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An Efficient and Cost-Effective Synthesis of 3-Ethoxy-4-ethoxycarbonyl-phenylacetic Acid: A Key Acid Synthon of Repaglinide†

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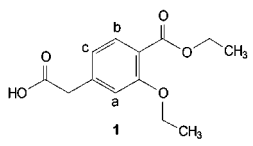
Abstract:

This report describes an efficient and commercially viable synthesis of 3-ethoxy-4-ethoxy-carbonyl-phenylacetic acid (1), a key intermediate for the preparation of repaglinide, an oral hypoglycemic agent, from 2-hydroxy-4-methylbenzoic acid in two steps. Thus, 2-hydroxy-4-methylbenzoic acid was first alkylated with ethyl bromide in a polar aprotic solvent and in the presence of an inorganic base to afford ethyl 2-ethoxy-4-methylbenzoate; deprotonation with lithium diisopropylamide (LDA) and quenching the resulting carbanion with carbon dioxide provided the desired compound with improved yield and excellent purity. This procedure is significantly better than a previously published synthesis which involves five steps and requires use of expensive and hazardous reagents.

Introduction

Repaglinide (**2**) is first member of a new class of oral hypoglycemic agents (meglitinides) for type-II non-insulin-dependent diabetes mellitus (NIDDM). It stimulates the secretion of insulin from pancreatic beta cells, acting via calcium channels. Hypoglycemic events are fewer after the administration of repaglinide as compared with those after the administration of other antidiabetic agents, and repaglinide offers a significantly better biological profile as compared with that of the sulphonyl urea class of hypoglycemic agents.[1−3]



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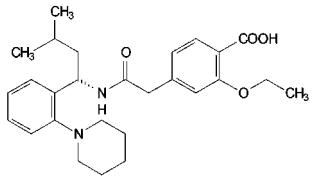

2 Repaglinide

Synthesis of repaglinide involves condensation of an appropriately substituted and chirally pure benzylamine derivative with an appropriately substituted phenylacetic acid derivative **1** followed by saponification.[4] The literature reports preparation of the key intermediate **1** in five steps and with an overall yield of about 30% of theory.[5] We undertook development of an alternate and more efficient synthetic strategy to prepare **1.**

Results and Discussion

There is a literature report[5] for the preparation of the target compound, 2-ethoxy-3-ethoxycarbonylphenylacetic acid (**1**), starting from ethyl 2-ethoxy-4-methylbenzoate (**4**) through substitution of benzylic proton. This method, however, is relatively lengthy and, more importantly, uses several toxic and potentially hazardous reagents. Thus, to accomplish substitution of the carboxy group in **4**, the literature procedure (Scheme 1) involved bromination of benzylic methyl (using NBS in carbon tetrachloride in the presence of AIBN), substitution of bromide with nitrile (using sodium cyanide in the presence of *N*-benzyl-tri-*n*-butylammonium chloride), conversion of nitrile to the corresponding ethyl ester (using ethanol and HCl gas), and finally selective ester hydrolysis. Furthermore, the literature procedure required maintaining very high temperature (150 °C) for 30 h to accomplish O-alkylation of 2-hydroxy-4-methyl benzoic acid (**3**) with ethyl bromide to produce **4**. Our aim was to develop a short and easy-to-scale-up process with improved overall yield and quality of the desired compound **1**.

We conceptualized that it should be possible to deprotonate the benzylic proton in **4** (keeping the temperature low) and quench the resulting carbanion with carbon dioxide to generate the desired acid (**1**) in a one-step process. Indeed, deprotonation (Scheme 2) of **4** with LDA and subsequent reaction of the resulting carbanion with carbon dioxide afforded the desired acid in good yields and excellent purity, obviating the use of a lengthy sequence, as reported. Thus, **4** was reacted with LDA in a mixture of anhydrous THF and dimethylpropylene urea (DMPU) at −75 °C; the resulting carbanion was then quenched by bubbling carbon dioxide gas. Use of a cosolvent was found to be necessary to get optimum yields of the desired acid (**1**).

We next turned our focus on the optimization of reaction conditions for O-alkylation of 2-hydroxy-4-methylbenzoic acid to generate **4**. The literature procedure requires an autoclave and high temperature (150 °C) for long periods of time (30 h) for this transformation. Substituting acetone (as used in the literature report) with anhydrous DMSO

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† A patent application (WO 2001035900 A2) incorporating parts of this report has been filed.

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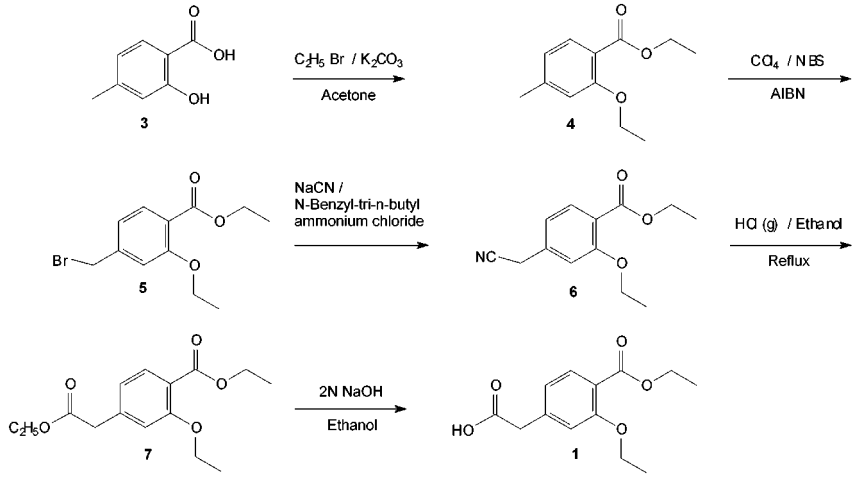
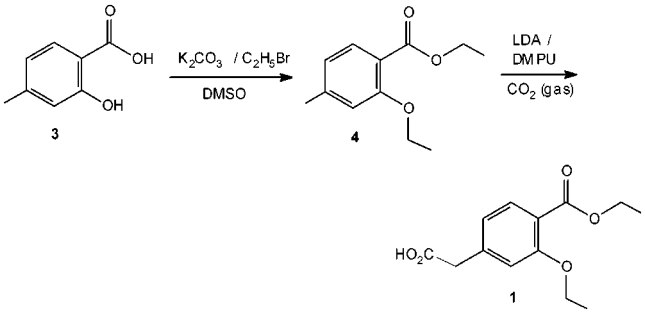
Scheme 1



Scheme 2



dramatically reduced the reaction time (total 8 h), and more importantly the reaction could be successfully carried out at 35−40 °C. Thus, 2-hydroxy-4-methylbenzoic acid was alkylated with ethyl bromide in anhydrous DMSO and in the presence of anhydrous potassium carbonate. Addition of ethyl bromide was optimized, and the desired compound was isolated in quantitative yields.

Conclusions

We have successfully developed an efficient two-step process for the synthesis of 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid (**1**). The reaction conditions are operationally simple, robust, and amenable to multikilogram scale.

Experimental Section

General. Starting materials were obtained from commercial suppliers and used without further purification. Gas chromatography was performed with HP 50 (30 mm × 0.53 mm column, fused silica coated with 50% methyl- and 50% phenylpolysiloxane as stationary phase, 1.0 mm film thickness). HPLC was performed with a Waters' instrument (version 3.05.01) using Kromosil C-18 (5 μ, 250 mm × 4.6 mm) column. ^{1}H NMR spectra were recorded using a Bruker 300 MHz in $CDCl_3$. The chemical shift data is reported as δ (ppm) downfield from tetramethylsilane which was used as an internal standard.

Ethyl 2-ethoxy-4-methylbenzoate (4). Anhydrous potassium carbonate (190.5 g, 1.38 mol) was added to a well-stirred solution of 2-hydroxy-4-methylbenzoic acid (100 g, 0.658 mol) in dimethyl sulfoxide (250 mL). The mixture was heated to 35−40 °C, and the first lot of ethyl bromide (89.5 g, 0.82 mol) was added slowly, under stirring, over a period of 30 min. The mixture was stirred for 2 h at 35−40 °C, and a second lot of ethyl bromide (89.5 g, 0.82 mol) was added over a period of 30 min, maintaining the temperature at 35−40 °C. The reaction mixture was further stirred at 35−40 °C for 8 h, cooled to 20−25 °C, and diluted with toluene (300 mL). The inorganics were removed through filtration and washed with toluene (200 mL). The combined filtrate was diluted with water (250 mL) and stirred for 30 min, and the organic layer was separated. The aqueous layer was further extracted with toluene (200 mL), and the combined toluene layer was washed with water (250 mL). The solvent was removed under vacuum to afford ethyl 2-ethoxy-4-methylbenzoate 136.3 g (99.6%). ^{1}H NMR δ 1.35 (t, 3H, $CH_2C\underline{H}_3$, J = 7.1 Hz), 1.43 (t, 3H, $CH_2C\underline{H}_3$, J = 6.9 Hz), 2.33 (s, 3H, $ArC\underline{H}_3$), 4.05 (q, 2H, $-OC\underline{H}_2CH_3$, J = 6.9 Hz), 4.32 (q, 2H, $-OC\underline{H}_2CH_3$, J = 7.1 Hz), 6.72−6.75 (m, 2H, $\underline{H}_a$ and $\underline{H}_c$) and 7.69 (d, 1H, $\underline{H}_b$, J = 8.3 Hz).

3-Ethoxy-4-ethoxycarbonylphenylacetic Acid (1). Under an atmosphere of nitrogen, *n*-butyllithium (400 mL, 15% w/w solution in hexane) was added to a solution of diisopropylamine (58.0 g, 0.57 mol) in anhydrous tetrahydrofuran (760 mL) at −30 °C. The mixture was stirred at −30 °C for 30 min and cooled to −75 °C, and anhydrous 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU, 240 mL) was added slowly. A solution of ethyl 2-ethoxy-4-methylbenzoate (80.0 g, 0.38 mol) in tetrahydrofuran (40 mL) was then added at −75 °C, and the mixture was stirred at this temperature for 2 h. Carbon dioxide gas was then purged into the reaction mixture at −75 °C until complete decolorization. The reaction mixture was then brought to room temperature and diluted with water (640 mL), and the pH was adjusted to 7.8 using 10% (v/v) aqueous sulphuric acid. The layers were separated; the aqueous layer was then acidified to pH 2.0 using 10% (v/v) aqueous sulphuric acid and extracted with diisopropyl ether (2 × 400 mL). The combined diisopropyl ether layers were washed with water (2 × 240 mL) and concentrated in vacuo. Crystallisation with toluene:petroleum ether (190 mL, 1:0.9) afforded 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid, 64.9 g (67%); mp 74−

76 °C (lit. mp 70−75 °C).[5] ^{1}H NMR δ 1.36 (t, 3H, $-C\underline{H_3}$, $J = 7.1$ Hz), 1.44 (t, 3H, $-CH_3$, $J = 6.9$ Hz), 3.64 (s, 2H, $-CH_2COOH$), 4.11 (q, 2H, $-OC\underline{H_2}CH_3$, $J = 6.9$ Hz), 4.33 (q, 2H, $-OC\underline{H_2}CH_3$, $J = 7.1$ Hz), 6.87 (m, 2H, H_a and H_c) and 7.73 (d, 1H, H_b, $J = 8.2$ Hz). Mass (M + 1) (*m*/*z*) 253.

Alternate Method. Under an atmosphere of nitrogen, *n*-butyllithium (25 mL, 15% w/w solution in hexane) was added to a solution of diisopropylamine (3.6 g) in anhydrous tetrahydrofuran (30 mL) at −30 °C. The mixture was stirred at −30 °C for 30 min and cooled to −75 °C, and anhydrous hexamethylphosphoramide (HMPA, 10 g) was added slowly. A solution of ethyl 2-ethoxy-4-methylbenzoate (5 g) in anhydrous tetrahydrofuran (10 mL) was then added at −75 °C, and the mixture was stirred at this temperature for 2 h. Carbon dioxide gas was then purged into the reaction mixture at −75 °C until complete decolorization (the reaction mixture turned yellow from dark red). The reaction mixture was then stirred at −75 to −70 °C for 30 min and then brought to 10 °C, diluted with water (50 mL), and extracted with hexanes (2 × 25 mL). The aqueous layer was acidified with 10% (v/v) aqueous sulphuric acid to pH ≈ 2 and extracted with dichloromethane (2 × 25 mL). The combined dichloromethane layer was washed with water (2 × 25 mL) and concentrated in vacuo. The oily product thus obtained was dissolved in diethyl ether (50 mL) and washed with water (3 × 20 mL). The ether layer was then concentrated in vacuo to afford a thick oil which solidified on being kept at room temperature to afford 3-ethoxy-4-ethoxy-carbonyl-phenylacetic acid, 4.4 g (72.7%). The spectral data and melting point matched those of the authentic sample, as prepared above.

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