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Convenient One-Pot Preparation of Dimethyl Bicyclo[2.2.2]octane-1,4-dicarbolylate, a Key Intermediate for a Novel Adenosine A_1 Receptor Antagonist

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Abstract: Dimethyl bicyclo[2.2.2]octane-1,4-dicarboxylate (4), a key starting material for a novel adenosine A_1 receptor antagonist, was prepared in a one-pot reaction with convenient workup and improved yield.

Keywords: dimethyl bicyclo[2.2.2]octane-1,4-dicarboxylate, one-pot preparation, stoichiometry

INTRODUCTION

Since the discovery that adenosine receptors modulate a number of important physiologic functions,[1] variety of xanthine derivatives have been prepared as potent, selective adenosine antagonists.[2] One such xanthine derivative is 3-[4-(2,6,-dioxo-1,3-dipropyl-2,3,6,7-tertrahydro-1*H*-purin-8-yl)-bicyclo[2.2.2]octan-1-yl]-propionic acid BG9928 (**1**), a potential drug candidate for congestive heart failure, currently in clinical development, possesses high affinity and selectivity for the adenosine A_1 receptor.[3]

As indicated in Fig. 1, dimethyl bicyclo[2.2.2]octane-1,4-dicarboxylate **(4)** is one of the starting materials used to assemble BG9928. In addition, 1,4-disubstituted bicyclo[2.2.2]octanes possess interesting physical properties

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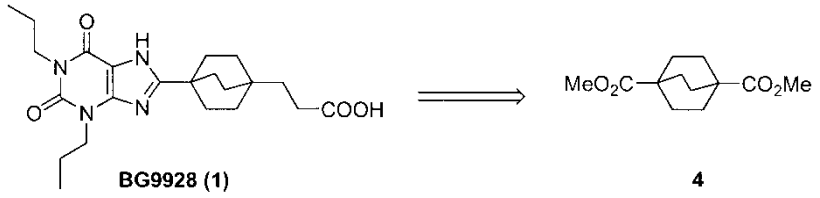
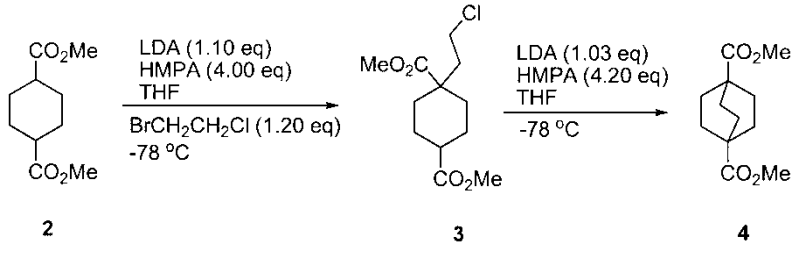


Figure 1. Derivation of starting materials for BG9928.

and have been used in the synthesis of liquid-crystalline (rod-like) molecules.[4] They are also components of constrained glutamate analogues, intended for the treatment of neurological disorders.[5]

Three distinct methods for the preparation of bicyclo[2.2.2]octane-1,4-dicarboxylates were reported. The first, a self-condensation reaction with diethyl succinate and subsequent ring closure with 1,2-dibromoethane, gave diethyl bicyclo[2.2.2]octane-1,4-dicarboxylate in low yield (23%) after a four-step sequence.[6] The second, based on a Diels–Alder reaction between diethyl cyclohexa-1,3-diene-1,4-dicarboxylate and ethylene,[7] proceeded under pressures of 1000 atm.[8,9] The third route, a sequential alkylation and intramolecular ring closure of dimethyl cyclohexane-1,4-dicarboxylate, was developed by Della and Tsanaktsidis[10] (Scheme 1). Methods one and two suffer from long reaction sequences or low yields. Of the available synthetic routes to obtain the bicyclo[2.2.2]octane core structure, the third appeared to be the most promising for further development because it had relatively few steps, had an opportunity to telescope the alkylation and cyclization reactions, and utilized inexpensive, commercially available starting materials.

As shown in Scheme 1, the chloroethyl chain was installed by treatment of **2** with an excess of lithium diisopropylamide (LDA) and 1.2 equiv of 1-bromo-2-chloroethane; then the mixture was worked up by evaporative concentration, dilution with water, extraction with pentane, washing, drying, and evaporation. The chloride **3** was obtained in 62% yield after column chromatography



Scheme 1. Two-stage alkylation synthesis of bicyclo[2.2.2]octane.

(silica). Compound **3** was subsequently treated again with excess LDA to induce cyclization to the bicyclo[2.2.2]octane ring system. The same extractive workup procedure and column chromatography were applied as with the chloride, and the final dimethyl bicyclo[2.2.2]octane-1,4-dicarboxylate **(4)** was obtained in 57% yield. Overall, **4** was obtained in 35% yield in the two-step process from the saturated diester **2**.

The reaction to prepare compound **4** went smoothly as the aforementioned two-stage process, but all attempts to telescope the reaction failed.[10]

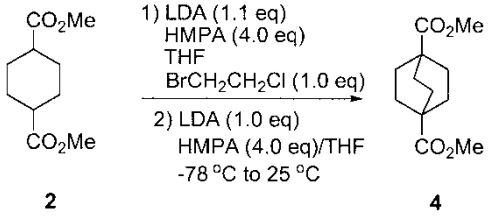
RESULTS AND DISCUSSION

To obtain an easy scale-up procedure, we studied the possibility of a one-pot reaction leading to compound **4**, and it turns out that the stoichiometry of 1-bromo-2-chloroethane is the key for success.

In our initial attempt at a one-pot preparation of **4**, we eliminated the isolation of the intermediate chloride **3** and simply added a second molar equivalent of LDA after the alkylation step. None of the expected diester could be detected, and a brown to black oil was noticed. Similar results were observed when the starting material was treated with more than 2 equiv of LDA and excess 1-bromo-2-chloroethane. Further work explored controlled addition rates and reversal of the order of addition, all of which met with little success.

We then focused on the ratio of diesters to 1-bromo-2-chloroethane. In all the attempted reactions, at least 1.2 equiv of 1-bromo-2-chloroethane was added. The unreacted halide, if not removed, could be deprotonated by LDA and then reacted with other 1-bromo-2-chloroethane to generate polymeric by-products. Such by-products could dominate the reaction while the expected intramolecular cyclization proceeded slower than the intermolecular alkylation that leads to side products.

We then tried the one-pot alkylation-cyclization on diester **2** with 1.1 equiv of LDA, and 1.0 equiv of 1-bromo-2-chloroethane to generate the chloroethyl intermediate **3**. Then another molar equivalent of LDA was added, and the reaction was allowed to warm gradually to 25°C (Scheme 2). With almost



Scheme 2. One-pot conversion to bicyclo[2.2.2]octane diester.

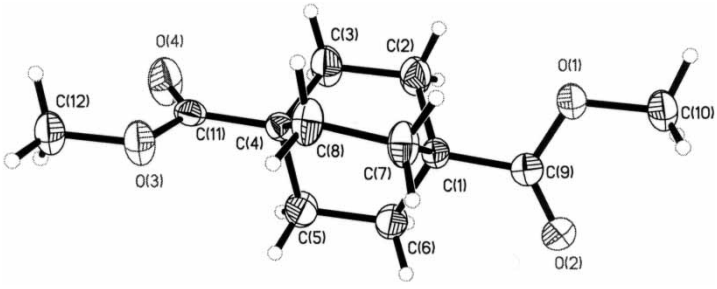


Figure 2. Crystal structure of dimethyl bicyclo[2.2.2]octane-1,4-dicarboxylate(4)

the same final extractive workup as previously reported,[10] the desired bicyclo[2.2.2]octane **4** was isolated in 63% yield, almost double that of the original two-step procedure.

Some effort was then put into simplification of the extractive workup method. The reaction mixture was diluted with water, and the precipitated product was collected by filtration; this eliminated the extraction, washing, drying, and concentration. Because the diester was slightly soluble in water, the yield from this procedure diminished to 53%; however the use of saturated brine solution restored the overall yield of the final product.

In conclusion, a convenient one-pot reaction to prepare bicyclo[2.2.2]octane **4** was developed. The diester **4** was produced in yields 18% to 28% higher than the original two-step literature method. In addition, precipitation of the product with water avoided extraction with hexanes or pentane, which increased the safety and minimized waste. Future work will be focused on the replacement of hexamethylphosphoramide (HMPA) with more environmentally friendly and less toxic substitutes.

Figure 2 shows the crystal structure of dimethyl bicyclo[2.2.2]octane-1,4-dicarboxylate **(4)**.

EXPERIMENTAL

Starting materials and reagents were used as purchased from Sigma-Aldrich. Melting points were measured on a Mettler Toledo FP62 digital melting-point apparatus and are not corrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker spectrometer (400 MHz) in $CDCl_3$, Chemical shifts are expressed as δ (ppm) values. The X-ray structure for dimethyl bicyclo[2.2.2]octane-1,4-dicarboxylate **(4)** was determined on a Bruker Smart CCD diffractometer. The crystal used for the diffraction study showed no decomposition during data collection. The crystal showed signs of twin for the mixture, and the percentage of twin was 29%. The full structural information is available as electronic supporting information (hexi.chang@biogenidec.com).

Dimethyl Bicyclo[2.2.2]octane-1,4-dicarboxylate (4)

To a stirred solutin of *N,N*-diisopropylamine (84.5 mL, 600 mmol) in THF(700 ml) cooled to $-30^{\circ}C$ under N_2, *n*-BuLi (220 mL, 2.5 M in hexane, 550 mmol) was added by a syringe. The mixture was stirred for 30 min at $-30^{\circ}C$ and then cooled to $-78^{\circ}C$. HMPA (360 mL, 2000 mmol) was added, and a solution of dimethyl cyclohexane-1,4-dicarboxylate (100 g, 500 mmol) in THF (100 mL) was charged subsequently over 30 min. The mixture was stirred further for 40 min, and then 1-bromo-2-chloroethane (41.5 mL, 499 mmol) was added dropwise. After the mixture was stirred at $-78^{\circ}C$ for 1 h, a solution of HMPA (360 ml, 2000 mmol) in THF (600 mL) was added slowly. By cannula, freshly prepared LDA [200 mL of *n*-BuLi (2.5 M in hexane, 500 mmol) added to *N,N*-diisopropylamine (78 mL, 556 mmol) in THF (700 mL) at $-78^{\circ}C$]was transferred to the reaction mixture at $-78^{\circ}C$ over a period of 1 h. The resultant mixture was stirred at $-78^{\circ}C$ for 1.5 h. The cold bath was removed, and the mixture was stripped further for 4–6 h. The clear brown solution was then quenched with saturated aqueous NH_4Cl(400 mL) and concentrated in vacuo (bath temperature 30–35°C) to remove THF.

Workup Method A

The residue was diluted with 800 mL of water and extracted with hexane (3×600 mL). The combined extracts were washed with brine (700 mL), dried with Na_2SO_4, and concentrated in vacuo (bath temperature 35°C) to give a yellow sticky solid. The solid was stirred with 60 mL of hexane at rt for 30 min. The resulting suspension was cooled to 0°C for 2 h and filtered to give light yellow crystalline solid (71.6 g, 63% yield), mp 92.8°C, ^{1}H NMR ($CDCl_3$) δ 3.61 (s, 3H, -OCH_3), 1.75(s, 6H, -CH_2); ^{13}C NMR ($CDCl_3$) δ 177.72, 51.65, 38.56, 27.68. Anal. calcd. for C_{12} H_{18} O_4: C, 63.70; H, 8.02. Found: C, 63.47; H, 8.10.

Workup Method B

While stirring, the residue was diluted slowly with 800 mL of water, and the resulting suspension was stirred for approximately 3 h at rt. The yellow solid was collected by suction filtration, washed with water, and dried under vacuum (60 g, 53% yield).

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