

Short Note

6-(4-(2-{2-[2-(2-Hydroxy-ethoxy)-ethoxy]-ethoxy}-ethyl)-10-oxa-4-aza-tricyclo[5.2.1.0^{2,6}]dec-8-ene-3,5-dione)

David M. Gooden

Small Molecule Synthesis Facility, Duke University, Durham, NC 27708, USA;

E-Mail: dm@duke.edu

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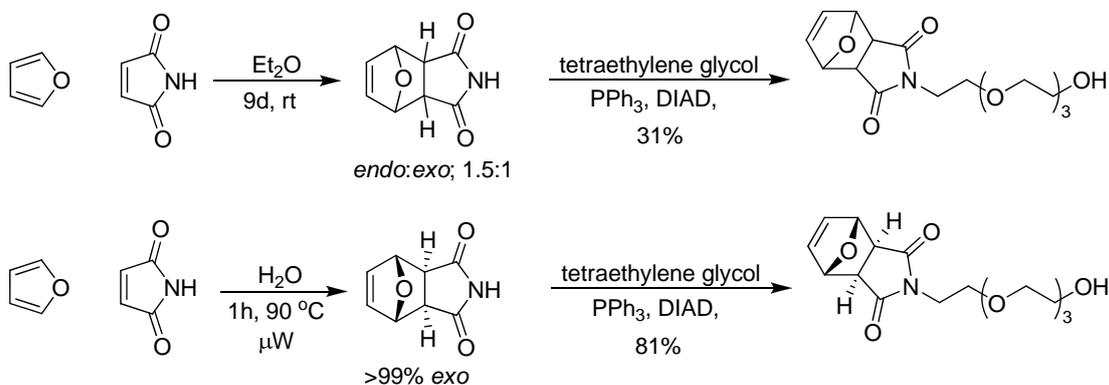
Abstract: Microwave irradiation of maleimide with an excess of furan in water exclusively yields the corresponding *exo*-cycloadduct in good yield (87%) in 1 hour at 90 °C. Alkylation of the imido nitrogen with tetraethylene glycol under Mitsunobu conditions gives the ROMP monomer in 81% yield.

Keywords: microwave synthesis; cycloaddition; maleimide; furan; Mitsunobu alkylation

1. Introduction

Alkylation of 7-oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboximide with tetraethylene glycol under Mitsunobu conditions gives an amphiphilic ROMP monomer [1]. Attempts to reproduce this alkylation in our facility fell far short of the reported yield and isolation of the product required lengthy chromatographic purification over a slow solvent gradient. Faced with potential production of the monomer on a multi-gram scale, a more efficient synthesis and purification protocol was necessary. Since the poorly reproducible alkylation was conducted with an *endo:exo* (1.5:1) mixture, it was surmised that dicarboximide stereochemistry might affect the outcome of the alkylation step. Specifically, the nitrogen of the *exo*-7-oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboximide isomer was thought to be less sterically hindered than that of the *endo* isomer. Conventional methods of *exo*-isomer preparation typically require heating solutions of maleimide and furan under high pressure conditions [2,3]. The Diels-Alder adduct can also be obtained under milder conditions (*e.g.*, stirring the organic solutions of the two reactants for 1 to 9 days at room temperature) but at a cost of stereochemical selectivity (*endo:exo*, 1.5:1 to 7:3) [2,4,5]. Given the recent report of *exo*-selectivity preference in water [5] and by the successful application of maleimide in Diels-Alder reactions under microwave conditions [6], attempting the cycloaddition under these combined conditions seemed a

reasonable approach to the desired product. By heating an aqueous mixture of maleimide and furan under microwave irradiation for 1 hour at 90 °C, the *exo* isomer precipitated from solution. Alkylation of this *exo*-dicarboximide under Mitsunobu conditions gave the desired product in 81%. Furthermore the final product was rapidly eluted from a short column of silica gel under isocratic solvent conditions.



2. Experimental

2.1. *endo/exo*-7-Oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboximide: Conventional method

A mixture of maleimide (0.42 g, 4.3 mmol), furan (0.48 mL, 6.6 mmol) and Et₂O (6 mL) were stirred at room temperature for 9 days. The resulting precipitate was isolated by vacuum filtration and dried in vacuo overnight. Recrystallization from benzene gave the cycloaddition adduct as a white solid (0.30 g, 42%) which was shown by ¹H NMR to be a mixture of isomers (*endo:exo*; 1.5:1) [2].

¹H NMR (CDCl₃, 300 MHz): δ 8.05 (bs, 1H), 7.70 (bs, 1H, *endo* isomer), 6.52 (s, 2H, *endo* isomer), 6.49 (s, 2H), 5.33–5.31 (m, 4H), 3.57 (dd, *J* = 1.8 Hz, 3.6 Hz, 2H, *endo* isomer), 2.85 (s, 2H).

EIMS *m/z*: 165 ([M]⁺).

2.2. *exo*-7-Oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboximide: Microwave method

A mixture of maleimide (0.855 g, 8.8 mmol), furan (1.1 mL, 15 mmol) and H₂O (10 mL) was heated in a 35 mL microwave reaction vessel to 90 °C (100W) for 1 h. The white crystalline material that precipitated upon cooling to room temperature was isolated by vacuum filtration, rinsed with H₂O (2 × 5 mL) and dried in vacuo overnight (1.3 g, 87%). M.p.: 160.0–161.5 °C (Literature: 162 °C [2]).

¹H NMR (CDCl₃, 300 MHz): δ 8.05 (bs, 1H), 6.49 (s, 2H), 5.28 (s, 2H), 2.85 (s, 2H).

¹³C NMR (CDCl₃, 75 MHz): δ 177.7, 135.9, 83.5, 55.9.

EIMS *m/z*: 165 ([M]⁺).

2.3. Mitsunobu alkylation of the *exo*-imide

Over a period of 10 minutes, diisopropyl azodicarboxylate (94%, 4.3 mL, 16 mmol) was added dropwise to a stirred, cooled (0 °C) solution of the *exo*-imide (2.31 g, 14.0 mmol), PPh₃ (4.2 g, 16 mmol), and tetraethylene glycol (12 mL, 70 mmol) in anhydrous THF (120 mL). The cooling bath was removed and the reaction mixture was stirred for 16 h, then concentrated to dryness under reduced pressure. The resulting oily residue was partitioned between diethyl ether (100 mL) and H₂O (50 mL). The aqueous phase was separated and the organic phase was extracted with H₂O (2 × 50 mL). The combined aqueous extracts were extracted with CHCl₃ (3 × 50 mL). The chloroform extracts were combined and dried (MgSO₄). The drying agent was removed by filtration and the filtrate was concentrated under reduced pressure giving a yellow oily residue. Purification by silica gel flash column chromatography (2.5% methanol in dichloromethane) afforded the product as a clear, yellow oil (4.2 g, 81%).

¹H NMR (CDCl₃, 300 MHz): δ 6.46 (s, 2H), 5.22 (s, 2H), 3.66–3.56 (m, 20H), 2.83 (s, 2H), 2.61 (t, *J* = 6.0 Hz, 2H).

¹³C NMR (CDCl₃, 75 MHz): δ 176.2, 134.5, 83.9, 69.8, 64.9, 61.5, 55.2, 41.0.

EIMS *m/z*: 364 ([M+Na]⁺).

References and Notes

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