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Water-based biphasic media for exothermic reactions: green chemistry strategy for the large scale preparation of clofibric acid and analogues

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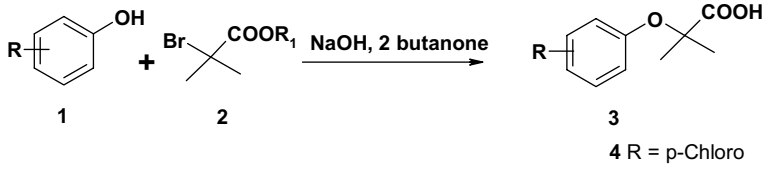
Abstract—A water-based biphasic reaction process has been developed for conducting exothermic reactions without organic solvents. This procedure is rapid, simple, and suitable for small scale synthesis as well as larger (multi-molar) scale reactions. The preparation of several hundred grams of clofibric acid and analogues by this eco-friendly and energy-efficient procedure is described. Smaller amounts of these compounds were prepared by the friction-activated 'Grindstone Chemistry' method described previously.

Current publications indicate renewed interest in derivatives of clofibric acid (**4**) which were used in earlier times as hyperlipidimia controlling drugs.[1] Thus, GlaxoSmithKline chemists have described a method for improving the earlier synthesis of 2-methyl-2-aryloxypropanoic acids (**3**) because of the present interest in this class of compounds for the potential treatment of type II diabetes.[2] The intermediate selected by them is 2-bromo-2-methylpropanoic acid (**2**) which is allowed to react with a phenolic compound (**1**). Reagent **2** is quite expensive and large volumes of organic solvents (2-butanone in particular) are also required (Scheme 1). It is worth noting that warming the reaction mixture to 50 °C is indicated although the reaction is stated to be quite exothermic.

An alternative synthesis of clofibric acid and analogues is the Bargellini reaction[3] published in 1906. This reaction involves the interaction of a phenol with acetone and chloroform in presence of sodium hydroxide. Heating under reflux for several hours and fairly lengthy work up provided low yields of clofibric acid and analogues. We attempted improvement of this reaction by using protocols developed in our laboratory. In preliminary work we noticed that this reaction is quite exothermic.

Water-based biphasic reaction media for exothermic reactions: We have recently studied the large-scale preparation of coumarin-3-esters[4a] (**5**) and dihydropyrimidinones[4b] (**6**) (Schemes 2 and 3).



Scheme 1.

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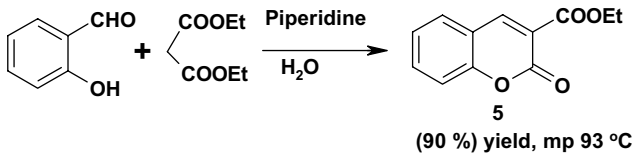


Scheme 2.

Both of these reactions are exothermic. We have found that the heat produced in exothermic reactions can be conveniently removed by a large volume of water that is mixed intimately with the solvent-free organic reagents.[4] A suitable reaction vessel and a powerful stirrer are the equipments needed. This method has been found to be efficient for allowing water-immiscible organic reagents to participate in exothermic reactions without the presence of an organic solvent.

The method used (Bargellini reaction[3]) by Gilman and Wilder[5] for clofibric acid (and analogues) involved heating the reagents under reflux for 4 h, and the yield was 37.2%.[5] We have successfully employed our water-based biphasic reaction for preparing large quantities of **4** and analogues more efficiently as described below.

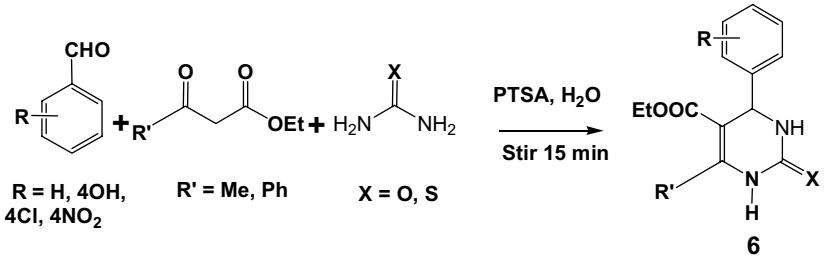
The synthesis of clofibric acid and analogues presented a problem for us because two of the reagents (acetone and chloroform) are fairly volatile. This problem was solved by conducting the preparative reaction below 30 °C by using a cooling bath for the reaction vessel. After some experimentation the following convenient procedure was developed for the preparation of clofibric acid and analogues on several hundred grams scale.

A preparative reaction (Scheme 4) was conducted on 2 M scale (257 g of chlorophenol). The phenol was dissolved in dilute sodium hydroxide solution (300 g of sodium hydroxide in 300 mL of water) and the solution was chilled. A mixture of acetone (8 mol, 590 mL), chloroform (3 mol, 240 mL) and water 700 mL were added with vigorous stirring while using a cooling bath for the reaction mixture. The initial temperature was 18 °C and the final temperature rose to 28 °C. The loss of chloroform and acetone by evaporation was thus eliminated by keeping the reaction mixture at a low temperature. This reaction was conducted in a hood.

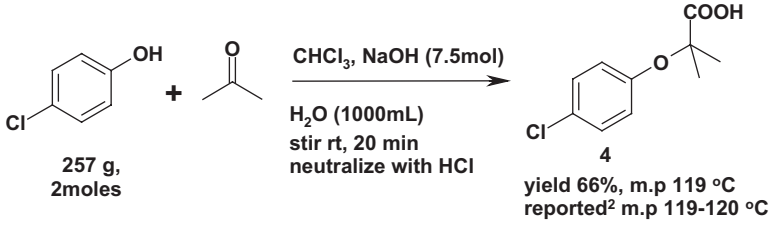
After 25 min of stirring, the aqueous reaction mixture was acidified with cold hydrochloric acid when the 2-methyl-2-aryloxypropanoic acid separated as a light, yellow colored, thick liquid that was left overnight in a refrigerator. A solid material was thus obtained which was dissolved in sodium bicarbonate solution and reprecipitated by acidification with cold hydrochloric acid (Scheme 4). The product, which was a white solid, was filtered, washed thoroughly with cold water and air-dried. The yield was 66%, mp 119 °C (lit.[2] mp 120–121 °C).

This method is suitable for conducting the reaction in a larger scale. Thus, 0.5 kg of clofibric acid was prepared by using this low temperature, water-based biphasic reaction. This method is more efficient than the procedures described earlier for clofibric acid and analogues.[2,5]

Grindstone Chemistry Procedure. In the course of studies on exothermic reactions we have devised methods for modifying some widely used conventional procedures to make them more energy efficient. One such method is known in our laboratory by the descriptive name of 'grindstone chemistry' which is a more evolved version of the method of Toda, Tanaka and coworkers for solvent-free reactions by grinding solids together.[6] We have shown that reactions between solid/solid, solid/liquid,



Scheme 3.



Scheme 4.

Table 1. Grindstone synthesis of *para*-substituted analogues of clofibric acid

Entry	*para*-Substituted analogue of clofibric acid	Mp (°C)	Mp (°C)[5]	Yield (%)	
				Present work	Reported[5]
1	4-Fluoro	83	83	73	32.3
2	4-Bromo	134–135	135	70	39.6
3	4-Iodo	131–133	135	79.8	37.8

and even liquid/liquid can be conducted by grinding with the help of coarsely crystalline $MgSO_4 \cdot 7H_2O$ or sand as a friction enhancing agent.[7]

Noting that the formation of 2-methyl-2-aryloxypropanoic acid is highly exothermic, we submitted to vigorous mixing (as an alternative to grinding) a mixture of 1 mol (128.56 g, 1 mol) of *p*-chlorophenol (**1**), sodium hydroxide pellets (150 g, 3.75 mol), excess of acetone 232 g, 295 mL), and chloroform (179 g, 120 mL). The temperature of the reaction mixture rose rapidly and acetone and chloroform started to vaporize. This reaction was allowed to proceed for about 25 min. After the appropriate work up the reaction product proved to be 2-methyl-2-aryloxypropanoic acid of good quality; after one recrystallization from dichloromethane/hexane the pure product was obtained in 69% yield.

By using molar amounts of the substituted phenols, analogues of clofibric acid substituted in the *para*-position by the following groups were prepared by the 'grindstone chemistry' method in good yield after 10–15 min of reaction: bromo-, iodo-, and fluoro- (see Table 1).

In summary, 10 g of clofibric acid and derivatives can be conveniently prepared by grindstone chemistry. For larger quantities, it is more convenient to utilize the water-based biphasic medium protocol. For reactions involving water and an organic solution, the conventional method is to use a phase transfer catalyst. Our procedure is greener because no phase transfer catalyst is needed and the purification of the product is simpler.[8] The reaction is also energy efficient.

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