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A VERSATILE AND CONVENIENT SYNTHESIS OF BENZOFURANS

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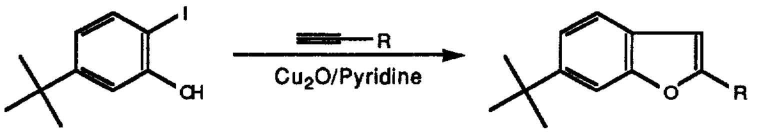
Abstract. A convenient, general, one-step synthesis of 2-substituted benzofurans from *o*-iodophenols and acetylenic compounds in the presence of cuprous oxide is presented.

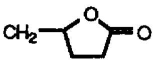
Previous work of Castro and coworkers[1,2] has shown that cuprous acetylides react with *o*-halogenophenols to give *o*-hydroxyaryl acetylenes which then cyclize to give benzofurans. The usefulness of this benzofuran synthesis is diminished by the need to prepare and isolate the cuprous acetylide. Some of these are reputed to be shock sensitive and explosive. Furthermore, many of the functionalized copper acetylides (e.g., hydroxyl, ester, nitrile) are soluble in or reactive towards the reaction mixtures used in their preparation.

In this paper we describe a convenient, one-step, one-pot route to substituted benzofurans (Scheme 1) which is free from these disadvantages. The yields, moreover, are typically 5-10% better than those obtained by the earlier procedure. The essence of our technique is to react the *o*-halogenophenol and the acetylene in the presence of cuprous oxide.



Scheme 1

(1) R = $(CH_2)_3CH_3$
(2) R = CH_2OH
(3) R = CH_2CH_2OH
(4) R = $CH_2CH(OH)CH_3$
(5) R = $(CH_2)_3CN$
(6) R = COOEt
(7) R = CH=CHOMe
(8) R = CH_2–



Two examples illustrate the procedure.

To cuprous oxide (0.5 g, 3.0 mmol) suspended in pyridine (20 ml) was added 1-hexyne (0.45 g, 5.0 mmol) and 5-*t*-butyl-2-iodophenol (1.3 g, 4.8 mmol). The mixture was refluxed for 14 h under nitrogen. Filtration of the copper salt, evaporation, and purification by flash chromatography (silica, hexane - ethyl acetate 4:1) yielded benzofuran (1) (0.9 g, 82%) as a light brown oil. δ_H (60 MHz, $CDCl_3$) 7.5-7.2 (3H, m, 3 x Ar-H); 6.3 (1H, s, 3-H); 2.85 (2H, t, CH_2); 1.3 (13H, m, 2 x CH_2 and *t*-Bu), and 1.0 (3H, m, CH_3). Found: C 83.5; H 9.8%. $C_{16}H_{22}O$ requires C 83.5; H 9.6%.

Propargyl alcohol (0.3 g, 4.8 mmol) on refluxing in pyridine under nitrogen with 5-*t*-butyl-2-iodophenol (1.3 g, 4.8 mmol) in the presence of cuprous oxide (0.5 g, 3.0 mmol) gave the hydroxymethylbenzofuran (2), (0.80 g, 83%) as a colorless oil, b.p. 80-81°C at 0.1 mm Hg. ν_{max} (film) 3337, 2370, and 1660 cm^{-1}. δ_H (60 MHz, $CDCl_3$) 7.5 (3H, m, 3 x Ar-H), 6.7 (1H, s, 3-H); 4.8 (2H, m, CH_2); 2.1 (1H, m, OH), and 1.3 (9H, s, *t*-Bu). Found: C 76.3; H 8.0%. $C_{13}H_{16}O_2$ requires C 76.5; H 7.9%.

Additional examples, listed below, show that the reaction can accommodate the presence of a variety of reactive functional groups such as hydroxyl, ester, lactone, enol ether, and acetal.

3. R = CH_2CH_2OH; Reflux 19 h; 75%; b.p. 92°/0.5 mm; C 77.0 (77.03), H 8.3 (8.31); δ_H 7.6-7.2 (3H, m, ArH), 6.3 (1H, s, CH), 3.8 (2H, t, CH_2), 2.9 (3H, t, CH_2 and OH), 1.4 (9H, s, *t*-Bu).
4. R = $CH_2CH(OH)CH_3$; Reflux 16 h; 65%; b.p. 70°/0.1 mm; C 77.5 (77.55), H 8.7 (8.68); δ_H 7.6-7.2 (3H, m, ArH), 6.3 (1H, s, CH), 4.1 (1H, m, CH), 2.8 (2H, d, CH_2), 2.5 (1H, s, OH), 1.3 (9H, s, *t*-Bu), 1.2 (3H, d, CH_3).
5. R = $(CH_2)_3CN$; Reflux 16 h; 75%; m.p. 53°, b.p. 98°/0.1 mm; C 79.5 (79.63), H 8.0 (7.94); δ_H 7.5-7.2 (3H, m, ArH), 6.4 (1H, s, CH), 2.9 (2H, t, CH_2), 2.6-2.0 (4H, m, CH_2CH_2), 1.3 (9H, s, *t*-Bu).
6. R = $COOCH_2CH_3$; 100°, 14 h in DMF; 60%; b.p. 95°/0.1 mm; C 73.1 (73.15), H 7.4 (7.37); δ_H 7.7-7.2 (4H, m, ArH and CH), 4.4 (2H, q, CH_2), 1.5-1.2 (12H, t and s, *t*-Bu and CH_3).
7. R = $CH{=}CHOCH_3$; Reflux 16 h; 70%; oil; δ_H 7.6-7.2 (3H, m, ArH), 6.7 (1H, s, CH), 6.2 (1H, d, CH), 5.4 (1H, d, CH), 3.8 (3H, s, OCH_3), 1.3 (9H, s, *t*-Bu).
8. R = $CH_2\text{-}\underbrace{CHCH_2CH_2COO}$; Reflux 14 h; 65%; m.p. 98-100°; C 75.0 (74.97), H 7.4 (7.40); δ_H 7.5-7.1 (3H, m, ArH), 6.4 (1H, s, CH), 4.9 (1H, m, CH), 3.1 (2H, m, CH_2), 2.4 (4H, m, CH_2CH_2), 1.3 (9H, s, *t*-Bu).

5-*t*-Butyl-2-iodophenol is prepared as follows: To 3-*t*-butylphenol (15.0 g, 100 mmol) in glacial acetic acid (200 ml) is added potassium iodate (4.28 g, 20 mmol) in water (50 ml) and iodine (10.2 g, 40 mmol). The mixture is stirred at room temperature 24-48 h, stripped, the residue is taken up in ether, washed with sodium bicarbonate and sodium thiosulfate solutions, dried ($MgSO_4$), and stripped to give 5-*t*-butyl-2-iodophenol (27 g, 98%), light brown crystals, m.p. 44-46°C. δ_H (60 MHz, $CDCl_3$), 7.5 (1H, d, J = 9 Hz, C3H); 7.05 (1H, d, J = 2 Hz, C6H); 6.7 (1H, dd, J = 2 Hz, 9Hz; C4H), 5.5 (1H, s, OH); 1.25 (12H, s, *t*-Bu).

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