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A simple method for chemoselective phenol alkylation

Pingli Liu,* Liang Huang and Margaret M. Faul

Chemical Process R&D, Amgen Inc., One Amgen Center Drive, Thousand Oaks, CA 91320, United States

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Abstract—A simple and effective method for chemoselective alkylation of phenol over carboxylic acid using a 40% aqueous solution of tetrabutylphosphonium hydroxide that affords the desired phenyl ethers in 82–99% yield is described.

Phenolic ethers and carboxylic acids are found in a variety of active pharmaceutical ingredients in the pharmaceutical industry, for instance the potent fibrinogen receptor antagonist MK-383 (**1**),[1] and the PPAR α/γ agonist (**2**)[2] (Fig. 1). In addition, phenol ethers are important intermediates in medicinal chemistry.[3] Synthesis of these compounds typically suffers from the need to use protecting groups to obtain improved chemoselectivity of ether formation relative to esterification. A variety of methods for chemoselective esterification have been developed,[4] however, a method for chemoselective alkylation of phenols over carboxylic acids has not been reported. Phenolic ethers are generally prepared in two ways: (i) Fisher ester formation, phenol alkylation, and ester saponification;[5] or (ii) dialkylation of both the phenol and carboxylic acid followed by selective ester saponification.[2,6] However, for rapid SAR evaluation or large scale synthesis of compounds in clinical development these methods are economically inefficient, time consuming, require an excess of reagents and/or precious alkylating agents, and are not suitable for molecules that are sensitive to acid and/or base.

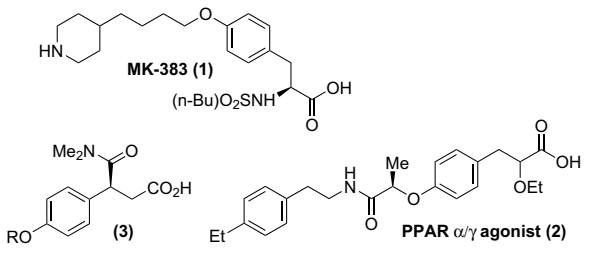

Figure 1.

In support of a recent medicinal chemistry SAR effort to evaluate ether analogs of **3**, we developed a one-step method for chemoselectively synthesizing phenolic ethers in the presence of carboxylic acid functional groups. Although the original medicinal chemistry procedure proceeded in three steps with reasonable yields via Fisher ester formation, phenol alkylation, and ester saponification, it was inefficient due to the number of steps and time required to perform this simple operation. Herein we report a new and practical method for the chemoselective alkylation of phenols in the presence of carboxylic acids. The process, which was demonstrated with a variety of alkylating agents and across multiple substrates, occurs in high yield (82–99%) using readily available reagents.

Our initial screen to evaluate the chemoselective alkylation of phenols over carboxylic acids used 4-hydroxybenzoic acid **4** as a representative substrate. Treatment of **4** with allyl bromide using a variety of bases (NaOH, KOH, $Cs(OH)_2$, and n-Bu_4NOH) and solvents (THF, *N*-methylpyrrolidinone, *N*,*N*-dimethylformamide, dimethyl sulfoxide, and ethanol), afforded a mixture of both allyl ether and allyl ester. The best selectivity was observed using n-Bu_4NOH. Using 2 equiv n-Bu_4NOH the bis-tetrabutylammonium salt of **4** was generated that upon reaction with 1 equiv allyl bromide afforded an 85:15 ratio[7] of allyl ether/allyl ester.

Tetrabutylphosphonium salts exhibit good chemical[8] and thermal stability[9] and have lower toxicity[10] than ammonium salts. In addition, tetrabutylphosphonium salts have been used to dramatically increase the nucleophilicity of the fluoride anion, which has been used to advantage in the chemoselective esterification of hydroxybenzoic acids in ionic liquids.[4b] Since the pK_a difference of phenol relative to carboxylic acid is

* Corresponding author. Tel.: +1 805 477 0599; fax: +1 805 375 4531; e-mail: mfaul@amgen.com

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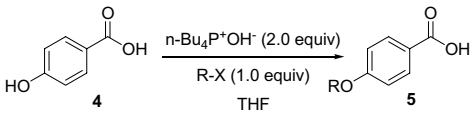
about five orders of magnitude (~9.7–4.7 in H_2O), chemoselective alkylation of phenol relative to a carboxylic acid should be feasible by selection of the right base, counterion, and solvent.

Thus, upon treatment of 4-hydroxybenzoic **4** with 2 equiv 40% aqueous tetrabutylphosphonium hydroxide (*n*-Bu_4POH) in THF at 0 °C, the bis tetrabutylphosphonium salt was generated that upon reaction with 1 equiv allyl bromide chemoselectively afforded 4-(allyloxy)benzoic acid **5** with no competing esterification. The scope of these conditions were evaluated using a variety of alkylating reactants (Table 1, Eq. 1). Ethyl, allyl, and benzyl bromide reacted chemoselectively to afford the corresponding ether in 91–94% yield. In addition, allyl chloride afforded an 86% yield of the corresponding allyl ether and a 90% yield of the benzyl ether, although the reaction times were longer.



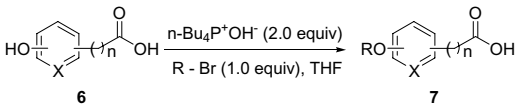
(1)

Table 1. Alkylation of 4-hydroxybenzoic acid **4** (Eq. 1)

Entry	R–X	Yield 5[a,b,c] (%)
1	Allyl –Br	91
2	Allyl–Cl	86
3	Ethyl–Br	93
4	Benzyl–Br	94
5	Benzyl–Cl	90[d]

[a] Reactions were carried at 5 mmol substrate in 10 mL THF with 2 equiv 40% aq *n*-Bu_4POH and 1 equiv R–X at 0 °C.
[b] Yields are isolated and unoptimized.
[c] All products exhibit satisfactory spectroscopic and physical properties.
[d] 72 h reaction time.

The scope of substrates was evaluated using allyl or benzyl bromide as the alkylating agent (Table 2, Eq. 2).[11] A variety of aromatic or heteroaromatic substrates afforded the corresponding allyl or benzyl ethers in 82–99% yield. All reactions were highly chemoselective (100:1) with no competitive esterification observed by HPLC.



(2)

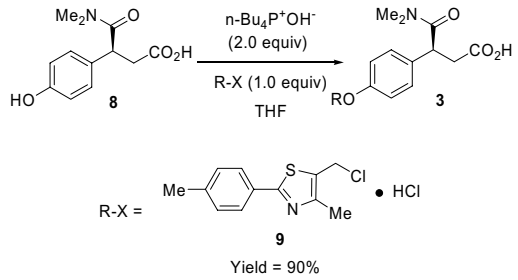
Table 2. Chemoselective alkylation of a variety of substrates (Eq. 2)

Entry	Substrate, **6**	R–Br	Yield 7[a,b,c] (%)
1	4-Hydroxyphenyl acetic acid	Allyl–Br	89
2	3-Hydroxyphenyl acetic acid	Allyl–Br	83
3	3-Hydroxy benzoic acid	Allyl–Br	84
4	4-Hydroxy-3-methoxy mandelic acid	Allyl–Br	99[d]
5	4-Hydroxy-3-methoxy mandelic acid	Bn–Br	83
6	2-Hydroxy nicotinic acid	Allyl–Br	85
7	2-Hydroxy nicotinic acid	Bn–Br	88
8	5-Hydroxy-1*H*–indole-carboxylic acid	Bn–Br	82

[a] Reactions were carried at 5 mmol substrate in 10 mL THF with 2 equiv 40% aq *n*-Bu_4POH and 1 equiv R–Br at 0 °C.
[b] Yields are isolated and optimized.
[c] All products exhibit satisfactory spectroscopic and physical properties.
[d] Weight percent assay yield.

Homogeneous, single-phase reaction mixtures were maintained throughout the alkylation process. Upon reaction completion, the mixtures were concentrated to remove THF, and the resulting aqueous solution was acidified to liberate the corresponding acid. All compounds described in Tables 1 and 2 could be isolated as a solid without chromatography. Those products that were oils, for example, 5-hydroxy-1*H*–indole-carboxylic acid (Table 2, entry 8) were converted into the corresponding salt to facilitate isolation.

Finally, this method proved generally applicable for the rapid synthesis of analogs of **3** for medicinal chemistry and in vivo evaluation. For example, treatment of hydroxy acid **8**, with thiazalyl chloride **9** afforded the desired ether **3** chemoselectively in 90% yield with no competing esterification. This method proved very robust for scaleup and further work in this area will be reported in due course.



(3)

In conclusion, we have developed a new method for the chemoselective alkylation of phenols over carboxylic acids using a 40% aqueous solution of tetrabutylphosphonium hydroxide that affords the corresponding phenol ethers in high yields (82–99%).

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.08.030.

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11. *General procedure for phenol alkylation*: To a solution of phenol (5 mmol, 1 equiv) and 40% aq *n*-Bu_4POH (10 mmol, 2 equiv) in THF (10 mL) was added the alkylating reagent (5 mmol, 1 equiv) at 0 °C. The reaction mixture was allowed to warm to ambient temperature and stirred until complete, as monitored by HPLC. Typical reactions times were 1–3 h using allyl bromide as the alkylating agent, although longer reaction times >48 h were observed using allyl chloride. With benzyl bromide reaction times of 4–24 h were common. Upon reaction completion, the solvent (THF) was removed in vacuo and the aqueous residue acidified with 2N aqueous HCl. The product precipitated out of solution and was isolated by filtration, followed by water wash. The resultant wet cake was dried in an oven under vacuum to give a white solid. Products that were oils were converted to salts prior to isolation (see Supplementary data).