An Improved Method for the Synthesis of DL-3-(2-Furyl)alanine

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DL-3-(2-Furyl)alanine (1) was prepared by the condensation of 2-(bromomethyl)furan (7) with diethyl formamidomalonate (2), followed by the traditional saponification–decarboxylation techniques.

Key words DL-3-(2-furyl)alanine; furan derivative; unnatural amino acid; 2-(bromomethyl)furan; diethyl formamidomalonate; 2-furanmethanol

DL-3-(2-Furyl)alanine (**1**) is useful as a precursor to peptides,[1] and as an agrochemical fungicide.[2] The most widely used preparation of DL-3-(2-furyl)alanine (**1**) involves the condensation of diethyl formamidomalonate (**2**) with 2-(chloromethyl)furan (**4**), which is prepared from the reaction of 2-furanmethanol (**3**) with thionyl chloride in the presence of pyridine,[3] to afford diethyl formamido(2-furfuryl)malonate (**5**). This is hydrolyzed using 10% sodium hydroxide to yield amino(2-furfuryl)malonic acid (**6**), which is decarboxylated with 50% acetic acid to afford **1**. In this procedure, 2-(chloromethyl)furan (**4**) is an important precursor of **5**, but it is extremely unstable and decomposes during purification by distillation to give hydrogen chloride, which catalyzes polymerization of the furan ring with explosive violence.[4] We tried to use cured 2-(chloromethyl)furan (**4**) without purification, but the reaction did not proceed well, probably because of the presence of water. Therefore, the above method is not entirely satisfactory for the synthesis of **5**.

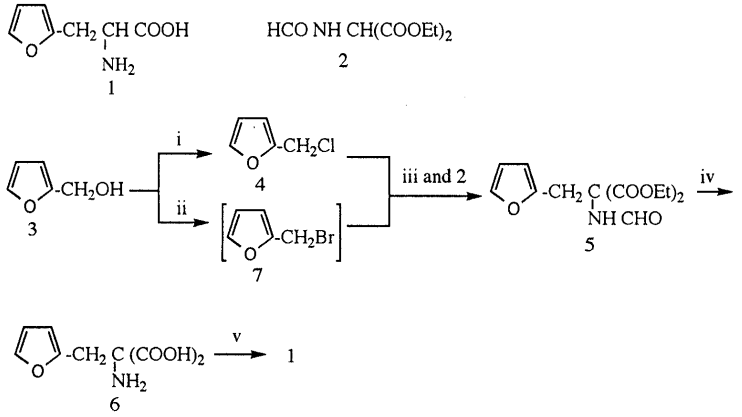
Recently, New *et al.* reported that 3-furanmethanol reacts with phosphorus tribromide in tetrahydrofuran (THF) to afford 3-(bromomethyl)furan.[5] The product could be extracted from the reaction mixture with ether, and used directly without further purification. An advantage of this method is that a base such as pyridine is not needed as a scavenger of hydrogen chloride. We were therefore interested in the feasibility of employing phosphorus tribromide to prepare 2-(bromomethyl)furan (**7**). The success of this reaction allowed us to develop a convenient method of preparation of DL-3-(2-furyl)alanine (**1**), using the bromo compound (**7**) in place of the chloro compound (**4**).

First, 2-furanmethanol (**3**) in THF was allowed to react with phosphorus tribromide at 0 °C for 1.5 h to yield 2-(bromomethyl)furan (**7**). This product was extracted with ether, and then the ether solution was dried over molecular sieves overnight. The crude 2-(bromomethyl)-furan (**7**) solution in the ether was directly treated with diethyl formamidomalonate (**2**) at 70 °C in the presence of sodium ethoxide as a base to afford diethyl formamido-(2-furfuryl)malonate (**5**) in 91% yield. The hydrolysis of **5** was carried out with 10% sodium hydroxide according to the reported procedure[3] to yield **6**, which was decarboxylated in refluxing 50% acetic acid to give the desired DL-3-(2-furyl)alanine (**1**) in 81% yield. This procedure represents an improved and convenient synthetic route to DL-3-(2-furyl)alanine (**1**).

Experimental

Melting points were taken on a Yanagimoto melting point apparatus. All melting and boiling points are uncorrected. IR spectra were measured on a Hitachi model 270-30 IR spectrophotometer. ^{1}H-NMR spectra were measured on a Bruker AM-400 spectrometer (400 MHz) using tetramethylsilane as an internal reference, and chemical shifts were recorded as δ-values. Diethyl formamidomalonate (**2**) was prepared as previously described.[6]

2-(Bromomethyl)furan (7) The procedure was similar to that of New *et al.*[5] Phosphorus tribromide (4.9 g, 18 mmol) was added dropwise to a solution of 2-furylmethanol (**3**) (5 g, 50 mmol) in THF (50 ml) at 0 °C. The resulting mixture was stirred at 0 °C for 1.5 h, then the reaction was quenched with water, and the mixture was extracted with ether (100 ml × 2). The ether layers were washed with saturated $NaHCO_3$ and



i $SOCl_2$, pyridine ii PBr_3 iii NaOEt iv 10% NaOH v 50% AcOH

Chart 1. An Improved Method for the Synthesis of DL-3-(2-Furyl)alanine

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brine, dried over molecular sieves (30 g) overnight, and filtered. The ether solution containing the crude product (**7**) was used for the next reaction without purification.

Diethyl Formamido(2-furfuryl)malonate (5) Diethyl formamidomalonate (**2**) (7.6 g, 38 mmol) was dissolved in a sodium ethoxide solution [prepared from 0.85 g of sodium (0.037 g-atm) and 100 ml of absolute ethanol]. To this stirred solution, the above-mentioned ether solution containing crude 2-(bromomethyl)furan (**7**) was added in a single portion. The mixture was distilled rapidly at atmospheric pressure until about 160 ml of ether had been collected, and the remaining reaction mixture was refluxed at 68—72 °C for 2 h. The ethanolic solution was concentrated *in vacuo*, the residue was poured into ethyl acetate (50 ml), and the resultant mixture was filtered to remove insoluble materials. The filtrate was washed with 3% HCl and water, then the ethyl acetate layer was dried over anhydrous Na_2SO_4. The organic solvent was evaporated *in vacuo* to give crude **5** (9.5 g, 91%), which was purified by recrystallization from ether/petroleum ether; colorless needles, mp 89—92 °C (lit.[3] 98—99.5 °C). IR (KBr): 1750 cm^{-1} (CO). ^{1}H-NMR ($CDCl_3$): 1.2—1.4 (m, 6H, $-CH_2C\underline{H}_3 \times 2$), 3.7 (s, 1H, –CH–), 4.2—4.3 (m, 4H, $-C\underline{H}_2CH_3 \times 2$), 6.0—6.1 (m, 1H, furan-4H), 6.1—6.2 (d, 1H, NH), 6.2—6.3 (m, 1H, furan-3H), 7.2—7.3 (m, 1H, furan-5H), 8.1—8.2 (d, 1H, CHO)

Amino(2-furfuryl)malonic Acid (6) This compound was prepared by hydrolysis of **5** under the conditions described by Watanabe *et al.*[3] Diethyl formamido(2-furfuryl)malonate (**5**) (3.9 g, 40 mmol) was refluxed with a 10% NaOH solution (20 ml) for 6 h. The resulting mixture was cooled and acidified with 10% HCl to yield 2.9 g (74%) of **6**: mp 282—285 °C (dec.) (lit.[3] mp 285—288 °C).

DL-3-(2-Furfuryl)alanine (1) This compound was prepared by the decarboxylation of **6** under the conditions described by Watanabe *et al.*[3] Amino(2-furfuryl)malonic acid (**6**) (0.65 g, 3.2 mmol) was refluxed with 6 ml of 50% acetic acid for 2.5 h, and then the solvent was removed on a rotary evaporator to give 0.41 g (81%) of crude **1**: 240—242 °C (dec.) (lit.[3] mp 244—247 °C).

References

1) Keller R., Mueller, W., Ger. Offen. DE 3,738,908 [*Chem. Abstr.*, **112**, 232298*n* (1990)].
2) Hoppe H., Wicke H., Schlingmann M., Keller R., Sachse B., Ger. Offen. DE 3,820,302 [*Chem. Abstr.*, **113**, 23677*s* (1990)].
3) Watanabe H., Kuwata S., Nakajima S., Koshida K., Hayashi M., *Bull. Chem. Soc. Jpn.*, **38**, 1461—1464 (1965).
4) Divald S., Chun M. C., Joullie M. M., *J. Org. Chem.*, **41**, 2835—2846 (1976).
5) New D. G., Tesfai Z., Moeller K. D., *J. Org. Chem.*, **61**, 1578—1598 (1996).
6) Kitagawa T., Ito J., Tsutsui C., *Chem. Pharm. Bull.*, **42**, 1931—1934 (1994).

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