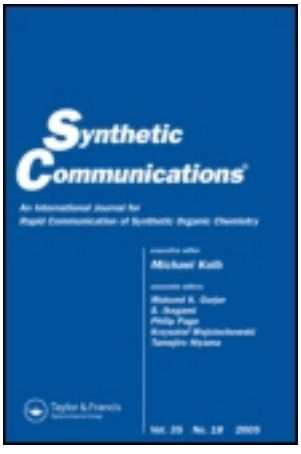

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Selective Phenol Alkylation: An Improved Preparation of Efaproxiral

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Selective Phenol Alkylation: An Improved Preparation of Efaproxiral

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Abstract: An improved, two-step synthesis of efaproxiral, used in breast cancer therapy, is described, utilizing inexpensive commodity chemicals for starting materials. Selective amide formation and O-alkylation in the presence of multi-reactive functional groups is demonstrated, thus avoiding protection/deprotection steps.

Keywords: Bargellini reaction, 2-bromo-2-methylpropanoic acid, efaproxiral, selective alkylation

We recently published an article[1] on the alkylation of phenols with 2-bromo-2-methylpropanoic acid that illustrates advantages over previous methods, specifically control of exotherm, exposure safety, and methacrylate polymer. One previous method required alkylation of an ester of 2-bromo-2-methylpropanoic acid, followed by saponification, and this approach resulted in formation of polyacrylates, which were not easily detected or cleaned from the reactors. A second and older method, the Bargellini reaction, required extremely large amounts of sodium hydroxide, resulting in large waste streams, and complex exotherm control. As described in the published article, the use of 2-bromo-2-methylpropanoate minimized polyacrylate formation, and whatever polymer did form was easily removed because of its solubility in water.

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To further investigate the scope, utility, and limitations of the reaction, we selected 2-(4-{2-[(3,5-dimethylphenyl)amino]-2-oxoethyl}phenoxy)-2-methylpropanoic acid, efaproxiral (Fig. 1), with its attendant complexity of phenol versus amide versus active methylene alkylation, as a target of synthesis.

We selected efaproxiral as an opportune target to demonstrate this selective chemistry, because efaproxiral, the active pharmaceutical ingredient in Allos Therapeutics' Efaproxyn, is completing Phase III clinical trials for treatment of brain metastasis originating from breast cancer. Although certain tumors survive radiation damage, due to hypoxia (oxygen starvation), 2,3-diphosphoglycerate (2,3-DPG) increases the susceptibility of tumors to radiation damage by reducing the oxygen-binding affinity of hemoglobin. 2,3-DPG is unable to cross the red-blood-cell membrane. The 2,3-DPG agonist, 2-(4-{2-[(3,5-dimethylphenyl)amino]-2-oxoethyl}phenoxy)-2-methylpropanoic acid, efaproxiral, is able to cross the red-blood-cell membrane and is therefore an improvement over 2,3-DPG at unloading oxygen from hemoglobin.[2] In effect, efaproxiral is designed to make tumors more responsive to radiation therapy by increasing the amount of oxygen in tumor cells. The therapy agent does not have to enter the tumor to be effective but is administered with supplemental oxygen. Because of the large quantities of therapy agent required for Phase III multicenter trials and the likely large tonnage required at launch, a simple, high purity, and environmentally benign process was essential.

Anilide formation in the presence of many other functional groups, such as phenol, in either reaction partner requires protection.[3] As we sought to avoid protection or deportation steps in our synthesis, we rejected typical stoichiometric activation reagents. Although other methods were successful for the direct coupling of N-(3,5-dimethylphenyl)-2-(4-hydroxyphenyl)-acetamide (e.g., trichlorotriazine,[4] benzotriazole reagents[5]), by far the simplest way to prepare this anilide was to heat a mixture of 3,5-dimethylaniline, 4-hydroxyphenylacetic acid, and catalytic boric acid under azeotropic water-elimination conditions (Dean–Stark trap) for 18–20 h in toluene (Scheme 1). For other examples of boric acid–catalyzed amide couplings, see Scheme 1.[6] The putative mixed anhydride, stabilized via hydrogen bonding, regenerates the catalytically active boric acid (Fig. 2). Once the reaction was complete, as judged by the disappearance of

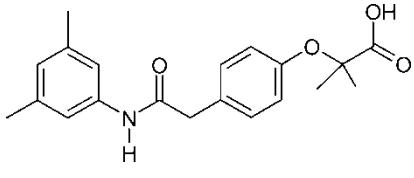
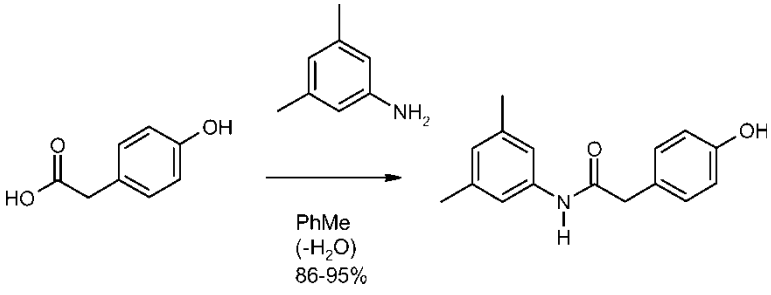


Figure 1. Efaproxiral.



Scheme 1.

4-hydroxyphenylacetic acid, the mixture was cooled and the resulting solid isolated by filtration. Interestingly, the presence of catalytic boric acid drastically reduced the reaction time and temperature compared to previously reported conditions, which had required 3 days under Dean–Stark conditions in xylenes.[7] Although other acids are likely to catalyze this reaction, the low cost, safety, and ease of removal of boric acid makes it an especially attractive catalyst.

Reaction of N-(3,5-dimethylphenyl)-2-(4-hydroxyphenyl)acetamide with 2-bromo-2-methylpropanoic acid under the conditions previously described (NaOH, 2-butanone) provided a single product in high yield and purity (Scheme 2). We demonstrated spectroscopically that this single product was alkylated exclusively at the phenol and was unequivocally the desired 2-(4-{2-[(3,5-dimethylphenyl)amino]-2-oxoethyl}phenoxy)-2-methylpropanoic acid. Through multiple bond correlations, NMR data confirm the presence of the protonated amide. Infrared bands consistent with a phenol moiety were not observed in the product spectrum, confirming alkylation at this site.

EXPERIMENTAL

All masses and volumes, except those defined by molar ratios, are approximate.

HPLC reaction monitoring and analysis was conducted on a Luna C18(2) column of 50 mm × 2 mm, 3 μm, at 40°C, with a flow rate of 1 mL/min, and UV visualization at 220 nm; mobile phase A: H_2O (0.05%), mobile phase B: CH_3CN (0.05%); gradient: 0–95% B over 8 min.

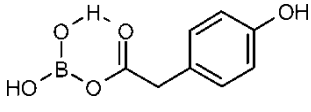
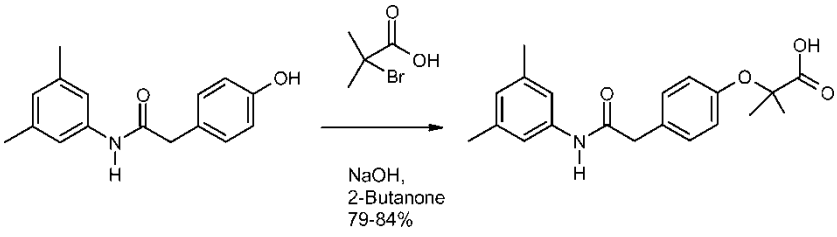


Figure 2. Mixed anhydride.



Scheme 2.

All temperatures are uncorrected. Starting materials, reagents, and solvents were purchased from bulk commercial sources and used without further purification.

N-(3,5-Dimethylphenyl)-2-(4-hydroxyphenyl)acetamide

A mixture of 4-hydroxyphenylacetic acid (0.26 mol, 40 g, 1.0 equiv), 3,5-dimethylaniline (0.31 mol, 39 mL, 1.2 equiv), boric acid (0.02 mol, 1.6 g, 0.1 equiv), and toluene (0.5 L) was heated under reflux with water elimination via a Dean–Stark trap for 18 h. The resulting mixture was cooled, and the solid was collected by filtration, washed sequentially with toluene (2×0.2 L) and water (2×0.2 L), and dried in vacuo at 50–55°C to give 56–62 g (86–95%) of N-(3,5-dimethylphenyl)-2-(4-hydroxyphenyl)acetamide. (Spectroscopic data were consistent with previously reported literature data: see Ref. 7.)

2-(4-{2-[(3,5-Dimethylphenyl)amino]-2-oxoethyl}phenoxy)-2-methylpropanoic Acid

A mixture of N-(3,5-dimethylphenyl)-2-(4-hydroxyphenyl)acetamide (0.2 mol, 49 g) and 20–40 mesh NaOH (1.1 mol, 44 g) in 2-butanone (0.5 L) was stirred and heated to 50°C. After 1–2 h, a solution of 2-bromo-2-methylpropanoic acid (0.34 mol, 57 g, 1.7 equiv) in 2-butanone (0.1 L) was added over approximately 1 h. The mixture was stirred at 50°C, until N-(3,5-dimethylphenyl)-2-(4-hydroxyphenyl)acetamide had been consumed (typically 2–3 h). Water (0.3 L) was added, and the biphasic mixture was cooled to 15–25°C. After separation of the aqueous (lower) layer, which contained no product as sodium salt, the organic (upper) layer was diluted with ethyl acetate (0.4 L), and the mixture acidified to pH < 3 with 1 M HCl (0.3 L). The organic phase was washed with water (0.3 L) and concentrated to 0.2 L under reduced pressure. A 1:1 mixture of toluene and heptane (0.3 L) was added to the solution. (Toluene–heptane as antisolvent

resulted in more robust crystallization than either toluene or heptane alone.) The resulting suspension was cooled to 0–5°C, and stirred for 30–60 min. The solid was collected by filtration, washed with heptane, and dried in vacuo at 80–95°C to give 54–57 g (79–84%) of 2-(4-{2-[(3,5-dimethylphenyl)amino]-2-oxoethyl}phenoxy)-2-methylpropanoic acid. Mp 138–139°C; ^{1}H NMR (400 MHz, DMSO): δ 13.03 (s, 1H, CO_2H), 9.98 (s, 1H, NH), 7.23 (s, 2H, ArH), 7.21 (d, 2H, $J = 8.0$ Hz, ArH), 6.79 (d, 2H, $J = 8.0$ Hz, ArH), 6.69 (s, 1H, ArH), 3.53 (s, 2H, CH_2Ar), 2.23 [s, 6H, $Ar(CH_3)_2$], 1.51 [s, 6H, $C(CH_3)_2$]; ^{13}C NMR (100 MHz, DMSO): δ 175.3, 169.4, 154.2, 139.3, 137.8, 130.0, 129.4, 124.9, 118.5, 117.1, 78.5, 42.7, 25.2, 21.3. Anal. calcd. for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.38; H, 6.89; N, 4.21.

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