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Papers

Tandem reductive cyclisation of diethyl 2-(2-nitro-1-arylethyl)malonate by zinc and ammonium chloride in aqueous medium

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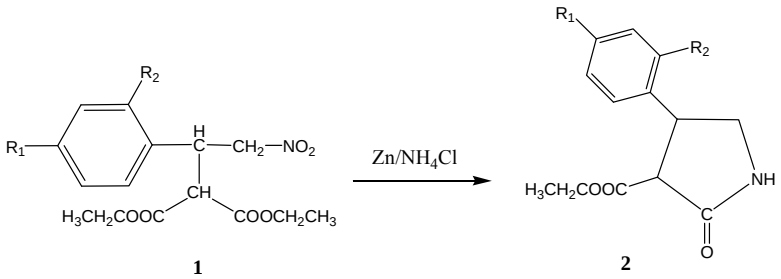
A tandem reductive cyclisation of diethyl 2-(2-nitro-1-arylethyl)malonate by zinc and ammonium chloride in aqueous medium leading to a one pot synthesis of ethyl 2-oxo-4-arylpyrrolidine-3-carboxylate in good yield has been described.

Keywords: Tandem reactions, zinc and ammonium chloride, reductive cyclisation, 2-pyrrolidinone

Pyrrolidine is a basic intermediate used in wide range of applications in organic synthesis, agrochemicals, pharmaceuticals, colorants, plasticizers, photographic chemicals, emulsifiers, corrosion inhibitors, rubber chemicals and curing agent for epoxy resins. For example, the structure–activity relationship studies indicate that the presence of pyrrolidine at the end of C-6 chain, benzoyl group at C-5, and benzyl groups at N-1, N-3 of the pyrimidine ring increases the anti-cancer activities of these molecules[1]. (*S*)-*N*-Benzoyl-3-pyrolidinol, obtained from *N*-benzoyl-3-pyrrolidinone, is widely used in the synthesis of pharmaceuticals as a chiral block[2]. The synthesis and enhanced antiviral activity of a series of 3,5-disubstituted pyrrolidinonebase HIV protease inhibitors is described[3]. The effect of substituents on the pyrrolidinone ring *in vitro* antibacterial activities against both gram-positive and gram-negative bacteria has been systematically investigated[4]. A series of 1-substituted pyrrolidin-2-one were tested for electrocardiographic, antiarrhythmic, and antihypertensive activity[5]. Synthesis of differently substituted pyrrolidinones have been synthesised involving Baylis-Hillman reaction[6], Suzuki-Miyaura cross coupling reaction[7] and a regioselective Baeyer-Villiger lactonisation[8]. A convenient method for the synthesis of 1,5-disubstituted pyrrolidin-2-ones by a novel C-N bond formation reaction has been recently reported[9]. Reduction of nitro compounds by zinc and ammonium chloride in water is the general way of preparing the hydroxylamines[10]. It must be mentioned that a detailed investigation on the reduction of hydroxy substituted aryl nitro compounds under this condition indicated the formation of unexpected completely reduced amino product[11]. Different methods of the reduction of nitro compounds with different reagents under different experimental conditions have been reported[12-14], but in every case the yields of isolatable products have been not good. In our continued interest on the zinc and ammonium chloride reduction of different nitro compounds in aqueous medium[11], we investigated the reduction of the aliphatic nitro system, namely diethyl 2-(2-nitro-1-arylethyl)malonate and the results are presented here.

Results and Discussion

Diethyl 2-(2-nitro-1-arylethyl)malonate have been synthesized by the Michael addition of diethyl malonate to differently substituted nitrostyrenes. The adducts, **1**, have other reducible functional group apart from nitro group. The adducts **1** were then subjected to reduction by zinc and ammonium chloride in aqueous medium in the hope of getting the corresponding hydroxylamine by selective partial reduction for further reaction towards construction of a new set of substituted isoxazolidines. Surprisingly, under the condition of the reaction, the reduction goes to completion giving amine rather than the hydroxylamine followed by the cyclisation involving one of the carbethoxy groups (**Scheme I**). Thus a one pot facile synthesis of the ethyl 2-oxo-4-arylpyrrolidine-3-carboxylate has been achieved in good yield. To the best of our knowledge, all the



1 **2**

	R_1	R_2
a	H	H
b	Cl	H
c	OCH_3	H
d	H	Cl
e	CH_3	H

Scheme I

synthesized compounds, except **2a**, are hitherto unknown. The products obtained have all been completely characterized by spectral methods.

This tandem process is a mild way of getting the pyrrolidine derivative without the use of mineral acids in the reduction process using the 'green' solvent. It is also found that the yield by this zinc/ammonium chloride method of reduction is good related to the zinc and hazardous mineral acid reduction carried out by us for comparison, wherein the yield is less than 50% in all the cases. Rapid and selective reduction of nitro compound is of importance for the preparation of amino derivatives in the organic derivatives when a molecule has other reducible groups[15-19] and the present work is one such attempt. The other reported methods of preparing related 2-oxo-4-arylpyrrolidine-3-carboxylate include the Raney-nickel reduction[20] or catalytic reduction[21,22] or reduction using low valent titanium[23] of diethyl 2-(2-nitro-1-phenylethyl) malonate. The synthesis of pyrrolidine **2** from other different precursors have also been reported[24-26].

Experimental Section

Melting point was determined in open capillaries and uncorrected. IR spectra were recorded in KBr on JASCO FT-IR spectrophotometer and ^1H and ^{13}C NMR spectra on Bruker 300/ 75 MHz instrument using $CDCl_3$ as solvent and TMS as internal reference. The starting materials **1** have been synthesised by the piperidine catalysed addition of equimolar amount of diethyl malonate and different chalcone in benzene under reflux modifying the reported method[22].

General procedure for the preparation of compound 2. Zinc powder (6 g, 0.083 mole) of 90% purity was added in portions to a mixture of ammonium chloride (2.5 g) and the adduct **1 (**0.209 g, 0.1 mole) in 80 mL of water with stirring while keeping the temperature around 60-65°C. After the addition, the mixture was stirred for a further period of 50-60 min. The zinc oxide formed was filtered off and washed with 25 mL of hot water. The filtrate obtained was extracted with diethyl ether dried, evaporated and purified through column chromatography to give **2**.

2-Oxo-4-phenyl-3-carbethoxypyrrolidine, 2a. Yield. 80%; m.p.113-14°C (reported[22] m.p.132°C); Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.74; H, 6.47; N, 6.03; IR (KBr):3214 (NH), 1735 (C=O), 1697 (C=O); ^1H NMR ($CDCl_3$): δ 1.30 (t, J = 7.2 Hz, 3H, CH_3), 3.40 (dd, J = 9.6, 8.7 Hz, 1H, CH_a H_b), 3.80 (dd, J = 9.6, 8.7 Hz, 1H, CH_a H_b), 3.55 (d, J = 9.9 Hz, 1H, *CH*-COOEt), 4.10 (m, 1H, *CH*-Ph), 4.25 (q, J = 7.2 Hz, 2H, CH_2), 7.35 (m, 5H, Ar-H), 7.60 (s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 14.5, 44.8, 46.4, 55.9, 62.1, 127.9, 128.0, 129.6, 140.2, 169.7, 174.2.

2-Oxo-4-(4′-chlorophenyl)-3-carbethoxypyrrolidine 2b. Yield. 78%; viscous liquid; IR (KBr):3216 (NH), 1732 (C=O), 1695 (C=O); ^1H NMR ($CDCl_3$): δ 1.26 (t, J = 7.55 Hz, 3H, CH_3), 3.40 (dd, J=9.6, 8.7 Hz, 1H, CH_a H_b), 3.80 (dd, J=9.6, 8.7 Hz, 1H, CH_a H_b), 3.52 (d, J=9.9 Hz, 1H, *CH*-COOEt), 4. 08 (m, 1H, *CH*-Ph), 4.23 (q, J = 7.55 Hz, 2H, CH_2), 7.20 (d, 2H, Ar-H), 7.31 (d, 2H, Ar-H), 7.55 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 14.0, 43.7, 47.6, 55.2, 61.8, 128.6, 129.0, 133.4, 138.7, 169.3, 172.6.

2-Oxo-4-(4′-methoxyphenyl)-3-carbethoxypyrro-lidine 2c.Yield. 80%; viscous liquid; IR (KBr): 3218 (NH), 1735 (C=O), 1693 (C=O); ^{1}H NMR ($CDCl_3$): δ 1.25 (t, *J* = 7.2 Hz, 3H, CH_3), 3.40 (dd, *J* = 9.6, 8.7 Hz, 1H, CH_a H_b), 3.78 (dd, *J* = 9.6, 8.7 Hz, 1H, CH_a H_b), 3.43 (d, *J* = 9.9 Hz, 1H, *CH*-COOEt), 3.79 (s, 3H, OCH_3), 4. 05 (m, 1H, *CH*-Ph), 4.25 (q, *J* = 7.2 Hz, 2H, CH_2), 6.80 (d, 2H, Ar-H), 7.33 (d, 2H, Ar-H), 7.65 (s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 13.0, 42.8, 46.9, 54.7, 55.5, 60.4, 113.2, 127.5, 130.6, 157.8, 168.4, 172.8.

2-Oxo-4-(2′-chlorophenyl)-3-carbethoxypyrro-lidine 2d. Yield. 75%; viscous liquid; IR (KBr): 3210 (NH), 1737 (C=O), 1692 (C=O); ^{1}H NMR ($CDCl_3$): δ 1.25 (t, *J* = 6.9 Hz, 3H, CH_3), 3.40 (dd, *J* = 9.9, 6.9 Hz, 1H, CH_a H_b), 3.78 (dd, *J* = 9.6, 8.7 Hz, 1H, CH_a H_b), 3.68 (d, *J* = 8.1 Hz, 1H, *CH*-COOEt), 4.05 (m, 1H, *CH*-Ph), 4.25 (q, *J* = 6.9 Hz, 2H, CH_2), 7.30 (m, 5H, Ar-H), 7.50 (s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 14.5, 41.6, 48.7, 55.2, 62.3, 128.2, 128.7, 129.2, 130.3, 135.2, 139.8, 169.4, 173.1.

2-Oxo-4-(4′-methylphenyl)-3-carbethoxypyrro-lidine 2e. Yield.80%; viscous liquid; IR (KBr) :3215 (NH), 1731 (C=O), 1697 (C=O); ^{1}H NMR ($CDCl_3$): δ 1.25 (t, *J* = 7.2 Hz, 3H, CH_3), 2.33 (s, 3H, CH_3), 3.40 (dd, *J* = 9.9, 6.9 Hz, 1H, CH_a H_b), 3.77 (dd, *J* = 9.9, 6.9 Hz, 1H, CH_a H_b), 3.55 (d, 1H, *CH*-COOEt), 4.06 (m, 1H, *CH*-Ph), 4.23 (q, *J* = 7.2 Hz, 2H, CH_2), 7.10 (m, 5H, Ar-H), 7.50 (s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 14.5, 21.4, 44.5, 48.3, 55.9, 62.2, 127.3, 129.6, 137.1, 137.6, 169.7, 173.5.

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