[14] The resulting reaction mixture could then be used directly in the subsequent bromination step, which essentially followed the reported preparation[15] of 2,3-dibromo-2-methylbutanenitrile **11**, substituting dichloromethane for carbon tetrachloride.

Sodium-ethoxide promoted conversion of the diastereomeric mixture **11** is reported to give (*E*)- and (*Z*)-3-bromo-2-methyl-2-butenenitrile, which can be separated by vacuum distillation.[15b] We elected not to try to isolate this intermediate and instead studied the in situ elimination as described by Kloetzer. After unsatisfactory initial experiments following this method directly, we settled on a procedure that substituted acetohydroxamic acid for hydroxyurea. Although this substitution provided little cost advantage, the reaction was much cleaner and workup was straightforward. In our optimized procedure, sodium methoxide solution was added slowly to a methanolic solution of **11** and acetohydroxamic acid, at a rate such that a gentle reflux was maintained. Precipitation of sodium bromide begins soon after the addition is initiated. The reflux is continued for several hours. Evaporation of solvent, extraction, and crystallization gave a 62% overall yield of **1** free base, with >98% purity and, importantly, very high isomeric purity (with respect to **6**).

In summary, we have developed a scalable, unambiguous synthesis of **1**. Although additional telescoping and cost-saving modifications to this route (e.g., in situ generation of acetohydroxamic acid) seem possible, the route has proven itself reliable and extremely convenient for preparation of multimole lots of **1**.

(7) For example, see: (a) Kume, T.; Goto, T.; Kamochi, A.; Yanagi, A.; Yagi, S.; Miyauchi, H. EP297378, 1989. (b) Iwai, I.; Nakamura, N. *Chem. Pharm. Bull.* **1966**, *14*, 1277−1286.

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(9) (a) Shutske, G. M.; Kapples, K. J. *J. Heterocycl. Chem.* **1989**, *26*, 1293−1298. (b) Palermo, M. G. *Tetrahedron Lett.* **1996**, *37*, 2885−2886.

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(11) Harsanyi, K.; Takacs, K.; Horvath, K. *Chem. Ber.* **1974**, *107*, 2563−2568.

(12) Bruylants, P. *Bull. Soc. Chim. Belges.* **1930**, *39*, 572−580.

(13) Suppliers include Fluka and TCI. Fluka 2-methyl-2-butenenitrile, catalog number 66085 (55−60.% assay), is a brown liquid, bp 115−120 °C. The corresponding TCI product (>70% assay), catalog number M0839, has a similar composition and appearance.

(14) Assignment of olefin geometry in **9E/Z** is by ^{1}H NMR using the C-3 olefinic proton chemical shifts: δ 6.43 ppm (*E*) vs 6.20 pm (*Z*). The corresponding calculated values (ACD Labs HNMR Predictor, v. 8.10) are 6.51 ppm (*E*) and 6.24 ppm (*Z*). The product mix contains approximately 5 mol % of the terminal olefin impurity present in the starting material (presumably 4-pentenenitrile), along with other minor impurities.

(15) (a) Chalchat, J. C.; Theron, F. *Bull. Soc. Chim. Fr.* **1974**, 953−957. (b) Chartier, H.; Vessiere, R. *Ann. Chim.* **1969**, 313−321.

Experimental Section

Technical grade 2-methyl-2-butenenitrile was obtained from Fluka or TCI. Acetohydroxamic acid was obtained from Fluka. Sodium methoxide solution (25 wt %) in methanol was obtained from Aldrich. Dichloromethane and methanol (HPLC grade) were used as received.

2,3-Dibromo-2-methylbutanenitrile 11 (Diastereomeric Mixture). Technical grade 2-methyl-2-butenenitrile (Fluka; **9Z/10** ratio ca. 6:4; 169 g, 1.98 mol) and dichloromethane (530 mL) were charged into a nitrogen-flushed 1 L round-bottom flask containing a magnetic stir bar. The flask was equipped with a nitrogen inlet/bubbler. The light brown solution was stirred and cooled to +7 °C in an ice bath, and then DBU (1.6 g, 11 mmol) was added. The color darkened. The cooling bath was removed, and the mixture was stirred and allowed to warm to rt over 16 h. ^{1}H NMR analysis of an aliquot (from which most dichloromethane was removed by evaporation under a gentle stream of nitrogen) showed essentially complete disappearance of 2-methyl-3-butenenitrile, along with formation of a 6:4 mixture of **9Z** and **9E**. ^{1}H NMR (300 MHz, $CDCl_3$) **9Z** δ 6.20 (q, 1H, J = 6 Hz); 1.95 (d, 3H, J = 6 Hz), 1.92 (s, 3H); **9E** δ 6.43 (qq, 1H, J = 1, 6 Hz), 1.86 (q, 3H, J = 1 Hz), 1.92 (qd, 3H, J = 1, 6 Hz).

The reaction mixture was cooled in an ice bath to +1 °C. Bromine (101 mL, 313 g, 1.94 mol) was added dropwise from an addition funnel over 90 min, keeping the temperature below +10 °C. The color of the reaction mixture lightened upon addition of the first few drops of bromine and then became dark brown as the addition progressed. When the addition was complete, the ice bath was removed and the stirred mixture was allowed to warm to rt over 16 h, with little color change. Aqueous sodium bisulfite solution (20% w/v, 100 mL) was added, and the mixture was poured into a separatory funnel (emulsion). Brine (100 mL) was added. The layers were separated, and the aqueous layer was washed with 1 × 100 mL of dichloromethane. The combined organic extracts were dried over sodium sulfate and concentrated to provide 469 g of a brown oil, which solidified upon storage at −35 °C. ^{1}H NMR analysis showed the two diastereomeric dibromide products in a 6:4 ratio, along with traces of (*E*)-2-methyl-2-butenenitrile and dichloromethane. ^{1}H NMR (300 MHz, $CDCl_3$) major isomer δ 4.23 (q, 1H, J = 7 Hz), 2.27 (s, 3H), 2.06 (d, 3H, J = 7 Hz); minor isomer δ 4.39 (q, 1H, J = 7 Hz), 2.15 (s, 3H), 1.90 (d, 3H, J = 7 Hz).

3-Amino-4,5-dimethylisoxazole (1). Methanol (400 mL) and the crude dibromide product **11** from the previous step (469 g, approximately 1.77 mol) were poured into a nitrogen-flushed 5 L three-neck round-bottom flask fitted with a reflux condensor, an addition funnel, and a mechanical stirrer. A slightly turbid solution resulted. Solid acetohydroxamic acid (126 g, 1.68 mol) was added, and the flask was fitted with a nitrogen inlet/bubbler. The endothermic partial dissolution of the acetohydroxamic acid cooled the reaction mixture to +11 °C. With stirring, and without external cooling, sodium methoxide solution (840 g of a 25 wt % solution in methanol, 3.9 mol) was added dropwise from the addition funnel over 2 h. The mixture became a clear brown solution within 5 min after the beginning of the addition, and after about 15 min a precipitate began to form. The temperature of the mixture rose during the addition, reaching +65 °C (reflux) after 740 g of sodium methoxide solution had been added. The final 100 g of sodium methoxide solution was added at such a rate as to maintain a gentle reflux. Following completion of the addition, the thick brown mixture was stirred and heated at +64 °C for 16 h. HPLC analysis of an aliquot immediately following completion of the sodium methoxide addition (aliquot diluted with 1:1 methanol/0.1 N HCl (aq)) showed 7 major peaks, of which **1** was most prominent (39%). Analysis at the end of the 16 h period showed this peak to be appoximately 64% of the mixture.

The reaction mixture was cooled and evaporated to dryness. 10% Aqueous sodium dihydrogenphosphate solution was added (final pH ca. 8), and the brown mixture was extracted with 3 × 300 mL ethyl acetate. The combined organic extracts were dried over sodium sulfate and concentrated. The solid residue was triturated first with 300 mL of 1:1 hexanes/ether and then with 100 mL of 1:1 hexanes/dichloromethane. The solid filter cake was dried briefly under a vacuum (ca. 10 mmHg/35 °C) to provide the title compound (137 g, 62% overall yield) as a light brown solid: mp 109−116 °C (lit.[2] 115−117 °C); MS (ESI) (M + 1) 113; HPLC purity >98%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.80 (br s, 2H), 2.22 (s, 3H), 1.81 (s, 3H) ppm; IR (KBr) 3445, 3310, 3203, 1668, 1634, 1528, 1481, 1206 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 164.1, 163.0, 100.7, 11.0, 6.0 ppm; homogeneous by ^{1}H and ^{13}C NMR. An analytical sample was prepared by crystallization from ethyl acetate/heptane: mp 116−117 °C. EA calcd C, 53.56; H, 7.19; N, 24.98. Found: C, 53.68; H, 7.10; N, 24.99%.

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