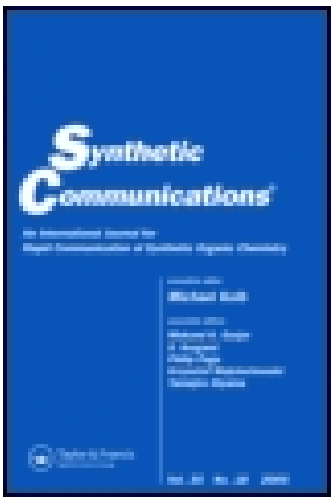

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A Convenient Synthesis of α-Benzylacrylic Acid

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A CONVENIENT SYNTHESIS OF α-BENZYLACRYLIC ACID

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ABSTRACT: A convenient and reliable two-stage synthesis of α-benzyl-acrylic acid (**2**) from diethyl benzylmalonate in 72% yield and good purity is reported. The synthesis compares favourably with the other procedures tested.

N-(Mercaptoacyl)amino acids have received attention for their ability to inhibit zinc metalloenzymes such as angiotensin-converting enzyme (ACE) and neutral endopeptidase-24.11 (NPE-24.11[1]). Captopril (**1**), an *N*-(mercaptoacyl)amino acid, has been synthesised[2] and shown to be an ACE inhibitor. In the synthesis of some captopril analogues, sulphur nucleophiles have been added to cyclic α,β-unsaturated carbonyl compounds with endo-[3] or exo-[4] cyclic double bonds. α-Benzylacrylic acid (**2**) is an important starting material for the synthesis of *N*-(2-benzyl-3-mercaptopropanoyl)amino acid, and we wished to prepare a series of these predesigned derivatives (**5**) for enzyme inhibition studies.[5]

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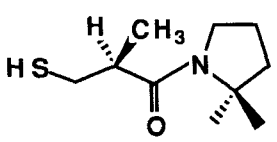
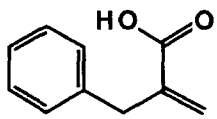


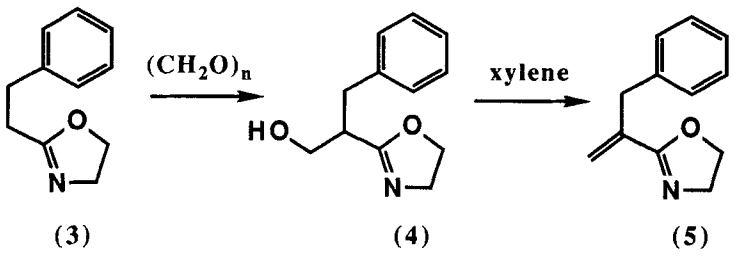
(1)



(2)

The acid (**2**) has been synthesised by Mannich and Rister,[6] who treated the diethyl ammonium salt of ethyl benzylmalonic acid with an excess of formaldehyde solution to form ethyl α-benzylacrylate which was then converted to α-benzylacrylic acid. The pyrolysis of 5-norbornene-2-benzyl-2-carbonitrile to α-benzylacrylonitrile by a retro Diels-Alder process followed by hydrolysis of the nitrile to the carboxylic acid also led to compound (**2**).[7] More recently, compound (**2**) has been synthesised in a one-pot process from 3-phenyl-propanoic acid via an oxazoline intermediate (**3**, Scheme I) the hydroxymethyl compound (**4**) and the α-vinyloxazoline (**5**) in an overall yield of 72%.[8]

Attempts to prepare (**2**) using the one-pot oxazoline method[8] failed to produce reasonable yields of pure product. This method was repeated with isolation and purification of the intermediate compounds. Condensation of 3-phenylpropanoic acid with 2-amino-2-methylpropanol to form oxazoline (**3**) was accomplished in 76% yield after distillation. The first step was performed without major modification of the literature method. Formylation of the oxazoline (**3**) with paraformaldehyde at 70°C for 16 h in the presence of a catalytic amount of potassium hydroxide was then effected. The base was added as a 10% solution in methanol and the methanol removed *in vacuo* before introducing the paraformaldehyde. The yield of the formylation reaction was high as assessed by ^{1}H NMR spectroscopy and thin-layer chromatography (TLC) and was used without purification. Two important observations were made on the formylation process:

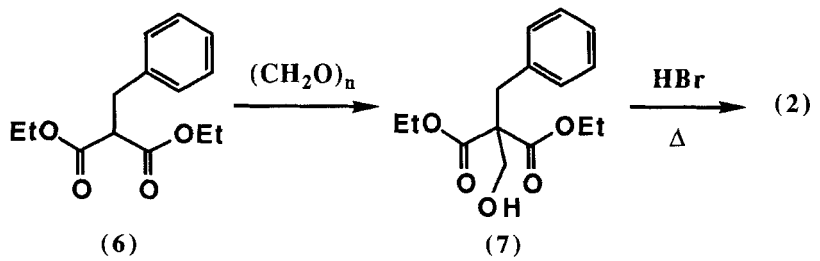


(3) (4) (5)

Scheme I

firstly, the formylation reaction did not proceed unless the methanol was removed completely and, secondly, a reaction temperature of 70°C was found to be necessary for efficient monoformylation. At reaction temperatures above 80°C, the undesirable formation of a bis-hydroxymethyl compound occurred. For the third step, the hydroxymethyl compound (**4**) was dehydrated by heating in xylene with orthophosphoric acid as the catalyst under Dean-Stark conditions to form the oxazoline (**5**) in 59% yield. α-Benzylacrylic acid (2) was obtained after acid hydrolysis of the oxazoline in 64% yield. The one-pot synthesis method was repeated with the inclusion of the above modifications; however, the best overall yield obtained was only 37%, well below the reported value of 72%.[6] As an alternative dehydration method, the hydroxymethyl compound (**4**) was treated with an excess amount of acetic anhydride and triethylamine at 80°C for 1 h. This modification improved the yield of the one-pot synthesis of (**2**) to 63%, a significant improvement over the phosphoric acid method.

We developed an improved two-stage synthesis of α-benzylacrylic acid (Scheme II) based on a literature procedure used for the synthesis of α-(bromomethyl)acrylic acid.[7] Diethyl benzylmalonate (**6**) was formylated with paraformaldehyde in the presence of a catalytic amount of base at 60°C. Diethyl 2-



Scheme II

benzyl-2-(hydroxymethyl) malonate (**7**) was obtained in excellent yield and purity, as shown by ^1H NMR spectra and TLC, and used in the next step without purification. The formylated compound (**7**) was treated with 48% aqueous hydrobromic acid solution in the presence of a cosolvent such as acetic acid or dioxane at 90°C for 18 h. Under these conditions the hydroxymethyl functionality was converted to a bromomethyl group and the esters were cleaved, which led to decarboxylation of one of the carboxylic acid groups and simultaneous elimination of the bromine to form α-benzylacrylic acid (**2**) in 73% yield. The two-stage synthesis is an improved method and found to be convenient, reproducible and gives the desired product in good purity and satisfactory yield.

α-Benzylacrylic acid (2)

Paraformaldehyde (9.14 g, 0.304 mol) was added to diethyl benzyl-malonate (70 g, 0.28 mol) and the suspension stirred and heated to 60°C. Powdered potassium hydroxide (50 mg, 0.8 mmol) was added and after 30 min the reaction mixture was cooled before addition of chloroform (100 ml). The solution was then filtered through a bed of silica (5 cm) and washed through with chloroform (2 x 50 ml). The solvent was removed *in vacuo* to yield diethyl 2-benzyl-2(hydroxymethyl)malonate (**7**) as a colourless oil (75.9 g, 98%) which was

used in the following step without purification: ^{1}H NMR ($CDCl_3$, 60 MHz) d 1.28 (t, J = 5 Hz, 6H, 2 x CH_3), 2.65 (br s, 1H, OH), 3.55 (s, 2H, PhCH_2), 4.1 (s, 2H, CH_2OH), 4.23 (q, J = 5 Hz, 4H, 2 x CH_2CH_3), 7.3 (s, 5H, Ph); IR (neat) 1730 (2 x C=O), 3500 (br, OH) cm^{-1}.

To compound (**7**) (75 g, 0.27 mol), hydrobromic acid (48%, 152 ml, 1.35 mol) and glacial acetic acid (50 ml) were added and the solution was stirred at 90°C for 18 h. During the reaction, bromoethane (bp 40°C) was formed as a by-product and continuously removed by distillation. The mixture was extracted with dichloromethane (2 x 200 ml). The organic layer was washed with brine (200 ml) followed by water (2 x 200 ml), dried (anhydrous magnesium sulphate), filtered, and the solvent removed *in vacuo*. The product was extracted into hot petroleum spirit (40–60) and, after standing for 15 min, the solvent was decanted from the brown residue. The petroleum spirit was removed *in vacuo* to yield a pale yellow oil which was distilled (bp 135–140°C/0.5 mm Hg) to afford a colourless oil (31.7 g, 72.4%) which solidified and was crystallised (hexane) to yield **2** as white needles, mp 68–70°C (lit. 66–68°C).[6] ^{1}H NMR ($CDCl_3$), 60 MHz) d 3.61 (s, 2H, CH_2), 5.52 (s, 1H, CH_2=C), 6.45 (s, 1H, CH_2=C), 7.20 (s, 5H, Ph), 12.9 (s, 1H, COOH); ^{13}C NMR [$(CD_3)_2SO$, 75.47 MHz] d 37.4 (CH_2), 125.7 (CH_2=C), 126.1 (C-4), 128.3 (C-3,5), 128.7 (C-2,6), 139.2 (C-1), 140.7 (CH_2=C), 167.8 (C=O); IR (KBr) 1630 (C=C), 1690 (C=O), 2900 (br, OH) cm^{-1}.

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