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A Facile, One-Pot Procedure for the Preparation of 2-Phenyl-1,3-propanediol Monocarbamate, a Metabolite of Felbamate

Thomas A. Miller,† Christine M. Dieckhaus, and Timothy L. Macdonald*

Columbia University, Department of Chemistry, 3000 Broadway, MC 3144, New York, New York 10027 and Department of Chemistry, University of Virginia, McCormick Road, Charlottesville, Virginia 22901

Abstract:

A simple, one-pot procedure for the preparation of 2-phenyl-1,3-propanediol monocarbamate (MCF) has been developed. This procedure represents the most efficient method for preparing MCF published to date, and it is amenable to the large-scale laboratory production of this biologically relevant metabolite of felbamate.

The anti-epileptic agent felbamate (Figure 1) has been associated with the development of idiosyncratic adverse drug reactions. The search for felbamate-replacement therapies has led to the evaluation of agents structurally related to felbamate, including the evaluation of metabolites of felbamate.[1] 2-Phenyl-1,3-propanediol monocarbamate (Figure 1, MCF), a major metabolite of felbamate, has been shown to possess activity similar to that of felbamate.[2] Our work with MCF and MCF-derived agents required that this material be made available in significant quantities, with a potential future need for this agent in kilogram quantities.

Despite its relatively simple structure, no efficient synthesis of racemic MCF has been reported in the literature. Several methods have been developed; however, these methods are characterized by a lack of efficiency, and as a result, these existing protocols are not particularly amenable to large-scale production.[3] We sought to develop an efficient and scaleable synthesis of MCF that would permit the laboratory-scale production of material to support our in vivo studies of its pharmacology and physicochemical properties.

Our efforts in this regard have centered around the desymmeterization of symmetric precursors to racemic MCF. Initially, the formation of MCF via the cyclic carbonate of 2-phenyl-1,3-propanediol by the method of Sarel et al. was assessed (Figure 2).[4] Despite numerous attempts with varied conditions, this method did not afford the requisite cyclic species in quantities amenable to large-scale synthesis. It has been noted that this method is substrate-dependent and is favored by 1,3-diols of increased substitution.[4]

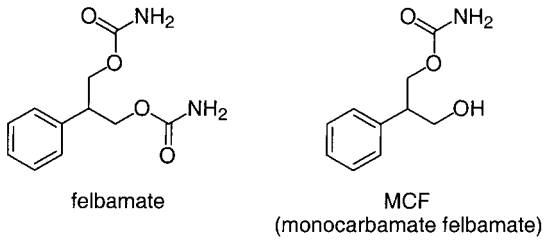

Figure 1.

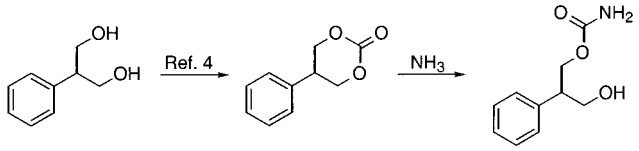

Figure 2.

Overall poor efficiency in the production of MCF by this method led us to consider other approaches. An efficient method for producing MCF was realized by the extension of an approach characterized by the work of McDougal and co-workers.[5] By our method, which is summarized in Figure 3, treatment of 2-phenyl-1,3-propanediol in THF successively with NaH (1 equiv), after 2 h, a trialkylsilyl-chloride such as TBDMS-Cl or TMS-Cl (1.1 equiv), then 1,1′-carbonyldiimidazole (1.5 to 2 equiv), and finally NH_3 (l) followed by silica gel chromatography affords the corresponding silyl-protected MCF in ≥90% isolated yield for the TBDMS derivative.[6]

This material is further treated with 10% methanolic HCl to afford, after silica gel chromatography, MCF in ≥85% overall yield. The elimination of chromatographic purifications was realized by the use of TMS-Cl in the silylation step. This has permitted the development of a "one-pot" procedure for the preparation of MCF from 2-phenyl-1,3-propanediol in ≥85% yield with purification via crystallization.

Experimental Section

All reactions were carried out under argon with magnetic stirring unless otherwise noted. All solvents were distilled from appropriate desiccant under nitrogen immediately prior to use in reactions unless otherwise noted. All nuclear magnetic resonance spectra were obtained with a General

† Current Address: Columbia University.

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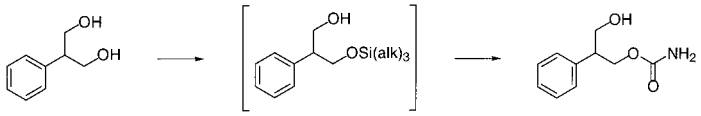

Reagents: NaH; $(alk)_3Si$-Cl; 1,1'-carbonyldiimidazole; NH_3; 20% HCl

Figure 3.

Electric QE300 spectrometer at 300 MHz and chemical shifts are reported in ppm. Elemental analysis was performed by Atlantic Microlab, Inc., Norcross, GA. Melting points were determined using a Thomas-Hoover UNI-MELT melting point apparatus and are uncorrected. Analytical thin-layer chromatography was performed on Merck silica gel 60 F-254 precoated plates (aluminum), and visualizations were effected with phosphomolybdic acid in ethanol. Column chromatography was performed on E. Merck silica 60 (230−400 mesh).

Representative Procedure. To 2-phenyl-1,3-propanediol[7] (100.0 g, 0.675 mol) in THF (1000 mL) was added NaH (95%, 17.0 g, 1.0 equiv) in five portions under argon with magnetic stirring. After 2 h a voluminous precipitate had formed, and TMS-Cl (77.0 g, 90.0 mL, 1.05 equiv) was added via syringe. After 10 min the precipitate had dissolved, and 1,1′-carbonyldiimidazole (164 g, 1.5 equiv) was added to the solution. After the mixture was stirred for 2 h under Ar(g), it was cooled to −78 °C and saturated with NH_3. After an additional 2 h of stirring, 20% HCl (200 mL) was added to the reaction vessel in open air. After 1 h, ethyl ether (1000 mL) was added, and the organic layer was separated and concentrated by rotary evaporation. After removal of the volitiles was complete, the residue was crystallized by dissolving it in a minimal amount of ethyl ether, and on standing this afforded MCF (110 g, 86%) as a white crystalline solid with purity >95% as judged by melting point (71−72 °C), LC−MS traces, ^{1}H NMR ($(CD_3)_2SO$) d 2.4 (bs, 1H), 3.1 (quin, 1H, J = 6.2 Hz), 3.84 (d, 2H, J = 6.2 Hz), 4.40 (d, 2H, J = 6.2), 4.8 (bs, 2H), 7.3 (m, 5H), and combustion analysis: Anal. Calcd for $C_{10}H_{13}NO_3$: C, 61.53; H, 6.71. Found: C, 61.37; H, 6.42.

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