Organic Process Research & Development **2004**, *8,* 291–292

A Simple Procedure for the Isolation of γ-Oxobenzenebutanoic Acid Derivatives: Application to the Synthesis of Fenbufen†

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Abstract:

A simple, convenient, and industrially viable process for the isolation of 4-oxobutanoic acid derivatives resulting from Friedel−Crafts acylation products of aromatic hydrocarbons with succinic anhydride is reported. The isolation procedure involves simple quenching of the reaction mixture followed by filtration of the product in good yield and with excellent purity. The generality of the procedure has been demonstrated with representative examples of aromatic hydrocarbon precursors and has also been applied to the isolation of fenbufen. The quantity of aluminum chloride used in the reaction has also been optimized to reduce the load on effluent.

Introduction

The structural moiety, γ-oxobenzenebutanoic acid, with suitable substitution on benzene nucleus and side chain is a useful structural moiety in the synthesis of several biologically active compounds such as fenbufen,[1] bucloxic acid,[2] menbutone,[3] trepibutone,[4] florantyrone,[5] etc., as shown in Chart 1. The same moiety, γ-oxobenzenebutanoic acid, is also an important precursor for the preparation of aromatic lactones in organic synthesis.[6]

Among the γ-oxobenzenebutanoic acid analogues, fenbufen occupies a special place due to its biological activity. Fenbufen is a non-steroidal antiinflammatory drug (NSAID), used to relieve the pain, stiffness, and inflammation that may accompany a number of disorders.[1] It is similar to aspirin in the way it works in that it acts as an analgesic as well as an antiinflammatory and is effective therapy for the symptoms of rheumatoid arthritis, osteoarthritis, and gout.[2] It also relieves pain following surgery and from soft-tissue injuries.

γ-Oxobenzenebutanoic acid analogues are generally prepared using Friedel−Crafts acylation of the corresponding aromatic hydrocarbon with succinic anhydride. Literature procedures for such a Friedel−Crafts reaction generally involve high molar equivalents of aluminum chloride and tedious isolation techniques. Herein, we report a simple and general procedure for the isolation of γ-oxobenzenebutanoic acid derivatives in good yields and high purity. The quantity of aluminum chloride required for the reaction has also been lowered to reduce the load on effluent.

Although Friedel−Crafts reaction of succinic anhydride with toluene using Lewis acid reagents such as aluminum chloride is known in the literature,[4] the procedure has its own disadvantages. The literature procedure involves the use of high molar equivalents of aluminum chloride and tedious workup and isolation procedures, which are difficult to operate on large scale. Recrystallization of the crude material is often recommended to achieve pure product to be able to use in the subsequent synthetic transformations. The literature procedures use aluminum chloride in excess of the required quantities (2.2 equiv wrt to succinic anhydride) and carcinogenic solvents such as benzene. The isolation of the material is also cumbersome and involves azeotropic distillation, charcoal treatment, and high-temperature operations. The material is generally isolated in low yields and also requires multiple extractions with organic solvents.

Results and Discussion

As a continuation to the ongoing program, we needed to prepare some analogues of γ-oxobenzenebutanoic acid. To address the above difficulties involved in the preparation of γ-oxobenzenebutanoic acid, better isolation protocols coupled with replacement of carcinogenic solvents, such as benzene, became the twin objectives of our approach. As a first step towards the process optimization, the carcinogenic solvent, benzene, was replaced with ethylene dichloride. Later, the quantity of aluminum chloride was reduced from 2.2 to1.3 equiv with respect to succinic anhydride. Reduction of the quantity of aluminum chloride not only made isolation of the product more simple but also decreased the waste stream.

After the completion of the reaction, the reaction mixture was poured into chilled aqueous HCl under stirring to precipitate the product directly. Although the material was isolated in two crops initially, after adjusting the quantities of ethylene dichloride, it was possible to isolate the product in single crop with good recovery and purity. The purity was checked by HPLC[7] technique.

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† DRL Publication No: 357.

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(7) HPLC conditions: Column: Symmetry shield (150 mm × 4.6 mm). Flow rate: 1.0 mL/min. Mobile phase: 0.01 M KH_2PO_4 (pH = 3.5):CH_3CN (55:45). UV = 250 nm. Run time: 60 min.

10.1021/op034173v CCC: $27.50
Published on Web 02/18/2004

Chart 1

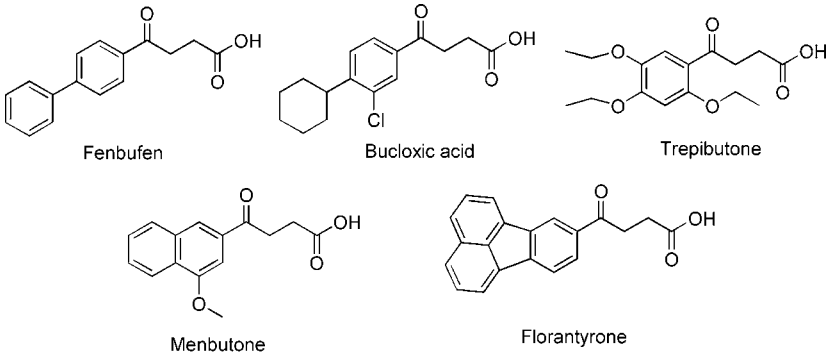
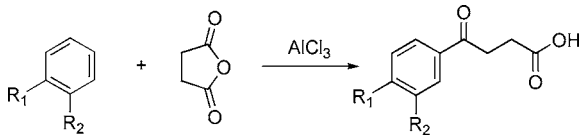
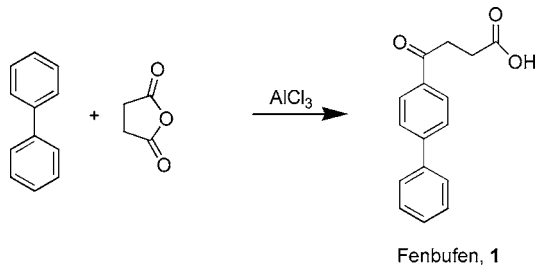


Table 1.



s. no.	R_1	R_2	yield	purity
1	H	H	60	99.5
2	CH_3	H	66	99.9
3	OMe	H	95	99.9
4	CH_3	CH_3	75	98.0
5	C_6H_5	H	80	99.0
6	SCH_3	H	79	98.1
7	F	H	61	99.8

Scheme 1



Fenbufen, **1**

The generality of the isolation procedure has been demonstrated with a few representative examples such as anisole, benzene, toluene, and xylene. See Table 1. The same approach could be extended to the synthesis and isolation of the drug, fenbufen. Friedel−Crafts reaction of biphenyl with succinic anhydride under identical conditions yielded fenbufen, in 80% yield, Scheme 1. The material, thus obtained, is generally very pure and does not require any recrystallization or reprocessing.

Conclusions

A simple and efficient process for the isolation of fenbufen, a nonsteroidal antiinflammatory drug (NSAID) has been demonstrated. The generality of the method has been demonstrated on Friedel−Crafts acylation of a few representative aromatic hydrocarbons, for example, toluene, benzene, anisole, xylene, flourobenzene, and thioanisole with succinic anhydride. The isolated products are duly characterized for their structural integrity and compared with literature data. The quantity of aluminum chloride is also reduced to lower the load on effluent.

General Experimental Procedure

To a solution of succinic anhydride (0.7 mmol) in ethylene dichloride in a 2-L round-bottom flask fitted with a thermometer, guard tube, and solvent addition funnel was added aluminum chloride (1.1 equiv). The reaction mass was cooled under stirring to 15 °C. Aromatic compound (0.7 mmol) was added dropwise to the above reaction mixture, maintaining the same temperature. The reaction mixture was stirred for 3−4 h at room temperature, the reaction was monitored by using TLC, and after completion of the reaction, the reaction mass was poured into a mixture of 1 kg of ice and 100 mL of concentrated hydrochloric acid under stirring; the precipitated solid was filtered and washed with petroleum ether (200 mL).

Acknowledgment

We thank the management of Custom Chemical Services, Dr. Reddy's Laboratories for permission to publish this work. Cooperation extended by all the colleagues of analytical research and development is highly appreciated.

Received for review November 27, 2003.

OP034173V