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Synthesis of 4-Cyano Pyrroles via Mild Knorr Reactions with β-Ketonitriles

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Abstract:

Mild methods for conducting Knorr chemistry with β-ketonitriles were developed. This enabled the preparation of 4-cyano-penta-substituted pyrroles and gave access to α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor potentiators for biological evaluation. In addition, a series of alkyl and aryl β-ketonitriles were employed in Knorr cyclizations to probe steric tolerance and the possibility of direct introduction of aromatic moieties via Knorr chemistry.

Introduction

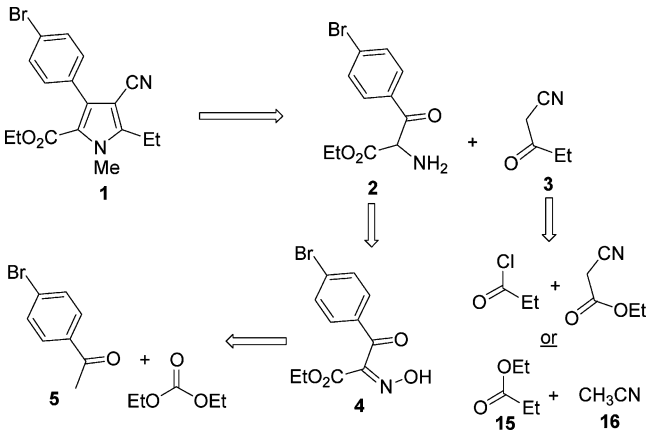
AMPA, an acronym for α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, represents a subclass of ionotropic glutamate receptors of the central nervous system. As such, they mediate the rapid excitatory synaptic response transmissions within the CNS and have been linked to cognitive disorders in Alzheimer's disease, cognitive impairment associated with schizophrenia, and depression.[1]

The 4-cyano-penta-substituted pyrrole **1** (Scheme 1) was identified as an important precursor molecule for the preparation of AMPA potentiators. This communication describes the mild Knorr chemistry that we developed in order to prepare kilogram quantities of aryl bromide **1** with high chemical purity.

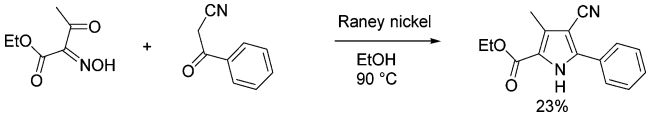
Results and Discussion

Scheme 1 is a retrosynthetic plan for the preparation of aryl bromide **1** which would require a Knorr pyrrole synthesis.[2] The retrosynthetic plan depicts an α-amino-β-ketoester **2** and a β-ketonitrile **3** as the necessary partners for a Knorr cyclization. After the Knorr cyclization, an *N*-methylation would provide the fully substituted pyrrole **1**. The α-amino-β-ketoester **2** would be derived from the α-isonitroso-β-ketoester **4** which would originate from the β-ketoester as a result of the Claisen condensation of 4-bromoacetophenone **5** with diethyl carbonate.[3] There are a number of documented ways to prepare the desired β-ketonitrile **3** ranging from reaction of an α-haloketone with

Scheme 1



Scheme 2



cyanide salts,[4] acylation of the anion of acetonitrile,[5] acylation of ethyl cyanoacetate followed by decarboxylation,[6] to rearrangement of isoxazoles.[7] Initially, we focused on an acylation decarboxylation protocol to prepare β-ketonitrile **3** due to the relatively nontoxic reagents and reliable nature of the transformations. We later became interested in the Claisen condensation of the anion of acetonitrile **16** with ethyl proprionate **15** for reasons of stability and analysis that are discussed within this communication.

Knorr chemistry with β-ketonitriles as coupling partners has very little literature precedent. The only reference we were able to find for the use of a β-ketonitrile in a Knorr reaction was the work of Winans and Adkins at the University of Wisconsin.[8] Winans and Adkins were applying Raney nickel in EtOH with heating to Knorr reactions in place of the classical zinc in acetic acid under refluxing conditions (Scheme 2).

The α-isonitroso-β-ketoester **4** (Scheme 1) required for the Knorr cyclization of interest has a close literature precedent, α-isonitroso-β-ketoester **7**, which was incorporated by Chu and Chu in a Knorr pyrrole synthesis (Scheme

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(1) Albaugh, P. A.; Dominguez-Manzanares, E.; Hong, J. E.; Hornback, W. J.; Jiang, D.; Ornstein, P. L.; Thompson, M. L.; Tromiczak, E. C.; Wu, Z.; Zarrinmayeh, H.; Zimmerman, D. M.; Castano-Mansanet, A. M.; Huffman, L. G.; Miller, B. D. Pyrrole and Pyrazole derivatives as Potentiators of Glutamate Receptors. (Eli Lilly & Co., Indiana, USA) PCT Int. Appl. WO 2005/040110, 2005 and references cited therein. Magnus, N. A.; Aikins, J. A.; Cronin, J. S.; Diseroad, W. D.; Hargis, A. D.; LeTourneau, M. E.; Parker, B. E.; Reutzel-Edens, S. M.; Schafer, J. P.; Staszak, M. A.; Stephenson, G. A.; Tameze, S. L.; Zollars, L. M. H. *Org. Process Res. Dev.* **2005**, *9*, 621.
(2) Knorr, L. *Ber.* **1884**, *17*, 1635. Knorr, L.; Lange, H. *Ber.* **1902**, *35*, 2998.
(3) Eid, C. N.; Konopelski, J. P. *Tetrahedron* **1991**, *47*, 975.
(4) Van Reymenant *Chem. Zentralbl*. **1901**, *I*, 72. Henry *Chem. Zentralbl*. **1900**, *I*, 1123.
(5) Levine, R.; Hauser, C. R. *J. Am. Chem. Soc.* **1946**, *68*, 760. Hackler, R. E.; Burow, K. W.; Kaster, S. V.; Wickiser, D. I. *J. Heterocycl. Chem.* **1989**, *26*, 1575. Eddington, N. D.; Cox, D. S.; Roberts, R. R.; Butcher, R. J.; Edafiogho, I. O.; Stables, J. P.; Cooke, N.; Goodwin, A. M.; Smith, C. A.; Scott, K. R. *Eur. J. Med. Chem. Chim. Ther.* **2002**, *37*, 635.
(6) McFadden, H. G.; Huppatz, J. L. *Aust. J. Chem.* **1991**, *44*, 1263.
(7) Claisen, L. *Chem. Ber.* **1903**, *36*, 3671.
(8) Winans, C. F.; Adkins, H. *J. Am. Chem. Soc*. **1933**, *55*, 4167.

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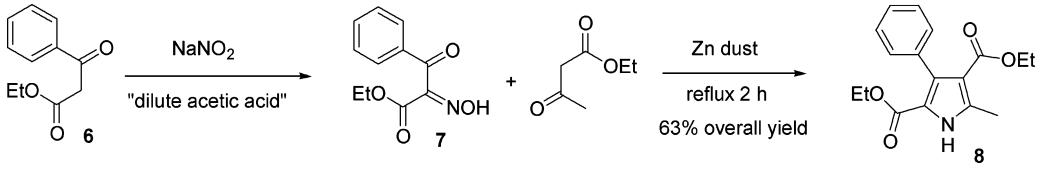
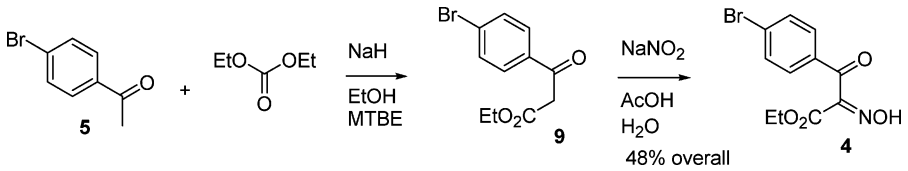
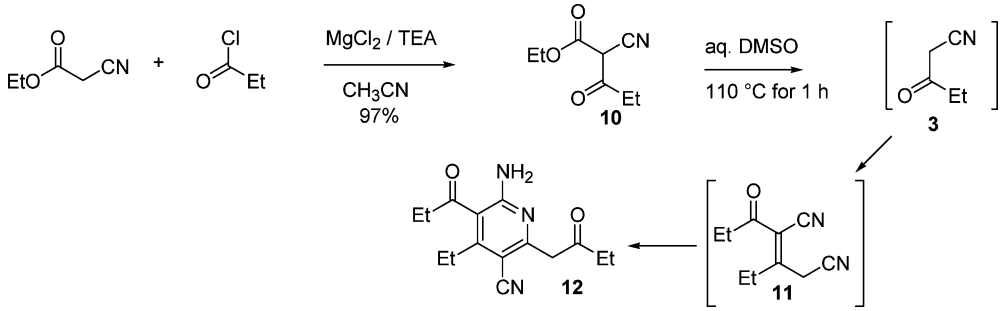
Scheme 3



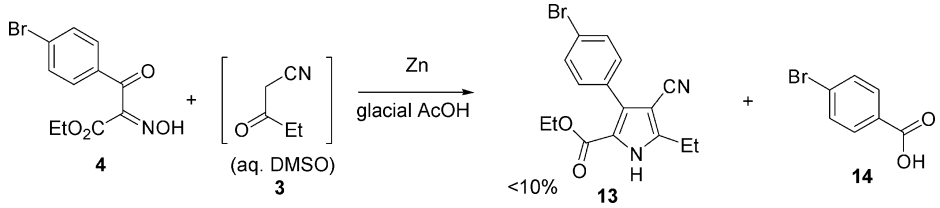
Scheme 4



Scheme 5



Scheme 6



3).[9] The Knorr chemistry described by Chu and Chu employed "dilute acetic acid" rather than the classical glacial acetic acid and achieved a 63% overall yield of pyrrole **8** starting from the β-ketoester **6**.

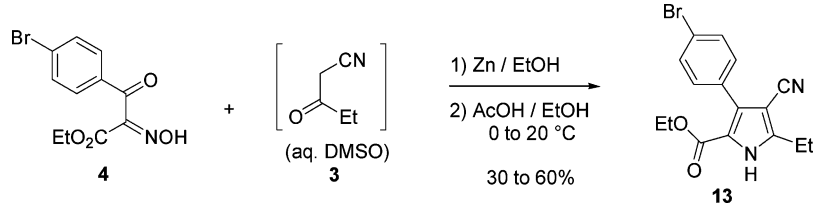
In order to evaluate the proposed preparation of 4-bromo-*N*-methyl-phenyl pyrrole **1** (Scheme 1) via Knorr cyclization, we prepared α-isonitroso-β-ketoester **4** and β-ketonitrile **3** (Schemes 4 and 5). The α-isonitroso-β-ketoester **4** was prepared by Claisen condensation of the sodium enolate of 4-bromoacetophenone **5** with diethyl carbonate and subsequent nitrosation in wet acetic acid to directly precipitate **4**.[3,10] We initially chose a two-step procedure for the preparation of β-ketonitrile **3**, which involved acylation of ethyl cyanoacetate with propionyl chloride to give the α-cyano-β-ketoester **10** followed by decarboxylation by heating in wet DMSO.[6] This preparation had the issues of not being able to readily monitor the production of β-ketonitrile **3** due to the lack of a chromophore and the product **3** having the propensity to dimerize and trimerize to give **11** and **12**, respectively.[11]

Despite the analysis and stability issues with the Scheme 5 preparation of β-ketonitrile **3**, we decided to test the Knorr chemistry before investing additional time in a more controlled preparation of **3**. Employing classical Knorr reaction conditions, the α-isonitroso-β-ketoester **4** was dissolved in glacial acetic acid in the presence of what was calculated to be 2 equiv of **3** as a wet DMSO solution, and the resulting mixture was treated with portions of zinc dust. This procedure gave less than a 10% yield of the desired pyrrole **13** and a considerable amount of 4-bromobenzoic acid **14** (Scheme 6).

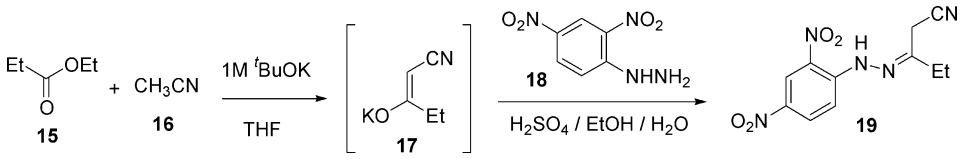
The 4-bromobenzoic acid **14** might be produced *via* denitrosation of α-isonitroso-β-ketoester **4** followed by a retro-Claisen condensation.[12] This brought our attention back to the article by Chu and Chu (Scheme 3) where Knorr chemistry involving the α-isonitroso-β-ketoester **7** afforded a 63% yield of pyrrole **8** with no mention of benzoic acid production.[9] The only obvious difference in the Chu and Chu Knorr chemistry, aside from a β-ketoester cyclization partner versus a β-ketonitrile, was the use of "dilute acetic acid" instead of the typical glacial acetic acid system. This prompted us to examine our Knorr pyrrole reaction in dilute acetic acid. We observed that the aqueous reaction system produced less 4-bromobenzoic acid **14**, but the insolubility of intermediates in the aqueous media resulted in poor yields

(9) Chu, J. E.; Chu, T. C. *J. Org. Chem.* **1954**, *19*, 266.
(10) Ehrhart, G. *Chem. Ber.* **1953**, *86*, 713, 716.
(11) Fahmy, S. M.; Mohareb, R. M. *Liebigs Ann. Chem.* **1985**, *7*, 1492.
(12) Castro, A. J.; Giannini, D. D.; Greenlee, W. F. *J. Org. Chem.* **1970**, *35*, 2815.

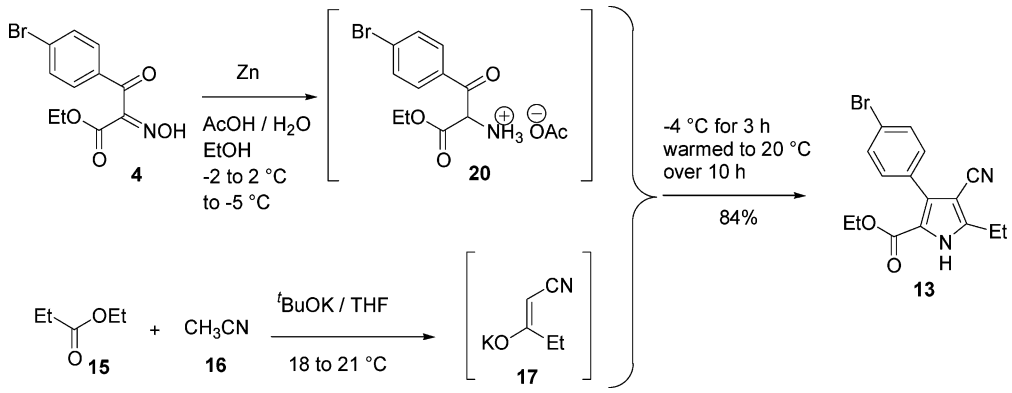
Scheme 7



Scheme 8



Scheme 9



(∼20%) of pyrrole **13**. Remembering the Winans and Adkins β-ketonitrile Knorr chemistry, where their Knorr chemistry was run in EtOH,[8] we thought to address the insolubility issues by replacing the water reaction solvent with EtOH which should be compatible with the ethyl ester of α-isonitroso-β-ketoester **4**. The Knorr pyrrole synthesis depicted in Scheme 7 was conducted as follows: the α-isonitroso-β-ketoester **4** was dissolved in cold EtOH, and zinc was added, followed by "freshly" prepared β-ketonitrile **3** as an aqueous DMSO solution. To this cold mixture was added an ethanolic acetic acid solution dropwise to gently induce the reduction/Knorr cyclization. After workup and crystallization, this mild Knorr reaction technique gave isolated yields as high as 60%, but the yields were often as low as 30% due to the unpredictable (i.e., instability) potency of the β-ketonitrile **3**.

To address the analytical and stability issues of the β-ketonitrile **3**, we decided to investigate its synthesis via the Claisen condensation method (Scheme 8).[5]

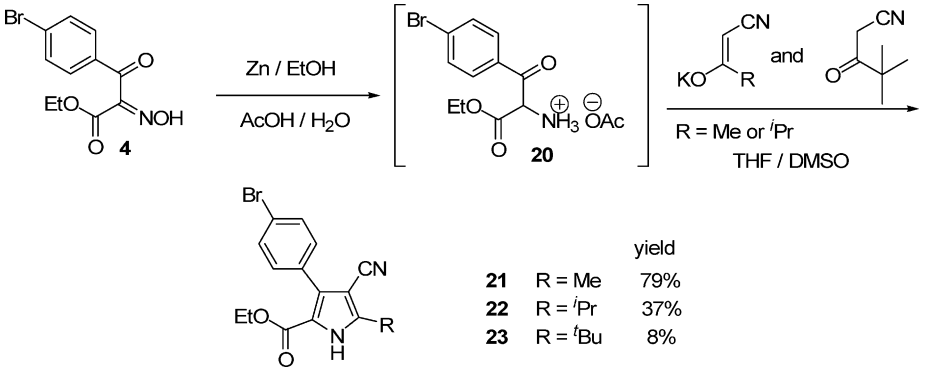
Ethyl propionate **15** was combined with acetonitrile **16**, and the resulting mixture slowly added to ^{t}BuOK in THF to give the potassium enolate **17** (Scheme 8). The enolate **17** had no capacity to condense with itself and represented a stable form of β-ketonitrile **3**. In order to monitor the production of the enolate **17**, we opted to make the DNP (1,3-dinitrophenyl) hydrazone derivative **19**.[13] The enolate **17** and the hydrazone **19** solved the issues of stability and analysis that the Scheme 5 acylation/decarboxylation preparation of β-ketonitrile **3** had presented.

In order to use enolate **17** in the Knorr reaction, we envisioned reducing the α-isonitroso-β-ketoester **4** to the α-amino-β-ketoester acetate salt **20** (Scheme 9) with enough acetic acid present so that the enolate **17** could be quenched into the reaction mixture to give the β-ketonitrile **3**. Before proceeding with this plan, we wanted to assess the stability of the intermediate α-amino-β-ketoester acetate salt **20** with regard to its propensity to condense with itself. We observed that the α-amino-β-ketoester acetate salt **20** was stable below 14 °C but was about 43% decomposed within an hour if allowed to warm to 23 °C. This result indicated that we should attempt to run the proposed Knorr reactions at or below 14 °C to avoid undesired side reactions.

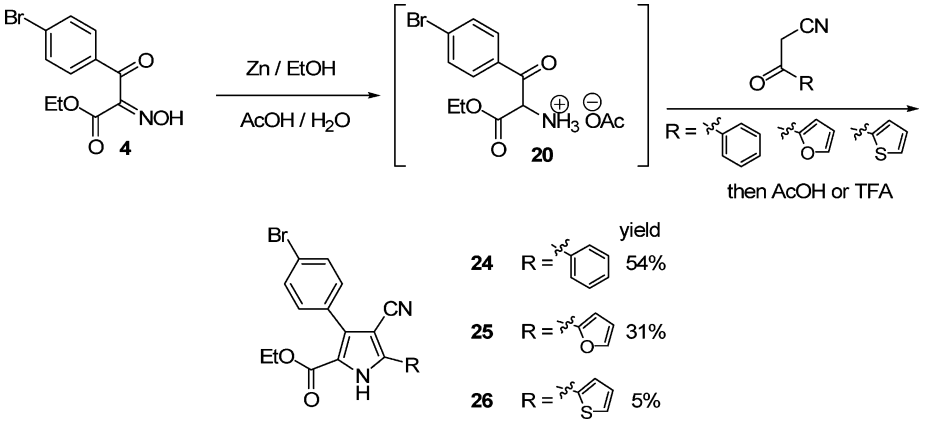
Armed with the stable enolate **17** form of the β-ketonitrile **3** and an operating temperature to avoid decomposition, we revisited the Knorr reaction of interest (Scheme 9). The α-isonitroso-β-ketoester **4** was dissolved in wet EtOH, and the resulting mixture was treated with zinc and cooled. Ethanolic acetic acid was added to the reaction mixture between −2 to 2 °C to affect reduction of **4** and produce the acetate salt **20**. In a separate reactor, the enolate **17** was generated as described in Scheme 8 and slowly quenched into the cold acidic solution of **20**. The resulting mixture was warmed very slowly to 20 °C to ensure a complete reaction, and after workup, the pyrrole **13** was crystallized in 84% yield.

(13) Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R. *Vogel's Textbook of Practical Organic Chemistry*, 5th ed.; John Wiley & Sons, Inc.: 1989; p 1218.
(14) Long, R. S. *J. Am. Chem. Soc.* **1947**, *69*, 990.

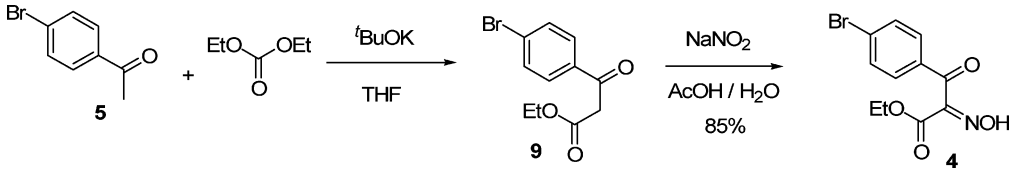
Scheme 10



Scheme 11



Scheme 12

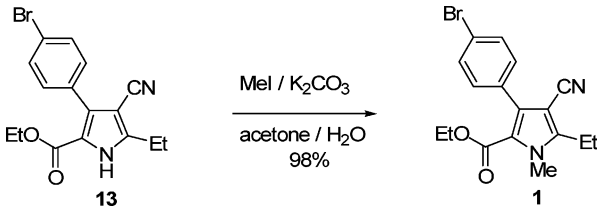


In order to assess the generality of β-ketonitriles for preparing 4-cyanopyrroles with α-isonitroso-β-ketoester **4**, we decided to prepare six analogues. First, we chose to vary the alkyl group of the β-ketonitrile to probe tolerance for steric encumbrance (Scheme 10). The 5-methyl pyrrole **21** was prepared in 79% yield employing an intermediate potassium enolate of the corresponding β-ketonitrile to suppress unwanted trimerization. The yield dropped sharply as steric hindrance was increased, with the 5-isopropyl pyrrole **22** afforded in just 37% yield again via the intermediate potassium enolate method. The 5-*tert*-butyl pyrrole **23** was isolated in only 8% yield using the requisite β-ketonitrile directly due to its inherent stability.

Next, we investigated aromatic rings in place of the alkyl group on the β-ketonitile (Scheme 11). Interestingly, the aromatic analogues required additional acid to dehydrate to the target pyrroles. The 5-phenyl pyrrole **24** was prepared in 54% yield. The pyrrole with furan at the 5-position, **25**, was afforded in 31% yield, and the 5-thiophene pyrrole **26** was not amenable to the reaction conditions giving only a 5% yield.

After the Knorr synthesis to prepare **13** had been developed to be useful, we revisited the synthesis of the α-isonitroso-β-ketoester **4**. For safety and practicality reasons, the conditions for the Claisen condensation of 4-bromoacetophenone **5** with diethyl carbonate were changed from NaH in EtOH/MTBE to ^{t}BuOK in THF (Scheme 12). After quenching the resulting potassium enolate of **9**, the wet THF mixture was taken directly into the nitrosation by adding AcOH and aqueous sodium nitrite. After the formation of the α-isonitroso-β-ketoester **4** was complete, a slow addition of water caused **4** to crystallize directly from the reaction in 85% yield.

Scheme 13



To complete the synthesis, the pyrrole **13** was converted in 98% yield to the desired *N*-methyl pyrrole **1** by reaction with methyl iodide and K_2CO_3 in wet acetone (Scheme 13).

Conclusion

In conclusion, a mild method of conducting Knorr chemistry with β-ketonitriles was developed. This enabled the preparation of pyrrole **1** in kilogram quantities and gave access to AMPA potentiators for biological evaluation. In addition, an analogue series of pyrroles was prepared varying the steric bulk of the alkyl group on the β-ketonitrile Knorr partner, which revealed a lack of tolerance for steric encumberance. Last, an analogue series of pyrroles was prepared with aromatic rings on the β-ketonitrile Knorr partner.

Experimental Section

Useful HPLC Method for Analyzing the Following Reactions. Column: YMC Pack Pro C18, 250 mm × 4.5 mm, 3 μm. UV = 218 nm. Oven temperature : 20 °C. Flow rate: 1 mL/min. Mobile phase: (A) 0.1% TFA in H_2O/CH_3CN 9:1 v/v; (B) CH_3CN. Gradient: $T = 0$ min 95% A 5% B, $T = 10$ min 50% A 50% B, $T = 18$ min 5% A 95% B, $T = 25$ min 5% A 95% B. THF = tetrahydrofuran, MTBE = methyl-*tert*-butyl ether.

3-(4-Bromophenyl)-2-hydroxyimino-3-oxo-propionic Acid Ethyl Ester (4). Step 1: Under a nitrogen atmosphere, potassium *tert*-butoxide (18.13 kg, 161.66 mol) and THF (116 L) were combined, and diethyl carbonate (18 L, 154.31 mol) was added to the mixture between 15 and 21 °C over 0.5 h. The resulting mixture was heated to 38 °C, and a THF (41 L) solution of 4-bromoacetophenone **5** (14.625 kg, 73.48 mol) was added over 0.5 h and stirred for an additional 3 h (HPLC indicated 99.29% conversion of the 4-bromoacetophenone **5**). **Workup:** The reaction mixture was cooled to 0 °C and quenched by the addition of 50% aqueous acetic acid (25 L) over 1 h. The resulting mixture was heated to 20 °C, and water (51 L) and MTBE (60 L) were added. After phase separation, the aqueous phase was extracted with MTBE (44 L), and the organic layers were combined. The organic layers were washed with saturated Na_2CO_3 solution (73 L) and with semisaturated brine (74 L). The organic solvent was reduced by distillation under reduced pressure at 50 °C to 27% of the starting volume. THF (44 L) was added, and the volume added was distilled. **Step 2:** To the solution of β-ketoester **9** in THF, acetic acid (160 L) and water (73 L) were added at 8 °C. To the resulting mixture, a solution of $NaNO_2$ (6.35 kg, 92.00 mol) in water (30 L) was added at 6 to 9 °C over 1.5 h and stirred at about 9 °C for 1.5 h (HPLC indicated 96.51% conversion of the β-ketoester **9**). **Workup:** At 4 to 7 °C, water (147 L) was added over 0.5 h. The resulting suspension was filtered, and the filter cake was washed with water (59 L) and heptane (60 L). The filter cake was dried under a constant flow of nitrogen for 13 h to afford α-isonitroso-β-ketoester **4** (18.73 kg, 85% yield) as a white powder. Mp 148.7−150.7 °C. IR (KBr) 3281, 3219, 3049, 2983, 2870, 1728, 1680, 1586, 1446 cm^{-1}. ^1H NMR (DMSO-d_6, 500.0 MHz) δ 1.22 (3H, t, J = 7.1 Hz), 4.27 (2H, q, J = 7.1 Hz), 7.75 (2H, d, J = 8.8 Hz), 7.83 (2H, d, J = 8.8 Hz), 13.18 (s, 1H). ^{13}C NMR (DMSO-d_6, 125.7 MHz) δ 14.3, 62.2, 129.6, 131.1, 133.1, 133.4, 148.4, 161.2, 191.1. Anal. Calcd for $C_{11}H_{10}BrNO_4$: C, 44.02; H, 3.36; Br, 26.63; N, 4.67. Found: C, 43.98; H, 3.31; Br, 26.65; N, 4.59.

3-(4-Bromophenyl)-4-cyano-5-ethyl-1*H*-pyrrole-2-carboxylic Acid Ethyl Ester (13). Preparation of enolate **17**: Under a nitrogen atmosphere, potassium *tert*-butoxide (13.097 kg, 117.29 mol) was dissolved in THF (68.2 L) at 20 °C. To the resulting mixture, a mixture of ethyl propionate **15** (12.2 L, 106.63 mol) and acetonitrile **16** (6.68 L) was added over 0.75 h at 18 to 21 °C and stirred for 1 h at this temperature (NMR (10 μL of reaction mixture in 1 mL of DMSO-d_6) indicated no **15** remaining). Preparation of pyrrole **13**: In a separate reactor under a nitrogen atmosphere, α-isonitroso-β-ketoester **4** (12.8 kg, 42.65 mol) was dissolved in EtOH (110 L) at 20 °C. The solution was cooled to 1 °C, and zinc (6.429 kg, 98.01 mol) was added portionwise over 0.5 h. A solution of acetic acid (19.5 L), water (2.5 L), and EtOH (11.5 L) was prepared. About 1 to 2% of the ethanolic aqueous acetic acid solution was added to the mixture of **4** and zinc in EtOH at 0 °C to give a slight exotherm and initiate the reduction. The rest of the ethanolic aqueous acetic acid solution was added to the mixture of **4** and zinc in EtOH over 1.5 h between −2 to 2 °C. The suspension was cooled to −5 °C and stirred for 0.25 h (HPLC indicated 98.3% conversion of **4**). The potassium enolate **17** suspension was added over 0.5 h to the zinc suspension at −9 to −2 °C. The reaction was stirred at −4 °C for 3.0 h, warmed to 20 °C over 10 h, and stirred at 20 °C for 3.0 h (HPLC indicated a complete conversion of intermediate **20**). The suspension was filtered, and the filter cake washed with EtOH (6 L). The mother liquor was distilled under reduced pressure at 55 °C to 28% of its original volume. IPA (66 L) was added followed by water (128 L) at 35 to 38 °C and the resulting suspension cooled to 10 °C over 6.0 h and stirred for 6.0 h. The suspension was filtered and washed with water (51 L). The filter cake was dried under a constant flow of nitrogen for 48.0 h to afford pyrrole **13** (12.49 kg, 84% yield) as pale yellow crystals (HPLC 99.73 area%). Mp 212.9−213.6 °C. IR (KBr) 3284, 2982, 2931, 2217, 1660, 1519, 1485 cm^{-1}. ^1H NMR (500.0 MHz, DMSO-d_6) δ 1.14 (3H, t, J = 5.5 Hz), 1.26 (3H, t, J = 7.6 Hz), 2.77 (2H, q, J = 5.5 Hz), 4.16 (2H, q, J = 7.6 Hz), 7.41 (2H dd, J = 6.6 Hz, J = 1.6 Hz), 7.64 (2H, dd, J = 6.6 Hz, J = 1.6 Hz), 12.6 (bs, 1H). ^{13}C NMR (125.7 MHz, DMSO-d_6) δ 13.6, 13.9, 19.7, 60.1, 92.4, 115.4, 117.9, 121.2, 130.6, 131.2, 131.4, 131.8, 146.9, 159.4. Anal. Calcd for $C_{16}H_{15}BrN_2O_2$: C, 55.35; H, 4.35; Br, 23.01; N, 8.07. Found: C, 55.13; H, 4.37; Br, 2.55; N, 7.84. Zinc analysis = 544 ppm.

3-(4-Bromophenyl)-4-cyano-5-ethyl-1-methyl-1*H*-pyrrole-2-carboxylic Acid Ethyl Ester (1). Under a nitrogen atmosphere, pyrrole **13** (625 g, 1.80 mol) and acetone (6.25 L) were combined. The resulting mixture was heated to 30 °C, and K_2CO_3 (powdered, 325 mesh, 497.6 g, 3.60 mol) and D.I. H_2O (62.5 mL, 10 wt % based on **13**) were added. MeI (510.98 g, 3.6 mol) was added to the above reaction mixture over 12 min. The pot temperature rose to a high of 34.1 °C over the following 30 min and then began to drift downward. The reaction was monitored by HPLC, with the complete consumption of starting material noted after 3.5 h.

After a total of 4.0 h at 30 °C, the reaction was cooled to ambient temperature. Water (8.325 L) was added over 2.5 h, causing the product to precipitate. After this addition was complete, the mixture was stirred at ambient temperature for 10 min and then cooled to 0 to 5 °C over ∼1.0 h. The mixture was filtered across a polypropylene pad. The solids were washed with D.I. water (7 L) and pulled dry on the funnel for 0.25 h. The filter cake was dried in a vacuum oven at 40 °C. *N*-Methyl pyrrole **1** was isolated as a pale yellow powder (639.2 g, 98.3% yield) (HPLC 100 area%). Mp 101.0−101.7 °C. IR (KBr): 3347, 2979, 2938, 2216, 1698, 1441, 1510, 1476 cm^{-1}. ^1H NMR (500.0 MHz, $CDCl_3$) δ 1.08 (3H, t, J = 7.1 Hz), 1.34 (3H, t, J = 7.1 Hz), 2.88 (2H, q, J = 7.1 Hz), 3.92 (s, 3H), 4.13 (2H, q, J = 7.1 Hz), 7.26 (2H, d, J = 8.8 Hz), 7.54 (2H, d, J = 8.8 Hz). ^{13}C NMR (125.7 MHz, DMSO-d_6) δ 12.9, 13.4, 18.8, 60.2, 92.0, 115.2, 119.9, 121.1, 130.7, 131.6, 131.9, 132.1, 147.9, 159.8. Anal. Calcd for $C_{17}H_{17}BrN_2O_2$: C, 56.52; H, 4.74; N, 7.75. Found: C, 56.32; H, 4.72; N, 7.73.

Supporting Information Available

Experimental procedures and spectral data for pyrroles **21**−**26**. This material is available free of charge via the Internet at http://pubs.acs.org.

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