Improved Preparation of Racemic 2-Amino-3-(heteroaryl)propanoic Acids and Related Compounds Containing a Furan or Thiophene Nucleus

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Racemic 2-amino-3-(heteroaryl)propanoic acids (1), mostly with a furan or thiophene nucleus as a heteroaryl group, were synthesized in 48—94% yield by the reduction of 3-(heteroaryl)-2-(hydroxyimino)propanoic acids (5) with zinc dust and formic acid in the presence of a catalytic amount of iron dust at 60 °C for 2 h. Under these conditions, unfavorable hydrogenolysis of bromine on the thiophene nucleus does not occur. Traditional N-formylation of the prepared 3-(heteroaryl)alanine (1) with a mixture of formic acid and acetic anhydride afforded 2-(formylamino)-3-(heteroaryl)propanoic acids (6) in 51—95% yield.

Key words 3-(furan-2-yl)alanine; unnatural amino acid; hydroxyimino acid; N-formyl amino acid; reduction

Unnatural l-amino acids, usually obtained via chemical synthesis, are key moieties in agrochemicals and drugs. 2,3) For instance, the L-form of 3-(furan-2-yl)alanine (1a), used as a 500 mg/l spray on tomatoes, completely prevented infection by Phytophthora infestans, 4) and the L-form of 3-(furan-3-yl)alanine (1b) has fungicidal activity. 5) Further, 3-(thiophen-2-yl)alanine (1d), 3-(pyridin-3-yl)alanine (1h), and 3-(1,3-thiazol-4-yl)alanine (1i) have been used as tools for drug discovery research, leading to antiasthmatic, anticonvulsant and antihistaminic agents containing a 3-(heteroaryl)alanine moiety. 6)

We have recently reported that 2-(chloroacetylamino)-3-(furan-2-yl)propanoic acid (2) showed root growth-inhibitory activity towards rape seedlings. 7) As a continuation of that work, we investigated a convenient route to a key intermediate, namely, racemic 3-(furan-2-yl)alanine (1a). This furan derivative (1a) has been synthesized in several ways, e.g., (i) diketopiperazine method, 8) (ii) hydantoin method, 9,10) (iii) rhodanine method, 11—13) and (iv) halomethylfuran-acylamidomalonate method. 14—18)

However, methods (i—iii) involve reduction using sodium amalgam, and subsequent disposal is damaging to the environment. Additionally, the utility of methods (i—iii) is limited by the difficulty of separating 1a from the reaction mixture containing inorganic by-products. Method (iv) utilizes halomethylfuran, which is extremely unstable and tends to decompose with explosive violence. 19) Hence, as shown in Chart 2, we considered that reduction of the hydroxyimino group of 3-(furan-2-yl)-2-(hydroxyimino)propanoic acid (5a) according to the rhodanine method (iii) would be the best way to obtain 3-(furan-2-yl)alanine (1a), if we were able to replace sodium amalgam with an effective reducing agent that could be used in a nonaqueous solvent.

Thus, we were interested in two reports regarding reagents for the reduction of a hydroxyimino group to an amino group. One described the treatment of 4-ethoxy-1-(hydroxyimino)-1-(pyridine-3-yl)butane with zinc/acetic acid in the presence of iron filings to afford the corresponding amino compound. 20) The other described the reductive formylation of diethyl 2-nitrosomalonate using zinc/formic acid to give diethyl formamidomalonate. 21—23) We decided to use iron dust in place of iron filings in the first method, and in the second one, we preferred the combination of zinc/formic acid as reducing agent.

Our results led us to examine the possibility that zinc/formic acid may be generally effective for the reductive conversion of α-hydroxyimino acids (5) to the corresponding 3-substituted alanines (1), as shown in Table 1.

First of all, reduction of 3-(furan-2-yl)-2-(hydroxyimino)-
propanoic acid (5a) in formic acid solution with zinc dust in the presence of a catalytic amount of iron dust afforded, after removal of unchanged zinc dust and by-products, 77% yield of 3-(furan-2-yl)alanine (1a), which was sufficiently pure for use in the subsequent reaction. There was no evidence of the formation of N-formyl-3-(furan-2-yl)alanine (6a) under the above reaction conditions.

The literature has indicated that hydrogenolysis of 3-(5-bromothiophen-2-yl)-2-(hydroxyimino)propanoic acid (5g) with 2% sodium amalgam affords 3-(thiophen-2-yl)-alanine (1d) as the result of the removal of bromine from the thiophene ring.24 As a check on the reducing ability, treatment of 5g with zinc/formic acid for 2 h at 60 °C gave the desired 3-(5-bromothiophen-2-yl)-alanine (1g) in 48% yield along with some tarry degradation products.

Next, we tried to prepare N-formyl-3-(heteroaryl)alanines (6), which should serve as starting materials for the examination of optical resolution using the brucine salt method.25 Thus, a formic acid solution of 3-(furan-2-yl)alanine (1a) was treated with acetic anhydride for 1 h at room temperature to give the corresponding N-formyl derivative (6a) in 82% yield. Incidentally, the in situ N-formylation of 3-(furan-2-yl)alanine (1a) in formic acid solution, after removal of unchanged zinc dust and zinc formate generated as a by-product, was achieved by direct reaction with acetic anhydride for 1 h at room temperature to afford the desired 6a in a lower yield (52%) than the 82% yield mentioned above. The similar in situ formylation of the other 3-(heteroaryl)alanines (1b–g) was accomplished in 51—95% yield.

In summary, the reduction of 3-(heteroaryl)-2-(hydroxyimino)propanoic acids (5) with zinc/formic acid in the presence of a catalytic amount of iron dust provided 3-(heteroaryl)alanines (1) in 48—94% yield. The improved reduction appears to have synthetic value, particularly for 3-(furan-2-yl)alanine (1a).

### Experimental

2-Furaldehyde, 3-furaldehyde, 5-methylfurfural, 2-thiophenecarboxaldehyde, 3-thiophenecarboxaldehyde, 5-bromo-2-thiophenecarboxaldehydes, 5-methyl-2-thiophenecarboxaldehyde, rhodamine, zinc dust, iron dust, and formic acid (about 99%) were purchased from commercial sources and used as received. The following 3-(heteroaryl)-2-thioxopropanoic acids (4) were prepared according to the directions of Julian and Sturgis,26 (furan-3-yl)- (4b), (5-methylfurfuran-2-yl)- (4c), (thiophen-3-yl)- (4e), (2-thiophen-2-yl)- (4f), (5-thiophenylfuran-2-yl)- (4l), (3-bromothiophen-2-yl)- (4g).

Melting points were taken on a Yanagimoto melting point apparatus and are uncorrected. IR spectra were measured on an Avanta model 320 FT-IR spectrometer. 1H-NMR spectra were measured on a Bruker DPX-400 spectrometer (400 MHz) using tetramethylsilane as an internal reference, and chemical shifts were recorded as delta values.

3-(Furan-3-yl)-2-(hydroxyimino)propanoic Acid (5b) The procedure of Plucker27 was employed with some modifications. Hydroxylamine hydrochloride (11.7 g, 168 mmol) in MeOH (120 ml) was allowed to react with sodium ethoxide [prepared from sodium metal (4.3 g, 187 mg atom) and anhydrous EtOH (200 ml)]. After removal of inorganic material by filtration, the filtrate containing free hydroxylamine was added to 3-(furan-3-yl)-2-thioxopropanoic acid (4b) (9.5 g, 56 mmol), and then the mixture was refluxed for 20 min. After removal of the solvent in vacuo, the residue was dissolved in water. The aqueous solution was acidified with 10% HCl and extracted with ether. Washing of the ether extract with water, followed by drying over sodium sulfate and evaporation of the solvent, left the crude product (5b), which was recrystallized from toluene to give 7.6 g (80%) of 5b, mp 158—160 °C. IR (single bounce ATR): 1698 (CO) cm\(^{-1}\). DMSO-\(_d_6\) \(\delta\) 3.54 (1H, s, CH\(_2\)), 6.30, 7.40 and 7.52 (each 1H, each m, 5, 7 Hz, CH), 5.91 (1H, dd, J = 2.18 (3H, s, CH\(_3\)), 3.07 (1H, s, CH\(_2\)), 5.85 and 5.91 (each 1H, each d, J = 3 Hz, furan-3H and -4H).

3-(Furan-3-yl)-2-(hydroxyimino)propanoic Acid (5c) Treatment of 3-(5-methylfurfuran-2-yl)-2-thioxopropanoic acid (4e) (3.9 g, 20 mmol) with hydroxylamine [prepared from hydroxylamine hydrochloride (4.2 g, 60 mmol) and sodium metal (1.4 g, 60 mg atom)] as described for the preparation of 5b gave 5c, yield 2.7 g (73%); mp 139—141 °C (from toluene) (lit.\(^{30}\)) 136—137 °C). IR (single bounce ATR): 1701 (CO) cm\(^{-1}\). \(\text{H-NMR (DMSO-}d_6\) \(\delta\) 2.18 (3H, s, CH\(_3\)), 3.78 (2H, s, CH\(_2\)), 5.85 and 5.91 (each 1H, each d, J = 3 Hz, furan-3H and -4H).

3-(Furan-3-yl)-2-(hydroxyimino)propanoic Acid (5d) Treatment of 3-(thiophen-3-yl)-2-thioxopropanoic acid (4e) (3.7 g, 20 mmol) with hydroxylamine [prepared from hydroxylamine hydrochloride (4.2 g, 60 mmol) and sodium metal (1.4 g, 60 mg atom)] as described for the preparation of 5b gave 5d, yield 3.5 g (89%); mp 167—169 °C (from toluene). IR (single bounce ATR): 1698 (CO) cm\(^{-1}\). \(\text{H-NMR (DMSO-}d_6\) \(\delta\) 2.15 (3H, s, CH\(_3\)), 3.07 (1H, s, CH\(_2\)), 6.94, 7.12 and 7.42 (each 1H, each m, thiophene-4H and -5H), 12.3 (1H, brs, COOH). Anal. Calcd for C\(_7\)H\(_7\)NO\(_4\): C, 56.80; H, 4.50; N, 9.55. Found: C, 56.33; H, 4.70; N, 9.53.

General Procedure for Preparation of 2-Amino-3-(heteroaryl)propanoic Acids (1) A solution of 3-(heteroaryl)-2-(hydroxyimino)propanoic acid (5) (35 mmol) in 60 ml of formic acid in the presence of catalytic amount of iron dust (100 mg), initially at 50 °C, was stirred vigorously, and zinc dust (6.8 g, 105 mg atom) was added in small portions at such a rate that the temperature was maintained at 50—55 °C. After the addition was complete, the mixture was heated at 60—65 °C for 2 h, and then filtered at room temperature. The filter-cake of unchanged zinc dust and zinc formate was thoroughly washed with formic acid (15 ml) and the combined filtrate was concentrated to dryness in vacuo to give the crude product (1), which was further purified by recrystallization using a mixture of EtOH and water.

2-Amino-3-(furan-2-yl)propanoic Acid (1a) Compound 1a was obtained in 77% yield, mp 235—238 °C (lit.\(^{14}\) mp 244—247 °C). IR (single bounce ATR): 1583 (COO\(^-\)) cm\(^{-1}\).

2-Amino-3-(thiophen-2-yl)propanoic Acid (1b) Compound 1b was obtained in 71% yield, mp 248—250 °C (lit.\(^{33}\) mp 255—257 °C). IR (single bounce ATR): 1587 (COO\(^-\)) cm\(^{-1}\).

2-Amino-3-(5-methylfurfuran-2-yl)propanoic Acid (1c) Compound 1c was obtained in 70% yield, mp 219—221 °C. IR (single bounce ATR): 1582 (COO\(^-\)) cm\(^{-1}\). H-NMR (D\(_2\)O) \(\delta\) 2.15 (3H, d, J = 6.0 Hz, CH\(_3\)), 3.07 (1H, dd, J = 7, 16 Hz, one proton of CH\(_2\)), 3.14 (1H, dd, J = 5, 16 Hz, one proton of CH\(_2\)), 3.87 (1H, dd, J = 5, 7 Hz, CH\(_3\)), 5.91 (1H, dd, J = 3, 16 Hz, furan-4H), 6.08 (1H, d, J = 3 Hz, furan-3H). Anal. Calcd for C\(_8\)H\(_7\)NO\(_3\): C, 56.80; H,
2-Amino-(3-thiophen-2-yl)propanoic Acid (1d): Compound 1d was obtained in 83% yield, mp 135—137 °C (lit.) 243—245 °C. IR (single bounce ATR): 1587 (COO) cm⁻¹.

2-Amino-(3-thiophen-3-yl)propanoic Acid (1e): Compound 1e was obtained in 94% yield, mp 260—262 °C (lit.) 265—267 °C. IR (single bounce ATR): 1586 (COO) cm⁻¹.

General Procedure for the Preparation of 2-(Formylamino)-3-(heteroaryl)propanoic Acids (6) The procedure of Watanabe14 was employed with some modifications. To a solution of 2-amino-3-(heteroaryl)propanoic acid (6a) was obtained in 86% yield, mp 171—147 °C (form EtOH–water), (lit. 25) 173—176 °C. IR (single bounce ATR): 1586 (COO) cm⁻¹. 

References and Notes
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