One-Pot Three-Component Reaction between 2-Aminopyridines, Aldehydes and Meldrum's Acid in Water: An Efficient Synthesis of β-Amino Acids

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Abstract: A novel, one-pot, three-component synthesis of β-amino acids is described. Heating an alkaline aqueous solution of a 2-aminopyridine, an aldehyde and Meldrum's acid afforded β-amino acids in good to excellent yields.

Key words: β-amino acids, 2-aminopyridines, aldehydes, Meldrum's acid, three-component reactions, synthesis in water

Water is a desirable solvent for chemical reactions because it is safe, nontoxic, environmentally friendly, readily available and cheap compared to organic solvents.[1] Although enzymatic processes in nature occur in aqueous environment by necessity, water has been avoided as a solvent for common organic reactions due to poor solubility and, in some cases, the instability of organic reagents or reaction intermediates in aqueous solutions. Since the pioneering studies on Diels–Alder reactions by Breslow,[2] there has been increasing recognition that organic reactions can proceed well in aqueous media and offer advantages over those occurring in organic solvents, such as rate enhancement and insolubility of the final products that facilitates their isolation.[1]

Multicomponent reactions (MCRs) have emerged as an efficient and powerful tool in modern synthetic organic chemistry due to their valued features such as atom economy, straightforward reaction design and the opportunity to construct target compounds by the introduction of several diversity elements in a single chemical event. Typically, purification of products resulting from MCRs is also simple since all the organic reagents employed are consumed and are incorporated into the target compound. MCRs, leading to interesting biologically active organic compounds, are particularly useful for the construction of diverse chemical libraries of 'drug-like' molecules.[3]

Development of new routes for β-amino acids synthesis has become an important and challenging endeavor for organic chemists due to their biologically important properties, their occurrence in natural products, and as potential precursors for β-lactams.[4] The β-amino acids in free form show interesting pharmacological properties. For instance, hypoglycemic and antiketogenic activities were observed in rats after oral intake of emeriamine (**1**; Figure 1).[5] Cispentacin (**2**; Figure 1) is an antifungal antibiotic.[4] Functionalized β-amino acids are key components of a variety of bioactive molecules such as taxol (**3**; Figure 1), one of the most active antitumor agents which contains phenylisoserine as its side chain.[4] Furthermore, β-amino acids, although not as abundant as their α-analogues, are also segments in peptidic natural products with various biological activities. β-Tyrosine, a β-aryl-β-amino acid, is present in jasplakinolide (**4**; Figure 1) which is a sponge metabolite with potent insecticidal, antifungal, and antihelminthic properties.[6]

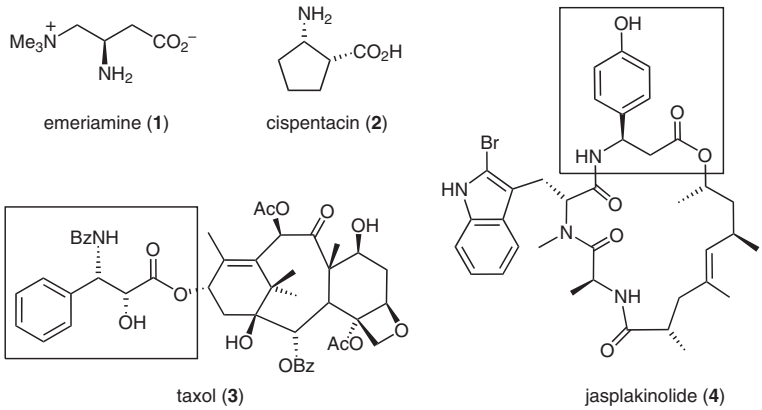

Figure 1

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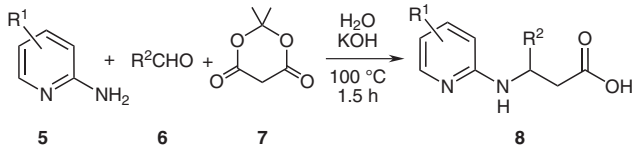
So far the most common synthetic routes reported for the synthesis of β-amino acids involve: i) homologation of α-amino acids, ia) Arndt–Eistert homologation, ib) synthesis of β-amino acids starting from aspartic acid, asparagine and its derivatives; ii) additions to double bonds, iia) addition of enolates, silyl enolates or Reformatsky reagents to imines and iib) addition of carbon nucleophiles to nitrones or oximes; iii) Curtius rearrangement of functionalized succinates; iv) conjugate addition of nitrogen nucleophiles to α,β-unsaturated acid derivatives (α,β-USADs) and carbon nucleophiles to β-amino-α,β-USADs; v) reductions, va) catalytic hydrogenation of β-amino-α,β-USADs and vb) reductive amination of α,β-USADs; and vi) amino hydroxylation of α,β-USADs.[4,7]

As part of our continuing effort on the design of new routes for the preparation of biologically active organic compounds,[8] herein, we describe a novel, one-pot, three-component synthesis of β-amino acids. Thus, a 2-aminopyridine **5**, an aldehyde **6** and Meldrum's acid (**7**) were condensed at 100 °C in alkaline aqueous solution to produce the corresponding β-amino acids **8** in 74–98% yields (Scheme 1, Table 1). All the reactions went to completion within 1.5 hours.[9] ^{1}H NMR analysis of the reaction mixtures clearly indicated formation of the corresponding β-amino acids **8a–q** in good to excellent yields.



5 6 7 8

Scheme 1

Table 1 Synthesis of β-Amino Acids **8a–q**[a]

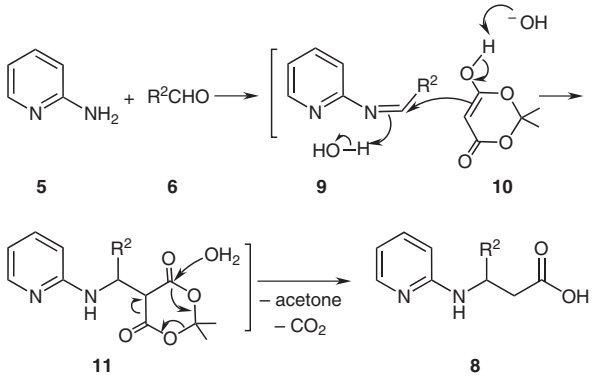
8	R^1	R^2	Yield (%)[b]
a	H	Ph	95
b	H	4-ClC_6H_4	95
c	H	4-FC_6H_4	90
d	H	4-MeC_6H_4	92
e	H	4-$MeOC_6H_4$	87
f	H	4-$O_2NC_6H_4$	95
g	4-Me	Ph	98
h	4-Me	4-FC_6H_4	94
i	4-Me	4-MeC_6H_4	93
j	5-Me	Ph	95
k	5-Me	4-FC_6H_4	87
l	5-Me	4-MeC_6H_4	90
m	5-Me	4-$MeOC_6H_4$	88
n	H	Pr	80
o	H	*i*-Pr	75
p	4-Me	Pr	82
q	4-Me	*i*-Pr	74

[a] Compounds **8a–m** were crystallized from the reaction mixture. Compounds **8n–q** were purified by column chromatography (eluent: EtOAc).
[b] Isolated yields.

The structures of the β-amino acids **8a–q** were deduced on the basis IR, ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry and elemental analysis. The mass spectrum of **8d** displayed the molecular ion [M^+] peak at m/z = 256 which was consistent with the product structure. The IR spectrum of **8d** showed absorptions at 3260, 2500–3350 (br) and 1713 cm^{-1} indicating the presence of NH, acid OH and acid C=O functionalities, respectively. The ^{1}H NMR spectrum of **8d** exhibited a sharp singlet (δ = 2.23 ppm) as arising from the methyl group. An ABX system ($CH_AH_BCH_X$) was observed for the two diastereotopic H atoms of the methylene group (δ_A = 2.63 ppm, dd, ^2J = 15.3 Hz, ^3J = 6.3 Hz; δ_B = 2.78 ppm, dd, ^2J = 15.3 Hz, ^3J = 8.4 Hz) and the adjacent methine H atom (δ_X = 5.29 ppm, multiplet). The characteristic signals for the eight H atoms of the 2-pyridyl and aryl substituents were seen with appropriate chemical shifts and coupling constants. A fairly sharp doublet (δ = 7.01 ppm, J = 8.5 Hz) was observed for the NH group because of coupling with the adjacent methine H atom. A broad signal (δ = 12.00 ppm) was observed for the carboxylic acid OH group. The ^{1}H decoupled ^{13}C NMR spectrum of **8d** showed four signals readily recognized as arising from a methyl (δ = 20.54 ppm), a methylene (δ = 41.91 ppm), a methine (δ = 51.01 ppm) and a carbonyl group (δ = 172.10 ppm) as well as nine distinct resonances in agreement with the proposed structure.[9]

A mechanistic rationalization for this reaction is provided in Scheme 2. The first step may involve condensation of the aldehyde with the 2-aminopyridine and formation of aldimine **9**, which may be attacked by enol tautomer of Meldrum's acid **10** leading to adduct **11**. This adduct may undergo nucleophilic addition of water followed by removal of an acetone and a carbon dioxide molecule to afford β-aryl-β-amino acids **8**. These events facilitate in alkaline solution.

In conclusion, herein, we have reported that the one-pot three-component reaction between 2-aminopyridines, aldehydes and Meldrum's acid in water provide a convenient, simple, efficient, and environmentally friendly approach for the synthesis of β-amino acids of potential synthetic and pharmacological interest. Use of water as a green medium, use of simple starting materials, good to excellent yields of the products and a simple purification process (for aromatic aldehydes) are the main advantages of this method. The simplicity of this method makes it an interesting alternative to other approaches.



Scheme 2

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(9) **Procedure for the Preparation of 3-Phenyl-3-(2-pyridylamino)propanoic Acid (8a)**: A mixture of 2-aminopyridine (0.188 g, 2 mmol), benzaldehyde (0.212 g, 2 mmol), Meldrum's acid (0.288 g, 2 mmol) and KOH (0.056 g, 1 mmol) in H_2O (5 mL) was stirred at 100 °C for 1.5 h, then the reaction mixture was cooled to r.t. and left overnight. The product was obtained as colorless crystals. Yield: 0.46 g (95%); mp 94–95 °C. IR (KBr): 3250 (NH), 2450–3300 (OH), 1710 (C=O), 1676, 1618, 1543, 1443, 1420, 1356, 1286, 1167, 1086, 962, 764, 700 cm^{-1}. ^1H NMR (500.1 MHz, DMSO-d_6): δ = 2.69 (dd, ^2J = 15.4 Hz, ^3J = 6.3 Hz, 1 H, CH), 2.83 (dd, ^2J = 15.4 Hz, ^3J = 8.5 Hz, 1 H, CH), 5.35–5.41 (m, 1 H, CH), 6.46 (dd, J = 6.2, 6.3 Hz, 1 H, CH), 6.51 (d, J = 8.4 Hz, 1 H, CH), 7.08 (d, J = 8.5 Hz, 1 H, NH), 7.20 (t, J = 7.5 Hz, 1 H, CH), 7.30 (dd, J = 7.4, 7.6 Hz, 2 H, 2 × CH), 7.34 (dt, J = 1.7, 7.9 Hz, 1 H, CH), 7.42 (d, J = 7.9 Hz, 2 H, 2 × CH), 7.93 (dd, J = 1.4, 4.5 Hz, 1 H, CH), 12.10 (br, 1 H, OH). ^{13}C NMR (125.8 MHz, DMSO-d_6): δ = 41.93 (CH_2), 51.26 (CH), 108.41, 111.90, 126.60, 126.67, 128.14, 136.67 (6 × CH), 143.64 (C), 147.36 (CH), 157.86 (NCN), 172.12 (C=O). MS: m/z (%) = 242 (58) [M^+], 224 (8), 197 (97), 183 (100), 122 (10), 104 (24), 94 (29), 78 (56), 67 (20), 51 (19). Anal. Calcd for $C_{14}H_{14}N_2O_2$ (242.28): C, 69.41; H, 5.82; N, 11.56. Found: C, 69.3; H, 5.9; N, 11.4.
3-(4-Methylphenyl)-3-(2-pyridylamino)propanoic Acid (8d): yield: 0.47 g (92%); colorless crystals; mp 99–100 °C. IR (KBr): 3260 (NH), 2500–3350 (OH), 1713 (C=O), 1676, 1620, 1541, 1512, 1462, 1444, 1410, 1364, 1285, 1078, 962, 818, 760, 723 cm^{-1}. ^1H NMR (500.1 MHz, DMSO-d_6): δ = 2.23 (s, 3 H, Me), 2.63 (dd, ^2J = 15.3 Hz, ^3J = 6.3 Hz, 1 H, CH), 2.78 (dd, ^2J = 15.3 Hz, ^3J = 8.4 Hz, 1 H, CH), 5.26–5.32 (m, 1 H, CH), 6.43 (dd, J = 5.9, 6.1 Hz, 1 H, CH), 6.47 (d, J = 8.4 Hz, 1 H, CH), 7.01 (d, J = 8.5 Hz, 1 H, NH), 7.07 (d, J = 7.9 Hz, 2 H, 2 × CH), 7.28 (d, J = 7.9 Hz, 2 H, 2 × CH), 7.31 (dt, J = 1.6, 7.8 Hz, 1 H, CH), 7.90 (d, J = 3.9 Hz, 1 H, CH), 12.00 (br, 1 H, OH). ^{13}C NMR (125.8 MHz, DMSO-d_6): δ = 20.54 (Me), 41.91 (CH_2), 51.01 (CH), 108.34, 111.82, 126.49, 128.66 (4 × CH), 135.66 (C), 136.61 (CH), 140.53 (C), 147.30 (CH), 157.85 (NCN), 172.10 (C=O). MS: m/z (%) = 256 (69) [M^+], 238 (17), 211 (94), 197 (100), 178 (9), 117 (25), 105 (20), 98 (13), 91 (28), 78 (56), 65 (11), 51 (13). Anal. Calcd for $C_{15}H_{16}N_2O_2$ (256.30): C, 70.29; H, 6.29; N, 10.93. Found: C, 70.3; H, 6.4; N, 10.8.
3-(2-Pyridylamino)hexanoic Acid (8n): yield: 0.33 g (80%); colorless crystals; mp 52–54 °C. IR (KBr): 3264 (NH), 2500–3400 (OH), 1707 (C=O), 1676, 1615, 1540, 1443, 1417, 1350, 1282, 1170, 1080, 980 cm^{-1}. ^1H NMR (300.1 MHz, DMSO-d_6): δ = 0.84 (t, J = 7.2 Hz, 3 H, Me), 1.22–1.40 (m, 2 H, CH_2), 1.42–1.54 (m, 2 H, CH_2), 2.31 (dd, ^2J = 14.9 Hz, ^3J = 6.9 Hz, 1 H, CH), 2.48 (dd, ^2J = 14.9 Hz, ^3J = 6.2 Hz, 1 H, CH), 4.18–4.23 (m, 1 H, CH), 6.32 (d, J = 8.0 Hz, 1 H, NH), 6.42 (dd, J = 6.0, 6.2 Hz, 1 H, CH), 6.44 (d, J = 8.0 Hz, 1 H, CH), 7.31 (dt, J = 1.6, 7.9 Hz, 1 H, CH), 7.92 (d, J = 4.3 Hz, 1 H, CH), 11.75 (br, 1 H, OH). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 14.38 (Me), 19.22, 36.84, 40.15 (3 × CH_2), 47.36 (CH), 108.83, 111.71, 136.98, 147.81 (4 × CH), 158.84 (NCN), 173.60 (C=O). MS: m/z (%) = 209 (100) [M^+ + 1], 208 (81) [M^+], 192 (18), 179 (9), 165 (36), 149 (72), 135 (16), 121 (84), 107 (19), 94 (55), 78 (57), 67 (25). Anal. Calcd for $C_{11}H_{16}N_2O_2$ (208.26): C, 63.44; H, 7.74; N, 13.45. Found: C, 63.2; H, 7.8; N, 13.2.

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