Preparation of 3-Bromo-2-methylfuran and 4-Bromo-2-methylfuran

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4-*endo*-5-*exo*-Dibromo-3-methyl-3,6-*endo*-oxyperhydrophthalic anhydride **3b** and 4-*exo*-5-*endo*-dibromo-3-methyl-3,6-*endo*-oxyperhydrophthalic anhydride **3c** were isolated from the bromo-adducts of 3-methyl-3,6-*endo*-oxy-1,2,3,6-tetrahydrophthalic anhydride **2**. When **3b** or **3c** was heated in quinoline, only 3-bromo-2-methylfuran **4** was obtained from **3b** and only 4-bromo-2-methylfuran **5** from **3c**.

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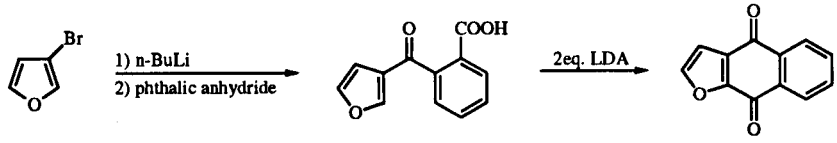
2-Acetylnaphtho[2,3-*b*]furan-4,9-dione isolated from *Tabebuia Cassinoides* (Lam.) has cytotoxic activity [1] and the derivatives are particularly interesting because of their biological activity. The authors have previously achieved the preparation of the parent naphtho[2,3-*b*]-furan-4,9-dione (**1**)[2] as an intermediate to obtain the derivatives. Compound **1** was synthesized by treating 2-(3-furancarbonyl)benzoic acid [2], which was prepared by the reaction of phthalic anhydride with 3-lithiofuran [3](from 3-bromofuran [4]), with lithium diisopropylamide (LDA). Further, various electrophilic substitutions of **1** were attempted to prepare the 2-substituted derivatives, but only 2-nitronaphtho[2,3-*b*]furan-4,9-dione [2] was obtained by the nitration of **1**. Therefore, with the goal of preparing 2-substituted naphtho[2,3-*b*]furan-4,9-diones, their cyclization must be carried out using 2-substituted-4-bromofurans, previously introduced with the appropriate substituent on the α-position of the furan ring.

The literature was searched to find a procedure for preparing 4-bromo-2-methylfuran, as one of the 2-substituted-4-bromofurans. As a result, only a few reports [5] were revealed but they were not used because all methods were not simple and produced low yields.

On the other hand, 3-bromofuran has been prepared by Šrogel *et al.* [4] as mentioned below, that is 3,6-*endo*-oxy-1,2,3,6-tetrahydrophthalic anhydride [6], formed by the reaction of furan with maleic anhydride, was brominated with bromine followed by the brominated compound 4,5-dibromo-3,6-*endo*-oxyperhydrophthalic anhydride [7], was degraded in quinoline to give 3-bromofuran. By applying Šrogel *et al.*'s method [4], a facile method for obtaining 3-bromo-2-methylfuran and 4-bromo-2-methylfuran from 2-methylfuran was found. In the present paper, the authors wish to report the selective route for the preparation of 3-bromo-2-methylfuran and 4-bromomethylfuran.

The bromination of 3-methyl-3,6-*endo*-oxy-1,2,3,6-tetrahydrophthalic anhydride (**2**) [8] has already been reported by Mantecón *et al.* [9]. However, 4,5-*exo-cis*-dibromo-3-methyl-3,6-*endo*-oxyperhydrophthalic anhydride **3a** and 4-*endo*-5-*exo*-dibromo-3-methyl-3,6-*endo*-oxyperhydrophthalic anhydride **3b** were isolated but 4-*exo*-5-*endo*-dibromo-3-methyl-3,6-endo-oxyperhydrophthalic anhydride **3c** could not be isolated, therefore **3c** was reported only as a mixture of **3b**.

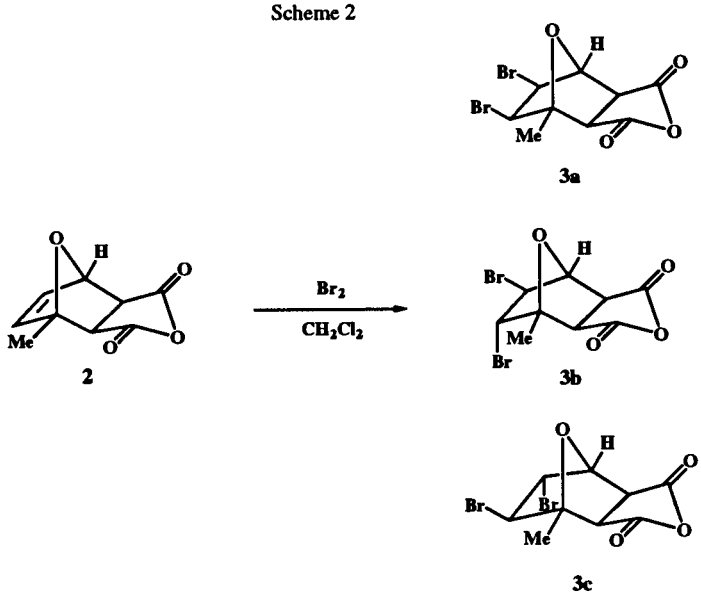
Scheme 1



1

In other studies, Kwart *et al.* [10] reported that *exo-cis* elimination predominated during the elimination of norbornyl bromide with base. Accordingly, it is expected that if **3b** or **3c** is heated in quinoline, only 3-bromo-2-methylfuran is obtained from **3b** and only 4-bromo-2-methylfuran, which is expected to serve as an intermediate for the 2-methyl derivatives of **1**, is obtained from **3c**. At first, various solvents were examined to separate the mixture of **3b** and **3c** obtained Mantecón *et al.* [9]. Consequently, when the mixture was treated with chloroform, the mixture was able to be separated into insoluble **3b** and soluble **3c**. Compound **3b** was isolated as white needles, mp 171-173°, while **3c** was isolated as white plates, mp 155-156°, and their structures were confirmed from various spectral data. By the way, Mantecón *et al.* [9] have suggested that, different from **3b** and **3c**, the formation of **3a** in methylene dichloride is caused by the radical addition of bromine to **2**. Accordingly, if a polar solvent, for example acetic acid, is used for the bromination of **2**, it is expected

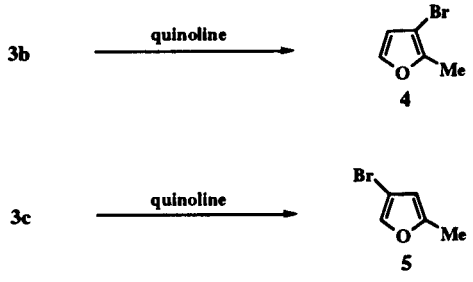
Scheme 2



that the formation of **3a** is reduced. The bromination of **2** was carried out in acetic acid to give **3b** and **3c** in 13% and 8% yield, respectively, but **3a** was not detected.

Finally, the thermal decomposition of **3b** and **3c** was carried out in quinoline to give 3-bromo-2-methylfuran (**4**) [11] in 39% yield and 4-bromo-2-methylfuran (**5**) [5] in 30% yield.

Scheme 3



In conclusion, the yields of **3b** and **3c** were not satisfactory but **3b** and **3c** were obtained from 2-methylfuran in two steps. Further, it has become quite apparent that **4** was selectively obtained from **3b** and **5** from **3c**.

EXPERIMENTAL

All melting points (open capillaries) and boiling points were uncorrected. The pmr spectra were determined at 60 MHz with Nippon Denshi JNM PMR-60SI NMR spectrometer with TMS as internal reference. The ir spectra were measured in a JASCO IR-810 spectrometer. The mass spectra were obtained on a Nippon Denshi DX-300 spectrometer at 70 eV.

4-*endo*-5-*exo*-Dibromo-3-methyl-3,6-*endo*-oxyperhydrophthalic Anhydride (**3b**).

A mixture of Diels-Alder adduct **2** [8] (76 g, 0.42 mole) and acetic acid (250 ml) was cooled to 20° and a solution of bromine 72 g in acetic acid (100 ml) was added with stirring. After stirring an additional 1.5 hours, the resulting product was filtered, washed with hexane, and recrystallized from chloroform to give **3b** 18.7 g (13%) as white needles mp 171-173° (mp 165-167° [9]); ir (potassium bromide): 1875, 1800 cm^{-1} (C=O); pmr (DMSO-d_6): δ 4.77 (1H, s, C-6), 4.53 (1H, d, C-5, 4 Hz), 4.37 (1H, d, C-4, 4 Hz), 3.88 (1H, d, C-1, 7 Hz), 3.66 (1H, d, C-2, 7 Hz), 1.51 (3H, s, Me); ms: m/z 259 (M^+-Br).

4-*exo*-5-*endo*-Dibromo-3-methyl-3,6-*endo*-oxyperhydrophthalic Anhydride (**3c**).

The mother liquor of the preceding preparation was evaporated, and the residue was recrystallized from chloroform to give **3c** 11.5 g (8%) as white plates mp 155-156°; ir (potassium bromide): 1875, 1785 cm^{-1} (C=O); pmr (DMSO-d_6): δ 4.95 (1H, d, C-5, 4 Hz), 4.57 (1H, s, C-6), 4.53 (1H, d, C-4, 4 Hz), 3.99 (1H, d, C-1, 7.5 Hz), 3.68 (1H, d, C-2, 7.5 Hz), 1.55 (3H, s, Me); ms: m/z 259 (M^+-Br).

3-Bromo-2-methylfuran (**4**).

When a mixture of **3b** (17 g, 0.05 mole) and quinoline (9 ml) was slowly heated to 220°, **4** distilled out. The crude distillate was dried over sodium sulfate and redistilled through a column to give **4**, 3.1 g (39%) as a colorless liquid, bp 124-127° (bp was not described by Weisner *et al.* [11]); pmr (deuteriochloroform): δ 7.12 (1H, d, F-5, 2 Hz), 6.27 (1H, d, F-4, 2 Hz), 2.23 (3H, s, Me); ms: m/z 160 (M^+), 162 (M^++2).

4-Bromo-2-methylfuran (**5**).

When a mixture of **3c** (17 g, 0.05 mole) and quinoline (9 ml) was slowly heated to 220°, **5** distilled out. The crude distillate was dried over sodium sulfate and redistilled through a column

to give **5** 2.4 g (30%) as a colorless liquid bp 126-129° (bp 132-134° [5a]); pmr (deuteriochloroform): δ 7.12 (1H, s, F-5), 5.90 (1H, s, F-3), 2.55 (3H, s, Me); ms: m/z 160 (M^+), 162 (M^++2).

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