

Martin A. Drinan and Timothy D. Lash*

Department of Chemistry, Illinois State University,
Normal, Illinois 61790-4160 USA

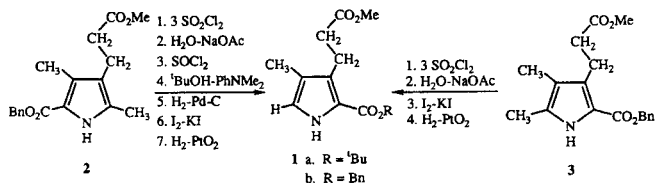
Received June 30, 1993

Condensation of methyl 4-oxobutanoate with nitroethane in the presence of 4-dimethylaminopyridine, followed by treatment with acetic anhydride, afforded a nitroacetoxyster **10b**. Subsequent reaction with isocyanacetate esters and DBU in refluxing tetrahydrofuran gave the synthetically valuable pyrroles **1a** and **1b**.

J. Heterocyclic Chem., **31**, 255 (1994).

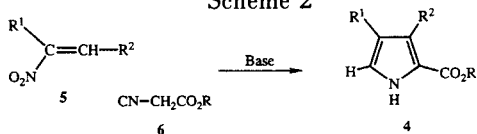
In relation to our ongoing studies on the later stages in the heme biosynthetic pathway [1], we required synthetic samples of a series of metabolic intermediates and their analogs. This work was hampered because the known synthetic routes to the important pyrrolic intermediates **1a** and **1b** were somewhat inadequate. *tert*-Butyl ester **1a** can be prepared in a series of steps [2,3] from the readily available pyrrole **2** (Scheme 1) and the benzyl ester **1b** can similarly be prepared [4] by application of the same type of chemistry starting from pyrrole **3**. Although this methodology provides viable routes to the required pyrroles **1a** and **1b**, the approach is laborious and overall yields are moderate. Hence, we set out to develop an improved route to these important synthetic intermediates [5].

Scheme 1

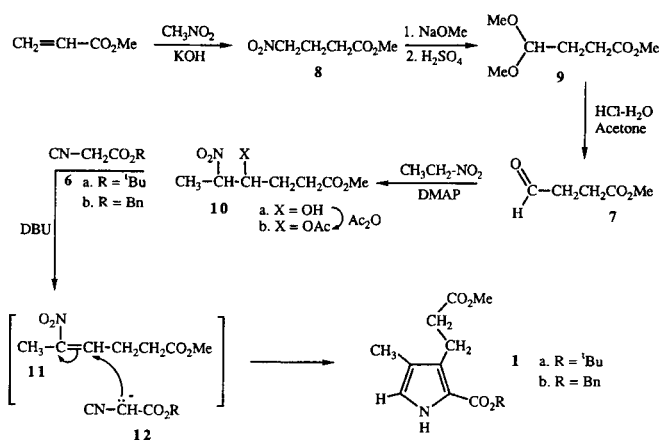


An excellent method for preparing 5-unsubstituted pyrrole-2-carboxylates **4** was recently reported [6] by Barton and Zard (Scheme 2). In this chemistry, nitroalkenes **5** are condensed with esters of isocyanoacetic acid **6** in the presence of a non-nucleophilic base to give the α -unsubstituted pyrroles **4**. This chemistry is a valuable addition to the arsenal of synthetic procedures available to pyrrole chemists and the methodology has been extensively exploited [7-15] in the synthesis of porphyrins and related macrocyclic systems. In order to prepare pyrroles **1a** and **1b** by the Barton and Zard method, methyl 4-oxobutanoate (**7**) was required as a key intermediate. The aldehyde **7** may be obtained from the corresponding nitroester **8** via the Nef reaction (Scheme 3).

Scheme 2



Scheme 3



Methyl 4-nitrobutanoate (**8**) was prepared by the base catalyzed condensation of nitromethane with methyl acrylate. Initially, we used a literature procedure [16] for the synthesis of **8**, but in our hands the yields were consistently much lower (12%) than had been reported. However, by modifying the conditions for this reaction, using aqueous potassium hydroxide as a base and ether as the solvent, the yield was increased to 44%.

Various modified Nef reactions [17,18] have been described in the literature. Oxidizing agents such as potassium permanganate [17] and hydrogen peroxide [18] are often utilized, although it is not always clear why this should be necessary. Our attempts to use this chemistry [17,18] in the preparation of **7** were totally unsuccessful. However, superior results were obtained using the more conventional conditions described by Jacobson [19]. Treatment of **8** with sodium methoxide in methanol generated the nitronate anion and subsequent reaction with concentrated sulfuric acid at -30° gave the acetal **9** in excellent yield. Hydrolysis with hydrochloric acid in aqueous acetone then afforded the required aldehyde **7**.

Condensation of **7** with nitroethane in the presence of 4-dimethylaminopyridine yielded **10a** and subsequent reaction with acetic anhydride gave the corresponding acetate **10b** (Scheme 3). Finally, condensation with *tert*-butyl

isocyanacetate [10,20] in the presence of two equivalents of DBU in refluxing THF gave the required pyrrole **1a** in 57% yield. One equivalent of DBU was required to eliminate a molecule of acetic acid from **10b** to give the nitroalkene **11**. The second equivalent of DBU generated the anion **12** and subsequent nucleophilic addition, cyclization and elimination of nitrous acid afforded the pyrrole. Acetate **10b** was also condensed with benzyl isocyanacetate [9,21] to give the pyrrole benzyl ester **1b** in good yields.

Shortly after this work had been completed, a similar study was reported by Jacobi and DeSimone [22]. These authors carried out the final condensation in the presence of the base *tert*-butyltetramethylguanidine, which is not commercially available, and obtained similar yields of *tert*-butyl ester **1a**, and a related ethyl ester, to those reported in this study. However, these parallel studies were reported [22] to not be suitable for preparing larger quantities (> 1 g) of these pyrroles. In contrast, the results reported in this paper provide a convenient and reproducible methodology for the preparation of multigram quantities of pyrroles **1a** and **1b** starting from inexpensive starting materials.

EXPERIMENTAL

Methyl acrylate, nitromethane, nitroethane and DBU were purchased from Aldrich Chemical Co. and were used without further purification. *tert*-Butyl isocyanacetate and benzyl isocyanacetate were prepared by adaptation of literature procedures [20,21]. Silica gel (70-230 mesh, 60 A) for column chromatography was obtained from Aldrich Chemical Co.; columns were prepared by slurry packing. Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. The ir spectra were recorded on a Perkin-Elmer 1600 Series FT-IR Spectrometer and nmr spectra were obtained on a Varian Gemini-300 nmr spectrometer.

Methyl 4-Nitrobutanoate (**8**).

Potassium hydroxide (28.0 g) in water (200 ml) was added dropwise to a stirred mixture of nitromethane (180 ml) and methyl acrylate (100 ml) in diethyl ether (200 ml). The reaction was highly exothermic and an ice bath was used to reduce losses of ether solvent. Once the addition was complete, the dark solution was vigorously stirred at room temperature overnight. The organic layer was separated and the aqueous phase extracted with ether. The combined organic solutions were dried over magnesium sulfate, filtered and the solvent evaporated on a rotary evaporator. The residue was distilled under reduced pressure to give methyl 4-nitrobutanoate (71.51 g, 44%) as a pale yellow liquid, bp 74-82° at 0.25 torr (lit bp [16] 81-82° at 1.5 torr); ir (neat): ν 1737 (C=O str), 1555, 1374 (NO₂ str); pmr (deuteriochloroform): δ 2.32 (2H, m, CH₂CH₂CH₂), 2.49 (2H, t, J = 7 Hz, CH₂CO), 3.71 (3H, s, OCH₃), 4.49 (2H, t, J = 6.6 Hz, CH₂NO₂).

Methyl 4,4-Dimethoxybutanoate (**9**).

A solution of the foregoing nitroester (41.89 g) in anhydrous methanol (150 ml) was added to a stirred 3M sodium methoxide

solution in methanol (110 ml) and the resulting mixture was stirred at room temperature for 20 minutes. Methanol (200 ml) was placed in a three necked 1000 ml round bottomed flask and cooled to -10° with a dry ice-acetone bath. Concentrated sulfuric acid (90 ml) was added dropwise to the stirred solution, while maintaining the temperature at -10°. The temperature of the mixture was lowered to -30°, at which point the nitroester/sodium methoxide solution was added while maintaining the temperature at -30°. After the addition was complete, the mixture was stirred at room temperature overnight.

The mixture was added to 700 ml of ice-water and 150 ml of dichloromethane. The organic phase was separated and the aqueous layer extracted with dichloromethane (2 x 75 ml). The combined organic solutions were washed with 1M sodium hydroxide solution (200 ml), dried over potassium carbonate, filtered and the solvent removed under reduced pressure. The resulting oil (36.66 g, 79%), which was essentially pure by nmr spectroscopy, was used without further purification; ir (neat): ν 1739 (C=O str); pmr (deuteriochloroform): δ 1.93 (2H, m, CH₂CH₂CO), 2.38 (2H, t, J = 7.3 Hz, CH₂CO), 3.33 (6H, s, 2 x OCH₃), 3.68 (3H, s, CO₂CH₃), 4.40 (1H, t, CH(OMe)₂).

Methyl 4-Oxobutanoate (**7**) [23].

Concentrated hydrochloric acid (5 ml) in water (200 ml) was added to a solution of methyl 4,4-dimethoxybutanoate (17.83 g) in acetone (100 ml) and the mixture stirred at room temperature for 1 hour. The mixture was saturated with sodium chloride, and extracted with dichloromethane (20 ml) and acetone/dichloromethane (1:2 v/v, 3 x 30 ml). The combined organic solutions were washed with potassium bicarbonate solution (5 g in 125 ml water) and the aqueous solution back extracted with dichloromethane (20 ml). The organic solutions were dried over magnesium sulfate, filtered and the solvent removed under reduced pressure to give methyl 4-oxobutanoate as a colorless oil (11.14 g, 87%). The aldehyde was used without further purification. Although the product was rather unstable, it could be stored in the freezer for several weeks; ir (neat): ν 2955, 2915 (sp³ CH str), 2838, 2737 (aldehyde CH str), 1737 (ester C=O str), 1720 (aldehyde C=O str); pmr (deuteriochloroform): δ 2.63 (2H, t), 2.81 (2H, t) (CH₂CH₂), 3.70 (3H, s, OCH₃), 9.82 (1H, s, CHO) [24].

tert-Butyl 3-(2-Methoxycarbonyl)ethyl-4-methylpyrrole-2-carboxylate (**1a**).

Nitroethane (16.79 g) was added dropwise to a stirred mixture of methyl 4-oxobutanoate (6.49 g) and 4-dimethylaminopyridine (1.37 g) in dichloromethane (30 ml) and the resulting mixture was stirred at room temperature for 30 hours. Acetic anhydride (16 ml) in dichloromethane (30 ml) was then added and the resulting mixture stirred for an additional 6 hours. The flask was cooled in an ice bath and methanol was added to destroy the remaining acetic anhydride. The reaction mixture was neutralized with potassium bicarbonate solution (5.0 g in 70 ml of water), the organic layer separated and the aqueous phase extracted with dichloromethane. The organic solutions were combined and the solvent was removed on a rotary evaporator, maintaining the temperature below 40°. The excess nitroethane was removed at 0.5 torr by attaching a vacuum pump to the rotary evaporator. The residue was chromatographed on a silica column (3.3 x 10 cm), eluting with toluene, and the solvent removed under reduced pressure to give methyl 5-nitro-4-acetoxyhexanoate (**10b**) as a pale yellow oil (7.82 g, 56%).

Methyl 5-nitro-4-acetoxyhexanoate (4.75 g) was added dropwise to a stirred solution of *tert*-butyl isocynoacetate (3.43 g) and 1,8-diazabicyclo[5.4.0]undec-7-ene (6.84 g) in tetrahydrofuran (14 ml), maintaining the temperature of the reaction mixture between 20-30° with the aid of an ice bath. Once the addition was complete, the mixture was stirred under reflux for 16-20 hours. The mixture was diluted with dichloromethane (50 ml) and washed with 10% hydrochloric acid (2 x 40 ml). The aqueous solutions were back extracted with dichloromethane (2 x 20 ml) and the combined organic layers dried over magnesium sulfate, filtered and evaporated under reduced pressure. The dark residue was chromatographed on a silica column (3.3 x 12 cm), eluting with toluene, and the solvent evaporated under reduced pressure to give the title pyrrole as a pale yellow oil (3.10 g, 57%). The product was identical (pmr, ir, tlc) to an authentic sample of **1a** prepared by literature procedures [2,3]; ir (neat): ν 3318 (NH str), 1738 (aliphatic ester C=O str), 1686 (pyrrole C=O str) cm^{-1} ; pmr (deuteriochloroform): δ 1.56 (9H, s, ^tBu), 2.03 (3H, s, pyrrole-CH₃), 2.53 (2H, t, J = 8.1 Hz, CH₂CO), 3.01 (2H, t, J = 8.1 Hz, pyrrole-CH₂), 3.67 (3H, s, OCH₃), 6.63 (1H, d, J = 2.3 Hz, pyrrole-H), 8.9 (1H, br, NH); cmr (deuteriochloroform): δ 9.8 (pyrrole-CH₃), 20.6 (pyrrole-CH₂), 28.5 (^tBu), 35.1 (CH₂CO), 51.4 (OCH₃), 80.8 (C(CH₃)₃), 119.8 (C-5), 120.0, 120.5 (C-2,4), 128.0 (C-3), 160.9 (pyrrole-C=O), 173.7 (aliphatic ester C=O).

Benzyl 3-(2-Methoxycarbonyl-ethyl)-4-methylpyrrole-2-carboxylate (1b).

The title pyrrole was prepared from **10b** (1.33 g) and benzyl isocynoacetate (1.00 g) by the procedure detailed above. The crude product was chromatographed on a silica column, eluting with toluene, to give **1b** as a pale straw colored oil which solidified on standing (0.91 g; 53%). A sample was recrystallized from dichloromethane-hexane to give fluffy white needles, mp 60.5-61° (lit mp [4] 57-58°); ir (nujol mull): ν 3312 (NH str), 1727 (aliphatic ester C=O str), 1669 (pyrrole C=O str) cm^{-1} ; pmr (deuteriochloroform): δ 2.03 (3H, s, pyrrole-CH₃), 2.52 (2H, t, J = 8.0 Hz, CH₂CO), 3.04 (2H, t, J = 8.0 Hz, pyrrole-CH₂), 3.63 (3H, s, OCH₃), 5.29 (2H, s, OCH₂), 6.68 (1H, d, J = 2.4 Hz, 5-H), 7.3-7.45 (5H, m, Ph), 8.8 (1H, br, NH); cmr (deuteriochloroform): δ 9.7 (pyrrole-CH₃), 20.5 (pyrrole-CH₂), 34.8 (CH₂CO), 51.4 (OCH₃), 65.9 (OCH₂Ph), 118.2, 120.4 (C-2,4), 120.6 (C-5), 128.2 (*p*-Ph), 128.3 (*o*-Ph), 128.6 (*m*-Ph), 129.6 (C-3), 136.2 (Ph C_{ar}), 160.8 (pyrrole-C=O), 173.6 (aliphatic ester C=O).

Acknowledgements.

The work was supported by a grant from the National Institutes of Health (Grant No. 1 R15 DK45206-01). We also thank the National Science Foundation (Grant No. CHE-9001175) for providing funds to purchase a Varian 300 MHz NMR spectrometer.

REFERENCES AND NOTES

- [1] T. D. Lash, *Biochem. J.*, **278**, 901 (1991).
 [2a] A. H. Jackson, G. W. Kenner and K. M. Smith, *J. Chem. Soc. (C)*,

502 (1971); [b] J. E. Bishop, J. F. O'Connell and H. Rapoport, *J. Org. Chem.*, **56**, 5079 (1991).

[3] A. H. Jackson, T. D. Lash and D. J. Ryder, *J. Chem. Soc., Perkin Trans. I*, 287 (1987).

[4] H. M. G. Al-Hazimi, A. H. Jackson, D. W. Knight and T. D. Lash, *J. Chem. Soc., Perkin Trans. I*, 265 (1987).

[5] An alternative route to this system was recently noted, using the Paal-Knorr condensation, but details of this work are not presently available. P. A. Jacobi and G. Cai, *Tetrahedron Letters*, **32**, 1765 (1991).

[6a] D. H. R. Barton and S. Z. Zard, *J. Chem. Soc., Chem. Commun.*, 1098 (1985); [b] D. H. R. Barton, J. Kervagoret and S. Z. Zard, *Tetrahedron*, **46**, 7587 (1990).

[7a] D. A. May, Jr. and T. D. Lash, *J. Org. Chem.*, **57**, 4820 (1992);

[b] T. D. Lash, R. P. Balasubramaniam, J. J. Catarello, M. C. Johnson, D. A. May, Jr., K. A. Bladel, J. M. Feeley, M. C. Hoehner, T. G. Marron, T. H. Nguyen, T. J. Perun, Jr., D. M. Quizon, C. M. Shiner and A. Watson, *Energy Fuels*, **4**, 668 (1990).

[8] T. D. Lash, *Advances in Nitrogen Heterocycles*, Vol **1**, C. J. Moody, ed, JAI Press, in press.

[9] J. B. Bellettini, M. S. Thesis, Illinois State University, 1992.

[10a] D. M. Quizon-Colquitt, M. S. Thesis, Illinois State University, 1992; [b] A. Watson, M. S. Thesis, Illinois State University, 1992.

[11] N. Ono, H. Kawamura, M. Bougauchi and K. Maruyama, *Tetrahedron*, **46**, 7483 (1990) and references cited therein.

[12] J. L. Sessler, M. R. Johnson, S. E. Creager, J. C. Fettinger and J. A. Ibers, *J. Am. Chem. Soc.*, **112**, 9310 (1990).

[13] J. L. Sessler, A. Mozaffari and M. R. Johnson, *Org. Synth.*, **70**, 68 (1991).

[14] C. Bauder, R. Ocampo and H. J. Callot, *Tetrahedron*, **48**, 5135 (1992).

[15] C. J. Medforth, M. O. Senge, K. M. Smith, L. D. Sparks and J. A. Shelnut, *J. Am. Chem. Soc.*, **114**, 9859 (1992).

[16] D. W. Chasar, *Synthesis*, 841 (1982).

[17] N. Kornblum, A. S. Erickson, W. J. Kelly and B. Henggl, *J. Org. Chem.*, **47**, 4534 (1982). Ono has reported [11] that methyl 4-oxobutanoate may be prepared by this approach, but in our hands oxidation to the corresponding carboxylic acid generally took place. The very large quantities of solvent required in this procedure also made this methodology far less desirable.

[18a] G. A. Olah, M. Arvanaghi, Y. D. Vankar and G. K. S. Prakash, *Synthesis*, 662 (1980); [b] R. Ballini and M. Petrini, *Synthesis*, 1024 (1986).

[19] R. M. Jacobson, *Tetrahedron Letters*, 3215 (1974).

[20] I. Ugi, U. Fetzer, U. Eholzer, H. Knuffer and K. Offermann, *Angew. Chem., Int. Ed. Engl.*, **4**, 472 (1965); V. Meduna, P. Sawlewicz and R. Vogt, *Synth. Commun.*, **19**, 1487 (1989); See also G. D. Hartman and L. M. Weinstock, *Org. Synth.*, **59**, 183 (1979).

[21] P. J. Claes and H. Vanderhaeghe, *Eur. J. Med. Chem.*, **11**, 359 (1976).

[22] P. A. Jacobi and R. W. DeSimone, *Tetrahedron Letters*, **33**, 6239 (1992).

[23a] K. Hirai, H. Suzuki, H. Kashiwagi, Y. Moro-Oka and T. Ikawa, *Chem. Letters*, 23 (1982); [b] A. Manzocchi, F. Astori and E. Santaniello, *Synthesis*, 324 (1983); [c] E. Kunkel, I. Reichelt and H.-U. Reißig, *Liebigs Ann. Chem.*, 802 (1984).

[24] In the pmr spectrum of methyl 4-oxobutanoate (**7**), no coupling was observed for the CH₂CHO fragment. This was in accord with previous literature reports for this compound [23b,c].