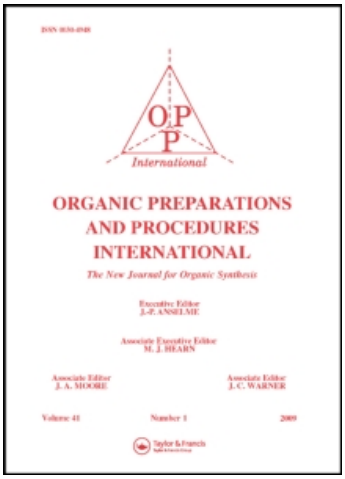

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IMPROVED SYNTHESIS OF 3-AMINOFURAZAN-4-CARBOXYLIC ACID

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OPPI BRIEFS

IMPROVED SYNTHESIS OF 3-AMINOFURAZAN-4-CARBOXYLIC ACID

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(03/30/04)

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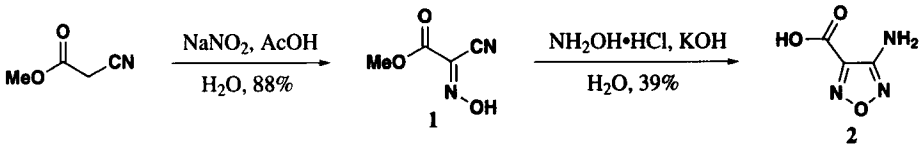
In the course of the synthesis of a variety of heterocyclic carboxylic acids for our studies on bioactive amides, a new route for 3-aminofurazan-4-carboxylic acid (**2**) was discovered. The advent of combinatorial chemistry and high-throughput screening has increased the need for a diverse pool of molecular building blocks that are used to construct libraries of biologically active compounds. Rare and unnatural β-amino acids such as **2** are useful molecules for these purposes.



Amino acid **2** was obtained in two convenient steps from readily accessible materials and, although the overall yield is 34%, the chemistry provides a safer, more direct route than previous accounts in which **2** was isolated as an unexpected side-product in the basic hydrolysis of a poly-oxime nitrile,[1] of the methyl iminoester of **2**,[2] and of 7-amino-4*H*-furazano[3,4-c][1,2,6] thiadiazine 5,5-dioxide.[3] Amino acid **2** was isolated as a fine white powder and has been prepared on a multi-gram scale.

EXPERIMENTAL SECTION

Melting points are uncorrected. All reagents were purchased and used without further purification. Proton and ^{13}C NMR spectra were obtained on a Varian Gemini 300 spectrometer. Infrared spectra were obtained on a Bio-Rad spectrophotometer. Mass spectra were obtained on a Hewlett-Packard Model 5989A mass spectrometer using the electron impact-direct insertion probe (EI-DIP) and are reported as *m/z*. Microanalyses were performed by Midwest Microlab of Indianapolis, Indiana.

Methyl 2-Cyano-2-(hydroxyimino)acetate (1): Acetic acid (11.5 mL, 0.200 mol) was added drop-wise to a 0°C suspension of methyl cyanoacetate (13.35 mL, 0.151 mol) and $NaNO_2$ (12.5 g, 0.181 mol) in H_2O (60 mL). The reaction was allowed to warm to ambient temperature and after 4 hr the mixture was cooled to 0°C and adjusted to pH = 1 with conc. HCl. The solution was extracted with EtOAc and the organic phase was dried ($MgSO_4$) and conc. *in vacuo* to give 17.0 g (88%) of a white solid, mp 118-119°C, *lit.*[4] mp 120-122°C, which was used without further purification; $[M]^+$ = 128. IR (KBr): 3388, 3238, 2848, 2231, 1740, 1450, 1310, 1069, 817, 762 cm^{-1}; ^1H NMR (300MHz, DMSO-d_6): δ 3.63 (s 3H) ppm; ^{13}C NMR (300MHz, DMSO-d_6): δ 161.0, 126.5, 109.0, 53.9 ppm.

3-Aminofurazan-4-carboxylic Acid (2): To a solution of hydroxylamine hydrochloride (8.13 g, 0.117 mol) in H_2O (120 mL) was added solid KOH (13.1 g, 0.234 mol) portionwise, followed by a solution of **1** (15.0 g, 0.117 mol) in H_2O (30 mL). After 1.5 hr, additional KOH (13.1 g, 0.234 mol) was added to the orange-red solution portion-wise and the reaction heated to 80°C. After 2 hr, the mixture was cooled to 0°C and acidified to pH < 1 with conc. HCl. The resulting white precipitate was collected and dried by azeotropic removal of water with toluene (2x) to yield 5.90 g (39%) of a white solid, mp 220°C (dec.)[5], *lit.*[3] mp 200°C; $[M]^+$ = 129. IR (KBr): 3444, 3332, 1746, 1620, 1510 cm^{-1}; ^1H NMR (300MHz, DMSO-d_6): δ 10.3 (1H, br s), 6.3 (3H, br s) ppm; ^{13}C NMR (300MHz, DMSO-d_6): δ 161.3, 157.1, 143.3 ppm.

Anal. Calcd for $C_3H_3N_3O_3$: C, 27.92, H, 2.34, N, 32.55. Found: C, 28.17, H, 2.06, N, 32.42

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5. The compound begins to decompose at 200°C, but does not melt until 220°C.

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