An Efficient and Inexpensive Multigram Synthesis of 3,4-Dibromo- and 3,4-Dichlorofuran-2(5*H*)-one

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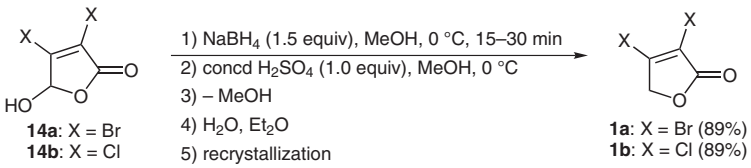
Abstract: The efficient and inexpensive synthesis of 3,4-dibromo- and 3,4-dichlorofuran-2(5*H*)-one on a multigram scale by sodium borohydride reduction of mucobromic and mucochloric acid, respectively, is reported.

Key words: furan-2(5*H*)-ones, reduction, sodium borohydride, polyfunctional compounds, regioselectivity



Scheme 1

3,4-Dibromofuran-2(5*H*)-one (**1a**) and 3,4-dichlorofuran-2(5*H*)-one (**1b**) are attractive and versatile polyfunctional building blocks that can be selectively manipulated at their electrophilic C3 and C4 sites. In particular, compound **1a**, the cyclic analogue of methyl (*Z*)-2,3-dibromopropenoate (**2**) (Figure 1), exhibits, similar to this dibromo ester **2**, regioselectivity in palladium-catalyzed C–C bond forming reactions,[1] which occur at the C4 site[2–9] even though the C3 site is also capable of undergoing these reactions. However, the reactivity of the C3 site is significantly lower than that of the C4 site and the palladium-catalyzed reactions at position 3 require more vigorous conditions.

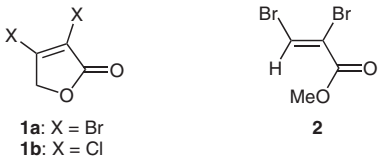


Figure 1

3,4-Dichlorofuran-2(5*H*)-one (**1b**) and **1a** exhibit the same selectivity but **1b** is more reluctant to undergo palladium-catalyzed reactions under the conditions employed for **1a**. In fact, **1b** is reluctant to oxidatively add to palladium(0) centers[10] and, thus, its palladium-catalyzed reactions require catalyst precursors and experimental conditions [5,11,12] different from those employed for **1a**.

It is also possible to predict the order and site of the palladium-catalyzed reactions that involve **1a** and **1b** taking into account that: (i) it is reasonable to assume that in many of these reactions oxidative addition is the stage of the catalytic cycle that is responsible for the observed regioselectivity; (ii) the initial site of the palladium-catalyzed reactions is at the more electron-deficient center; (iii) the oxidative addition occurs at the more electron-deficient site; (iv) the 4-position of **1a** and **1b** is more electron-deficient than the 3-position as evidenced by the fact that C4 in these dihalides has a higher ^{13}C chemical shift than C3 (Table 1).[13]

Table 1 ^{13}C Chemical Shifts of C3 and C4 in **1a** and **1b**

Compound	^{13}C NMR (δ)	
	C3	C4
1a	114.4	143.6
1b	121.2	148.9

Scheme 2 illustrates the structures of compounds **3a**,**b**, **7**, **9**, and **11a**,**b**, which have been prepared from **1a** and **1b** by palladium-catalyzed Stille couplings,[2,4] Suzuki-type couplings,[3,4–6,9,11,12] and Sonogashira reactions,[7] and those of furan-2(5*H*)-ones **4a**,**b**, **5**, **8**, **10**, **11**, and **13**, which have synthesized from these 4-substituted 3-halofuran-2(5*H*)-ones by Stille couplings,[2,3,7,8,12] Suzuki-type reactions,[5,8,9,12] Negishi couplings,[6,8] palladium-catalyzed triethylammonium formate reductions,[2] or, as in the case of compound **13**, by treatment of **11a** with activated zinc dust, followed by acidic hydrolysis.[7] Scheme 2 also shows the structures of (*Z*)-4-aryl-5-(arylmethylene)-3-halofuran-2(5*H*)-ones **6a** and **6b** prepared by functionalization

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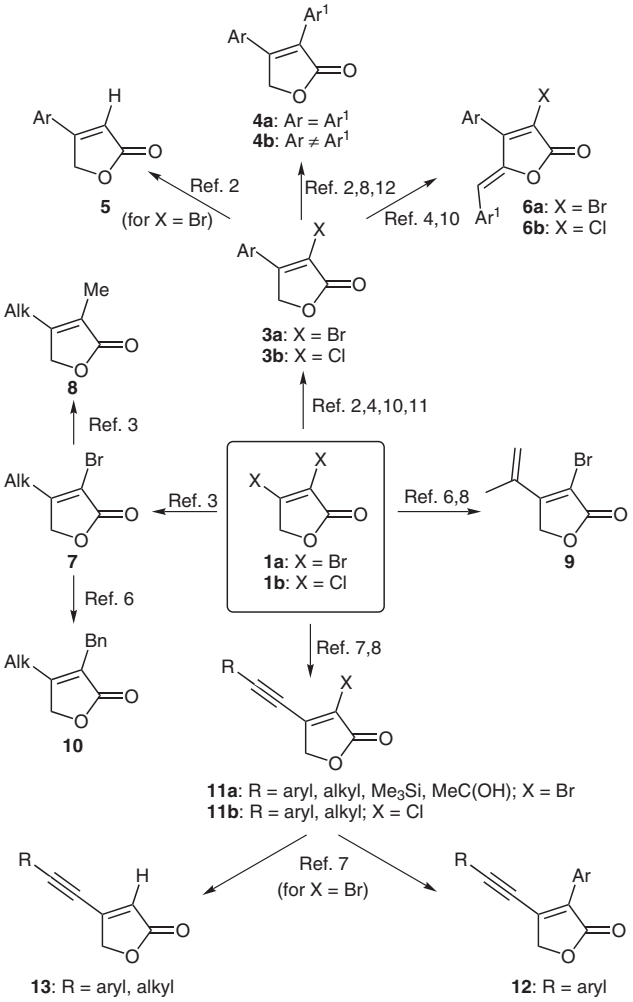
of **3a** and **3b**, respectively, at their C5 position via furanolate chemistry.[14]

In the past years, much attention has been devoted to the synthesis of 3,4-dibromofuran-2(5*H*)-one (**1a**)[2,4,5,15,16] and 3,4-dichlorofuran-2(5*H*)-one (**1b**),[5,12,17–21] but some synthetic procedures, which date back to the end of 1800[17] or before the 1960s,[15,16] are low yielding and involve the use of commercially unavailable starting materials and/or toxic reagents.



Scheme 2

However, **1a** and **1b** have been more recently synthesized from commercially available and inexpensive mucobromic acid [3,4-dibromo-5-hydroxyfuran-2(5*H*)-one, **14a**] and mucochloric acid [3,4-dichloro-5-hydroxyfuran-2(5*H*)-one, **14b**], respectively.[22,23] Thus, in 2002, Zhang et al.[5] prepared **1a** by treatment of **14a** with sodium triacetoxyborohydride (1.5 equiv) in chloroform at 0 °C followed by addition of acetic acid (2.7 equiv). The resulting mixture was stirred at 20–25 °C for three days, washed with water, and the crude product obtained by concentration of the organic phase was purified by silica gel chromatography followed by recrystallization to give **1a** in 57% yield, More recently, we prepared chemically pure **1a** on a multigram scale in 89% yield by reaction of **14a** with sodium borohydride (1.5 equiv) in methanol at 0 °C followed by treatment with concentrated sulfuric acid (1 equiv) in methanol at 0 °C (Scheme 1).

The procedure herein, which does not necessitate chromatographic purification, differs in the workup of the reaction mixture from our previously reported procedure.[2,4] In fact, it involves removal of methanol under reduced pressure before the crude reaction mixture undergoes the usual workup.

A very similar experimental procedure allows the preparation of chemically pure 3,4-dichlorofuran-2(5*H*)-one (**1b**) in 89% yield from **14b** (Scheme 2). In 1953, compound **1b** was prepared in 52% yield by oxidation of **14b** with aluminum isopropoxide and propan-2-ol[18] and subsequently this procedure was employed for the synthesis of **1b** in 65% yield.[19] On the other hand, Lalonde et al.[20] prepared **1b** in 92% yield by reduction of **14b** with sodium borohydride in methanol, followed by treatment with sulfuric acid. However, **1b** proved to be contaminated by a byproduct, which presumably corresponded to 3-chlorofuran-2(5*H*)-one.[20] In 2002, Zhang et al.[5] synthesized **1b** in 45% yield from **14b** using a protocol very similar to that which they had followed for the preparation of **1a** from **14a**. Finally, **1b** has been very recently prepared in 87% yield by the reaction of **14b** with sodium borohydride (1.5 equiv) and boron trifluoride–diethyl ether complex (0.65 equiv) in refluxing tetrahydrofuran, followed by hydrolysis and chromatographic purification of the crude reaction product.[21] However, **1b** so obtained proved to be contaminated by 7.4% of 2,3-dichlorobut-2-ene-1,4-diol.[21] Thus, our method for the preparation of **1b** from **14b** represents the synthetic procedure of choice.

3,4-Dibromofuran-2(5*H*)-one (1a)

$NaBH_4$ (6.31 g, 167.0 mmol) was rapidly added (5 min) in a portionwise manner (CAUTION! exothermic reaction) to a stirred soln of mucobromic acid (**14a**, 28.7 g, 111.2 mmol) in MeOH (160 mL) cooled to 0 °C; the mixture was stirred for an additional 15 min.[24] A soln of concd H_2SO_4 (10.9 g, 111.2 mmol) in MeOH (55 mL) cooled to 0 °C was added and the resulting opalescent mixture was maintained at this temperature for an additional 10 min; it was then concentrated at r.t. under reduced pressure. The residue was treated with brine (800 mL) and extracted with Et_2O (5 × 300 mL). The combined organic extracts were washed with brine (2 × 200 mL), dried, and concentrated under reduced pressure. The solid residue was recrystallized (hexane–Et_2O, 1: 1) to give **1a** as colorless needles; yield: 23.7 g (89%); mp 90–91 °C. TLC and GLC analyses showed that **1a** was chemically pure.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.90 (s, 2 H).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 74.1, 114.4, 143.6, 166.5.

MS (EI, 70 eV): *m*/*z* (%) = 244 [M^+ + 2] (19), 242 [M^+] (39), 240 [M^+ – 2] (19), 163 (86), 161 (100), 119 (19), 117 (17).

Anal. Calcd for $C_4H_2Br_2O_2$: C, 19.86; H, 0.84. Found: C, 19.67; H, 1.02.

3,4-Dichlorofuran-2(5*H*)-one (1b)

$NaBH_4$ (6.24 g, 165.0 mmol) was rapidly added (5 min) in a portionwise manner (CAUTION! exothermic reaction) to a stirred soln of mucochloric acid (**14b**, 18.5 g, 110.0 mmol) in MeOH (165 mL)

cooled to 0 °C; the mixture was stirred for an additional 30 min. A soln of concd H_2SO_4 (10.8 g, 110.0 mmol) in MeOH (55 mL) cooled to 0 °C was added and the resulting opalescent mixture was maintained at this temperature for an additional 10 min; it was then concentrated at r.t. under reduced pressure. The residue was treated with brine (800 mL) and extracted with Et_2O (5 × 300 mL). The combined organic extracts were washed with brine (2 × 200 mL), dried, and concentrated under reduced pressure. The solid residue was recrystallized (pentane–Et_2O, 1: 1) to give **1b** as colorless needles; yield: 15.0 g (89%); mp 49–50 °C. TLC and GLC analyses showed that **1b** was chemically pure.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.88 (s, 2 H).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 70.9, 121.0, 148.9, 165.7.

MS (EI, 70 eV): *m*/*z* (%) = 154 [M^+ + 2] (30), 152 [M^+] (47), 125 (65), 123 (100), 117 (52), 95 (28), 73 (30).

Anal. Calcd for $C_4H_2Cl_2O_2$: C, 31.41; H, 1.32. Found: C, 31.37; H, 1.27.

Acknowledgment

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