# 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 have 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 $\alpha$-hydroxyimino acids (**5**) to the corresponding 3-substituted alanine (**1**), as shown in Table 1.

First of all, reduction of 3-(furan-2-yl)-2-(hydroxyimino)-

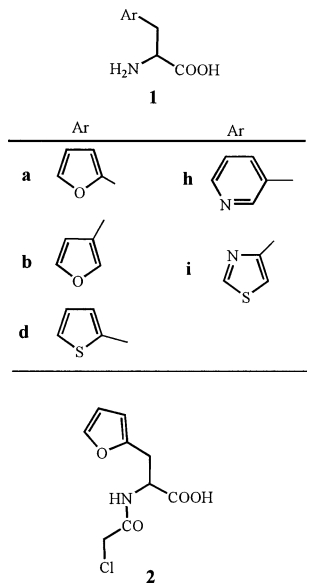


Chart 1

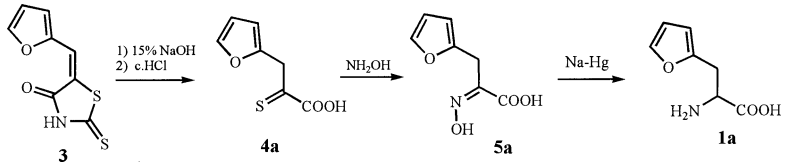


Chart 2. Preparation of 3-(Furan-2-yl)alanine (**1a**) Using the Rhodanine Method

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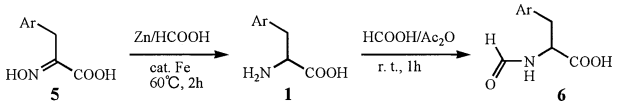
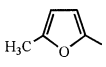
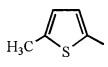
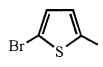
Table 1. Preparation of 3-(Heteroaryl)alanine (**1**) and Its *N*-Formyl Derivatives (**6**)




| **1**, **5** and **6** | Ar | Product (**1**) : yield (%) | Product (**6**) : yield (%) |
|---|---|---|---|
| **a** |  | **1a** : 77 | **6a** : 82 |
| **b** |  | **1b** : 71 | **6b** : 51 |
| **c** |  | **1c** : 70 | **6c** : 88 |
| **d** |  | **1d** : 83 | **6d** : 80 |
| **e** |  | **1e** : 94 | **6e** : 95 |
| **f** |  | **1f** : 77 | **6f** : 63 |
| **g** |  | **1g** : 48 | **6g** : 76 |

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 afford 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 *ex 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, rhodanine, 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-methylfuran-2-yl)-(**4c**), (thiophen-3-yl)-(**4e**). Similarly, 3-(heteroaryl)-2-(hydroxyimino)propanoic acids (**5**) were prepared according to the reported procedures: (furan-2-yl)-(**5a**),[12] (thiophen-2-yl)-(**5d**),[27,28] (5-methylthiophen-2-yl)-(**5f**),[29] (5-bromothiophen-2-yl)-(**5g**).[24]

Melting points were taken on a Yanagimoto melting point apparatus and are uncorrected. IR spectra were measured on an Avata model 320 FT-IR spectrometer. $^1$H-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 Plucker[12] 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): 1699 (CO) cm$^{-1}$. $^1$H-NMR (DMSO-$d_6$) $\delta$: 3.54 (1H, s, $CH_2$), 6.30, 7.40 and 7.52 (each 1H, each m, furan-4H, -2H and -5H), 12.3 (1H, br s, COOH). *Anal.* Calcd for $C_7H_7NO_4$: C, 49.70; H, 4.14; N, 8.28. Found: C, 49.75; H, 4.22; N, 8.12.

**2-(Hydroxyimino)-3-(5-methylfuran-2-yl)propanoic Acid (5c)** Treatment of 3-(5-methylfuran-2-yl)-2-thioxopropanoic acid (**4c**) (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$^{-1}$. $^1$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).

**2-(Hydroxyimino)-3-(thiophen-3-yl)propanoic Acid (5e)** 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 **5e**; yield 3.3 g (89%); mp 167—169 °C (from toluene). IR (single bounce ATR): 1698 (CO) cm$^{-1}$. $^1$H-NMR (DMSO-$d_6$) $\delta$: 3.79 (1H, s, $CH_2$), 6.94, 7.12 and 7.42 (each 1H, each m, thiophene-4H, -2H and -5H), 12.3 (1H, br s, COOH). *Anal.* Calcd for $C_7H_7NO_3S$: C, 45.40; H, 3.78; N, 7.56. Found: C, 45.33; H, 3.70; N, 7.53.

**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-(furan-3-yl)propanoic Acid (**1b**): Compound **1b** was obtained in 71% yield, mp 248—250 °C (lit.[31] mp 255—257 °C). IR (single bounce ATR): 1587 (COO$^-$) cm$^{-1}$.

2-Amino-3-(5-methylfuran-2-yl)propanoic Acid (**1c**): Compound **1c** was obtained in 70% yield, mp 219—221 °C. IR (single bounce ATR): 1582 (COO$^-$) cm$^{-1}$. $^1$H-NMR ($D_2O$) $\delta$: 2.15 (3H, d, $J$=0.5 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), 5.91 (1H, dd, $J$=1, 3 Hz, furan-4H), 6.08 (1H, d, $J$=3 Hz, furan-3H). *Anal.* Calcd for $C_8H_{11}NO_3$: C, 56.80; H,

6.50; N, 8.28. Found: C, 57.00; H, 6.49; N, 8.32.

2-Amino-3-(thiophen-2-yl)propanoic Acid (**1d**): Compound **1d** was obtained in 83% yield, mp 235—237 °C (lit.[32] 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.[33] 265—267 °C). IR (single bounce ATR): 1586 ($COO^-$) $cm^{-1}$.

2-Amino-3-(5-methylthiophen-2-yl)propanoic Acid (**1f**): Compound **1f** was obtained in 77% yield, mp 232—234 °C. IR (single bounce ATR): 1587 ($COO^-$) $cm^{-1}$. NMR ($D_2O$) $\delta$: 2.45 (3H, s, $CH_3$), 3.36 (1H, dd, $J$=7, 15 Hz, one proton of $CH_2$), 3.42 (1H, dd, $J$=5, 15 Hz, one proton of $CH_2$), 3.97 (1H, dd, $J$=5, 7 Hz, CH), 6.74 (1H, d, $J$=2 Hz, thiophene-4H), 6.82 (1H, d, $J$=3 Hz, thiphene-3H). *Anal.* Calcd for $C_8H_{11}NO_2S$: C, 51.89; H, 5.94; N, 7.56. Found: C, 51.62; H, 5.89; N, 7.51.

2-Amino-3-(5-bromothiophen-2-yl)propanoic Acid (**1g**): Compound **1g** was obtained in 48% yield, mp 230—233 °C (dec.) [lit.[34] 235—238 °C (dec.)]. IR (single bounce ATR): 1586 ($COO^-$) $cm^{-1}$.

**General Procedure for the Preparation of 2-(Formylamino)-3-(heteroaryl)propanoic Acids (6)** The procedure of Watanabe[14] was employed with some modifications. To a solution of 2-amino-3-(heteroaryl)propanoic acid (16 mmol) in formic acid (5 ml), acetic anhydride (16.6 ml) was added dropwise with ice-cooling. The reaction mixture was stirred for 1 h at room temperature, diluted with water (16 ml) and concentrated *in vacuo* to give the crude product (**6**), which was further purified by recrystallization.

2-Formylamino-3-(furan-2-yl)propanoic Acid (**6a**): Compound **6a** was given in 82% yield, mp 145—147 °C (from AcOEt) (lit.[14] mp 144—145 °C). IR (single bounce ATR): 3291 (NH), 1720 (CO) $cm^{-1}$. $^1$H-NMR (DMSO-$d_6$) $\delta$: 2.98 (1H, dd, $J$=8, 15 Hz, one proton of $CH_2$), 3.10 (1H, dd, $J$=5, 15 Hz, one proton of $CH_2$), 4.56 (1H, m, CH), 6.35, 6.55 and 7.52 (each 1H, each m, furan-4H, -3H and -5H), 8.01 (1H, br d, $J$=0.7 Hz, CHO), 8.37 (1H, br d, $J$=8 Hz, NH).

2-Formylamino-3-(furan-3-yl)propanoic Acid (**6b**): Compound **6b** was obtained in 51% yield, mp 144—146 °C. IR (single bounce ATR): 3248 (NH), 1736 (CO) $cm^{-1}$. $^1$H-NMR (DMSO-$d_6$) $\delta$: 2.74 (1H, dd, $J$=8, 14 Hz, one proton of $CH_2$), 2.87 (1H, dd, $J$=4, 14 Hz, one proton of $CH_2$), 4.46 (1H, m, CH), 6.40, 7.45 and 7.55 (each 1H, each m, furan-4H, -2H and -5H), 8.01 (1H, br s, CHO), 8.34 (1H, br d, $J$=8 Hz, NH). *Anal.* Calcd for $C_8H_9NO_4$: C, 52.45, H, 4.91, N, 7.65. Found: C, 52.23, H, 4.84, N, 7.65.

2-Formylamino-3-(5-methylfuran-2-yl)propanoic Acid (**6c**): Compound **6c** was obtained in 88% yield, mp 134—136 °C (from EtOH–water). IR (single bounce ATR): 3327 (NH), 1722 (CO) $cm^{-1}$. $^1$H-NMR (DMSO-$d_6$) $\delta$: 2.19 (3H, s, $CH_3$), 2.91 (1H, dd, $J$=8, 15 Hz, one proton of $CH_2$), 3.03 (1H, dd, $J$=5, 15 Hz, one proton of $CH_2$), 4.52 (1H, m, CH), 5.93 and 6.00 (each 1H, each d, $J$=6 Hz, furan-3H and -4H), 8.01 (1H, br s, CHO), 8.36 (1H, br d, $J$=8 Hz, NH). *Anal.* Calcd for $C_9H_{11}NO_4$: C, 54.82; H, 5.58; N, 7.10. Found: C, 54.73; H, 5.54; N, 7.07.

2-Formylamino-3-(thiophen-2-yl)propanoic Acid (**6d**): Compound **6d** was obtained in 80% yield, mp 171—147 °C (form EtOH–water), (lit.[25] 173—176 °C). IR (single bounce ATR): 3290 (NH), 1722 (CO) $cm^{-1}$. $^1$H-NMR (DMSO-$d_6$) $\delta$: 3.15 (1H, dd, $J$=8, 15 Hz, one proton of $CH_2$), 3.38 (1H, dd, $J$=4, 15 Hz, one proton of $CH_2$), 4.52 (1H, m, CH), 6.89, 6.94 and 7.35 (each 1H, each m, thiophene-5H, -4H and -3H), 8.03 (1H, br d, $J$=0.7 Hz, CHO), 8.41 (1H, br d, $J$=8, NH).

2-Formylamino-3-(thiophen-3-yl)propanoic Acid (**6e**): Compound **6e** was obtained in 95% yield, mp 151—153 °C (from EtOH–water). IR (single bounce ATR): 3209 (NH), 1737 (CO) $cm^{-1}$. $^1$H-NMR (DMSO-$d_6$) $\delta$: 2.93 (1H, dd, $J$=9, 14 Hz, one proton of $CH_2$), 3.08 (1H, dd, $J$=5, 14 Hz, one proton of $CH_2$), 4.51 (1H, m, CH), 6.99, 7.21 and 7.44 (each 1H, each m, thiophene-3H, -5H and -4H), 8.00 (1H, br d, $J$=0.7 Hz, CHO), 8.35 (1H, br d, $J$=8 Hz, NH). *Anal.* Calcd for $C_8H_9NO_3S$: C, 48.24; H, 4.52; N, 7.03. Found: C, 48.16; H, 4.57; N, 7.02.

2-Formylamino-3-(5-methylthiophen-2-yl)propanoic Acid (**6f**): Compound **6f** was obtained in 63% yield, mp 173—175 °C (from EtOH–water). IR (single bounce ATR): 3291 (NH), 1721 (CO) $cm^{-1}$. $^1$H-NMR (DMSO-$d_6$) $\delta$: 2.49 (3H, s, $CH_3$), 3.05 (1H, dd, $J$=8, 15 Hz, one proton of $CH_2$), 3.19 (1H, dd, $J$=4, 15 Hz, one proton of $CH_2$), 4.52 (1H, m, CH), 6.60 and 6.65 (each 1H, each m, thiophene-3H and -4H), 8.02 (1H, br s, CHO), 8.36 (1H, br d, $J$=8 Hz, NH). *Anal.* Calcd for $C_9H_{11}NO_3S$: C, 50.70; H, 5.16; N, 6.57. Found: C, 50.49; H, 5.13; N, 6.55.

3-(5-Bromothiophen-2-yl)-2-(formylamino)propanoic Acid (**6g**): Compound **6g** was obtained in 76% yield, mp 158—160 °C (from EtOH). IR (single bounce ATR): 3273 (NH), 1720 (CO) $cm^{-1}$. $^1$H-NMR (DMSO-$d_6$) $\delta$: 3.10 (1H, dd, $J$=8, 15 Hz, one proton of $CH_2$), 3.26 (1H, dd, $J$=4, 15 Hz, one proton of $CH_2$), 4.50 (1H, m, CH), 6.74 and 7.04 (each 1H, each m, thiophene-3H and -4H), 8.04 (1H, br s, CHO), 8.44 (1H, br d, $J$=8 Hz, NH). *Anal.* Calcd for $C_8H_8BrNO_3S$: C, 34.53; H, 2.87; N, 5.03. Found: C, 34.27; H, 2.93; N, 4.77.

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