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AN IMPROVED SYNTHESIS OF 2-*n*-(PROPYL)-1*H*-IMIDAZOLE-4,5-DICARBOXYLIC ACID DIETHYL ESTER

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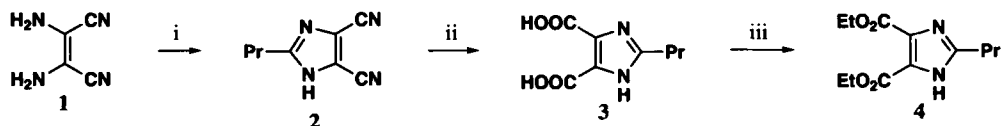
18. N. Bourne, A. Williams, K. T. Douglas and T. R. Penkava, *J. Chem. Soc., Perkin Trans. 2*, 1827 (1984).
19. F. Pavanetto, M. Mazza, L. Montanari and T. Modena, *Farmaco, Ed. Sci.*, **34**, 808 (1979).
20. K. Yoshida, M. Isobe, K. Yano and K. Nagamatsu, *Bull. Chem. Soc. Jpn*, **58**, 2143 (1985).
21. H. K. Oh, J. E. Park, D. D. Sung and I. Lee, *J. Org. Chem.*, **69**, 3150 (2004).
22. T. Mizuno, I. Nishiguchi and T. Hirashima, *Tetrahedron*, **49**, 2403 (1993).
23. M. Koketsu, C. Kobayashi and H. Ishihara, *Heteroatom Chem.*, **14**, 374 (2003)

**AN IMPROVED SYNTHESIS OF
2-*n*-(PROPYL)-1H-IMIDAZOLE-4,5-DICARBOXYLIC ACID DIETHYL ESTER**

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Diethyl 2-(*n*-propyl)-1H-imidazole-4,5-dicarboxylate (**4**) is an intermediate in the synthesis of *olmesartan*, a non-peptide angiotensin II receptor antagonist.¹⁻² Yanagisawa *et al.*³⁻⁴ reported using diaminomaleonitrile and trimethyl orthobutyrate as starting materials. Thus, diaminomaleonitrile was treated with trimethyl orthobutyrate in acetonitrile to provide the 2-(*n*-propyl)-1H-imidazole-4,5-dicarbonitrile (96% yield) which was then hydrolyzed under acidic conditions to afford **3** (80%). Esterification of **3** in ethanol in the presence of hydrogen chloride gave **4** in 86% yield (*Scheme 1*).

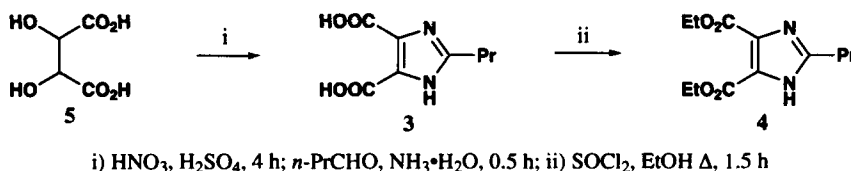


i) *n*-PrC(OMe)₃; MeCN, Δ, 5 h, xylene, 7 h; ii) HCl, H₂O, Δ, 8 h; iii) HCl (gas), EtOH, 3 h

Scheme 1

However, this method is not practical for large-scale preparation because diaminomaleonitrile is toxic and expensive, requiring long reaction times and tedious work-up. To overcome

these limitations, we report herein an improved approach for the preparation of **4** starting from tartaric acid (**5**), an easily available, inexpensive and bio-renewable substrate (*Scheme 2*), in a two-step procedure with improved overall yield (70%). In this procedure treatment of tartaric acid



Scheme 2

with *n*-butyraldehyde and aqueous ammonia to give 2-*n*-propyl-1*H*-imidazole-4,5-dicarboxylic acid **3** in 74% yield, followed by esterification of **3** with thionyl chloride in ethanol at reflux for 1.5h to give a 94% yield of **4**. When reaction was complete, the reaction mixture was poured into saturated sodium bicarbonate solution without distilling the thionyl chloride.

EXPERIMENTAL SECTION

^1H NMR spectra were recorded using a Bruker AC 500 instrument with TMS as the internal standard. Mass spectra were obtained on a Micromass LCT KC317. IR spectra were determined on a Nicolet Magna IR 550 in KBr discs. Mps were taken on a WRS-1 capillary apparatus and are uncorrected.

2-(*n*-Propyl)-1*H*-imidazole-4,5-dicarboxylic Acid.- To a solution of tartaric acid (100.0 g, 0.67 mol) in fuming nitric acid (400 mL) was added dropwise conc. sulfuric acid (400 mL) at room temperature under mechanical stirring. After standing for 2 h, the precipitated solid was collected, suspended in ice-water (1000 mL), and basified to pH 8 with conc. aqueous ammonia. To this stirred mixture was added slowly a mixture of *n*-butyraldehyde (202.0 g, 2.81 mol) and aqueous ammonia (228.0 g, 6.51 mol). The temperature was controlled at 0°C with ice-water bath. After 0.5 h, the resulting mixture was acidified to pH 3 and the precipitate thus formed was collected, washed with ethanol and dried under vacuum to give a white solid (97.0 g, 74%), mp. 262-264°C, *lit.*³ 261-263°C. MS (EI) m/z (%): $[\text{M}]^+ = 198$. IR (KBr): 3310 (N-H), 1645 (C=O) cm^{-1} . ^1H NMR (CDCl_3): δ 0.97 (t, 3H, $J = 7.5$ Hz, $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.77 (m, 2H, $J = 7.5$ Hz, $\text{CH}_2\text{CH}_2\text{CH}_3$), 2.72 (t, 2H, $J = 7.5$ Hz, $\text{CH}_2\text{CH}_2\text{CH}_3$), 10.12 (s, 1H, N-H). ^{13}C NMR (CDCl_3): δ 169.56, 160.12, 136.73, 35.56, 25.67, 14.16.

Diethyl 2-(*n*-Propyl)-1*H*-imidazole-4,5-dicarboxylate.- To a stirred solution of **3** (20.0 g, 0.10 mol) and conc. hydrochloric acid (0.5 mL) in ethanol (300 mL) was slowly added thionyl chloride (26.2 g, 0.22 mol) dropwise while the temperature was maintained below 5°C. After addition, the mixture was stirred at 5°C for 10 min and then heated to gentle reflux for 1.5h. The reaction mixture was cooled to room temperature and neutralized to pH 7 using saturated aqueous sodium bicarbonate. The mixture was extracted with ethyl acetate (250 mL). The combined organic layers were dried (Na_2SO_4), and evaporated under reduced pressure to afford

the desired product **4** as a white solid (24.2 g, 94%), mp. 83-85°C, *lit.*³ mp. 84-86°C. MS (EI) m/z (%): $[M]^+ = 254$. IR (KBr): 3320, 1748, 1722, 1535, 1066 cm^{-1} ; ^1H NMR (CDCl_3): δ 0.97 (t, 3H, $J = 7.5$ Hz, $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.79 (m, 2H, $J = 7.5$ Hz, $\text{CH}_2\text{CH}_2\text{CH}_3$), 2.78 (t, 2H, $J = 7.5$ Hz, $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.38 (t, 6H, $J = 7$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$), 4.39 (q, 4H, $J = 7$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$), 10.15 (s, 1H, N-H). ^{13}C NMR (CDCl_3): δ 166.42, 159.23, 133.51, 62.25, 35.54, 25.59, 15.46, 14.17.

REFERENCES

1. M. Greathouse, *Congest Heart Failure*, **8**, 313 (2002).
2. J. M. Neutel, W. J. Elliott, J. L. Izzo, C. L. Chen and H. N. Masonson, *J. Clinical Hypertension*, **4**, 325 (2002).
3. H. Yanagisawa, Y. Amemiya, T. Kanazaki, Y. Shimoji, K. Fujimoto, Y. Kitahara, T. Sada, M. Mizuno, M. Ikeda, S. Miyamoto, Y. Furukawa and H. Koike, *J. Med. Chem.*, **39**, 323 (1996).
4. H. Yanagisawa, Y. Shimoji, K. Fujimoto, T. Kanazaki, Y. Amemiya, H. Koike, and T. Sada, *EP* 503785, (1992); *Chem. Abstr.*, **118**, 22240 (1992).

A NEW, EFFICIENT AND SIMPLE METHOD FOR THE SYNTHESIS OF THIOAMIDES FROM NITRILES

Submitted by Babak Kaboudin*, Dawood Elhamifar and Fatemeh Farjadian
(12/21/05)

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Since organic sulfur compounds have become increasingly useful and important in organic synthesis, the development of convenient and practical methods for the preparation of thioamides is desirable. Thioamides are valuable intermediates useful as building blocks in many areas of chemistry especially in the Hantzsch thiazole synthesis.¹ The following methods have been reported in the literature: (i) three-component condensation of an aldehyde, elemental sulfur and an amine at high temperature and long reaction times,² (ii) thionation of the corresponding amide with an electrophilic reagent such as Lawesson's reagent, phosphorous pentasulfide or reaction with a nucleophilic thionating reagent, by electrophilic activation of an amide,³ (iii)