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Efficient and Connective Assembly of Highly Functionalized Benzofurans Using *o*-Hydroxyphenones and Dichloroethylene

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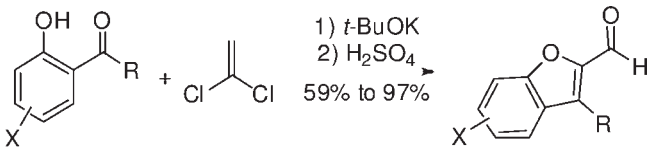
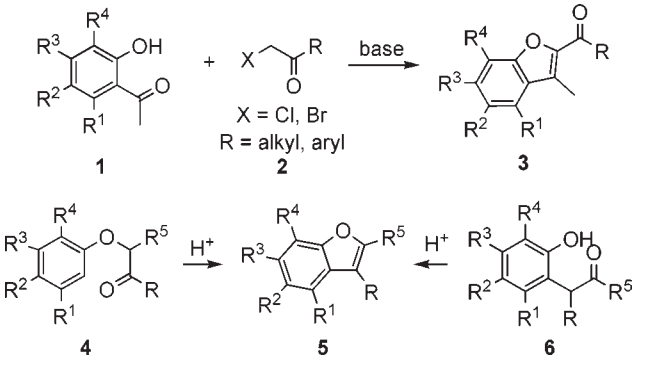
ABSTRACT



The preparation of highly functionalized benzofurans by a unique and connective transformation is reported. Base-catalyzed condensation of *o*-hydroxyphenones with 1,1-dichloroethylene generates the corresponding chloromethylene furans. These labile intermediates undergo a facile rearrangement into benzofuran carbaldehydes under mild acidic conditions.

Benzofurans are important heterocyclic molecules because of their ubiquitous and varied biological activities.[1] It is therefore little surprising that an enormous amount of research has been carried out to develop efficient synthetic methods for their assembly. The most pertinent and often employed strategies involve the one-pot etherification and dehydrative cyclization of *o*-hydroxyacetophenones **1** under basic conditions,[2−5] the dehydrative cyclization of *o*-hydroxybenzyl ketones **6** or α-(phenoxy)alkyl ketones **4** (Scheme 1),[5−7] and the cyclization of arylacetylenes using transition-metal catalysis.[8−14]

Scheme 1



(1) For a selection of pertinent references, see: (a) Diyasena, M.; Sotheeswaran, S.; Surendrakumar, S.; Balasubramanian, S.; Bokel, M.; Kraus, W. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1807. (b) Dai, J.; Hallock, Y.; Cardellina, J.; Boyd, M. *J. Nat. Prod.* **1998**, *61*, 351. (c) Engler, T.; La Tessa, K.; Iyengar, R.; Chai, W.; Agrios, K. *Bioorg. Med. Chem.* **1996**, *4*, 1755. (d) Romagnoli, R.; Baraldi, P.; Carrion, M.; Cara, C.; Cruz-Lopez, O.; Tolomeo, M.; Grimaudo, S.; Di Cristina, A.; Pipitone, M.; Balzarini, J.; Zonta, N.; Brancale, A.; Hamel, E. *Bioorg. Med. Chem.* **2009**, *17*, 6862. (e) Hayakawa, I.; Shioya, R.; Agatsuma, T.; Furukawa, H.; Naruto, S.; Sugano, Y. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 455.

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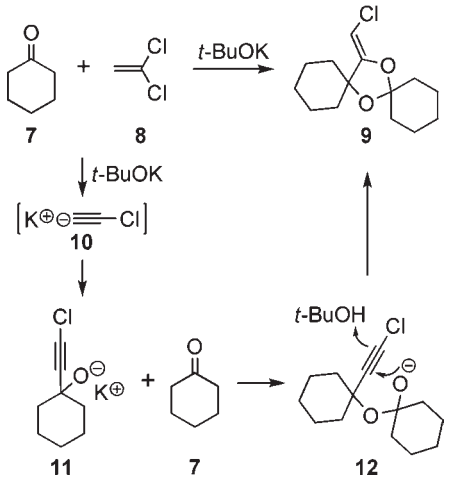
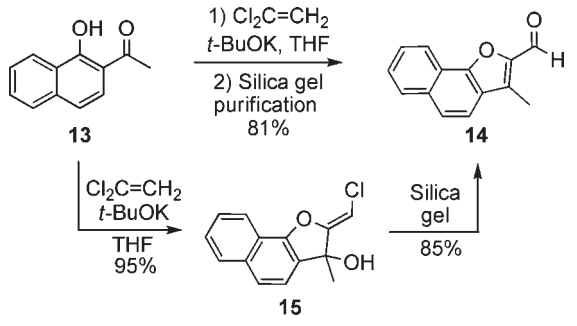
Recently, we reported a novel transformation leading to the formation of a rare heterocyclic motif, the (*Z*)-chloromethylene ketal[15] substructure **9** (Scheme 2). Thus, addition of *t*-BuOK to dichloroethylene **8** leads rapidly to the formation of the acetylenide anion **10**, which adds to the ketone **7** to afford the adduct **11**. Condensation of **11** with a second equivalent of ketone produces the hemiketal alkoxide **12** that undergoes an irreversible 5-*exo*-*dig* cyclization, culminating in the obtention of the geometrically pure chloromethylene ketal **9**.

Scheme 2



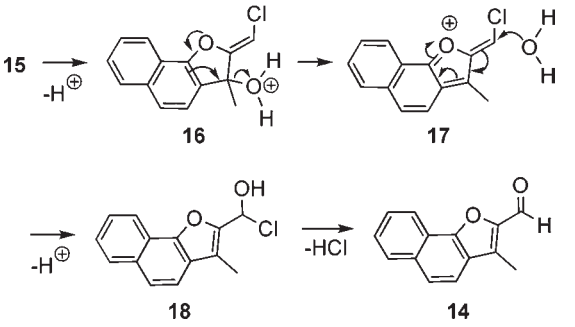
In an attempt to further broaden the scope of this condensation, ketone **13** was employed as the substrate. Much to our surprise, benzofuran carbaldehyde **14** was obtained in excellent yield after purification of the crude product by silica gel column chromatography (Scheme 3).

Scheme 3



Repeating the experiment but obviating the purification step afforded the expected chloroacetylene addition product **15** in essentially quantitative yields. This intermediate could be isolated and characterized by NMR after workup. However, its lifetime, even in a pure phase, is too short for fully detailed analyses. Submitting **15** to silica gel treatment smoothly gave rise to aldehyde **14** in 85% yield. These experiments strongly suggest that **15** is the likely precursor of **14**. A plausible mechanism is depicted in Scheme 4.

Scheme 4



Protonation of **15** by the acidic silica generates the hydronium cation **16** which loses a water molecule, leading to the oxonium species **17**. Conjugate addition of water at the terminal position provides, after loss of a proton, the α-chlorohydroxybenzofuran **18**. Spontaneous elimination of HCl finally yields aldehyde **14**. While the silica gel treatment proved to be efficient in some cases, it was not generally applicable. Therefore, the acid-catalyzed rearrangement−hydrolysis step was subsequently performed using sulfuric acid in the biphasic system[16] H_2O/CH_2Cl_2. Under these conditions, a variety of commercially available *o*-hydroxyphenones were successfully transformed into the corresponding benzofurans in 59−97% isolated yield. Some pertinent examples are collected in Table 1.

As can be seen from Table 1, the reaction proves to be quite general and high yielding, proceeding efficiently with both alkyl- and aryl-substituted phenones (entries 1−5). It tolerates various substituents, including halides (entries 2 and 3) and methoxy group (entries 6 and 7).

A limitation of the *tert*-butoxide-based protocol was uncovered when aromatic aldehydes were used as substrates. In these cases, a rapid degradation of the reaction mixture was observed. Therefore, it was decided to modify our procedure, and LDA, instead of *t*-BuOK, was employed to prepare the chloroacetylene anion. Dropwise addition of salicylaldehyde **28** to the lithiated alkyne, followed by the usual acid-catalyzed rearrangement,

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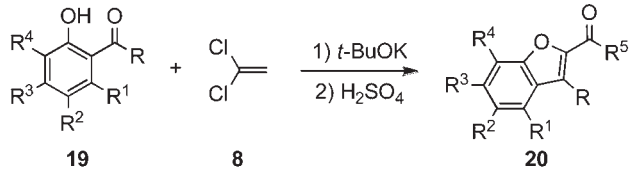
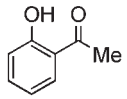
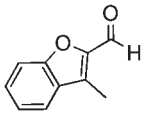
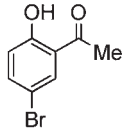
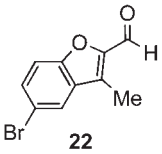
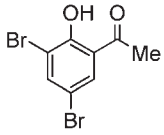
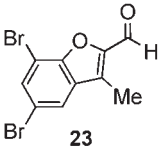
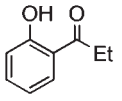
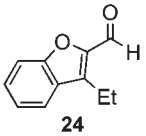
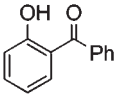
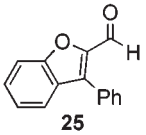
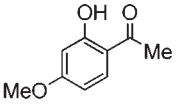
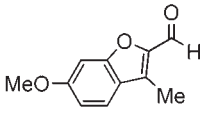
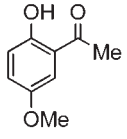
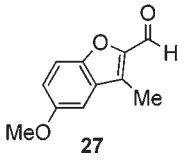
(15) Schevenels, F.; Markó, I. *Chem. Commun.* **2011**, *47*, 3287.
(16) When HCl was employed as the acid, fomation of the corresponding dichloride was observed.

Table 1[a]

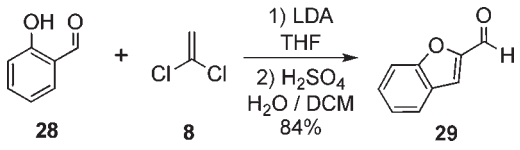


entry	substrate	product	yield[a]
1		 **21**	97%
2		 **22**	93%
3		 **23**	78%
4		 **24**	92%
5		 **25**	94%
6		 **26**	88%
7		 **27**	93%

[a] All yields are for pure, isolated products.

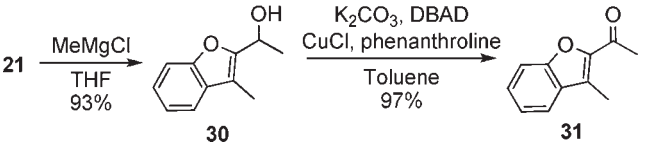
resulted gratifyingly in the isolation of benzofuran-2-carbaldehyde in 84% yield (Scheme 5).

Scheme 5



Nerolione **31** is a well-known scent[17] benzofuran. Starting from aldehyde **21**, nerolione could be obtained, after addition of methylmagnesium chloride and oxidation using our previously reported copper-catalyzed procedure,[18] in excellent overall yields (Scheme 6, Table 1).

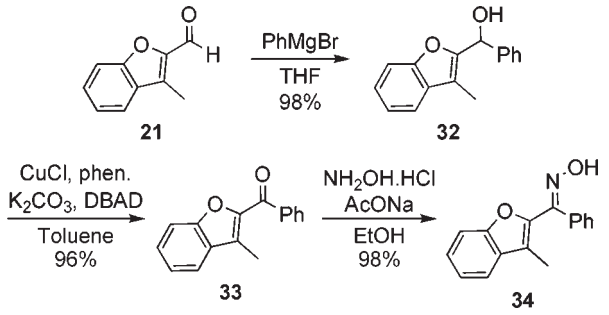
Scheme 6



Unfortunately, our spectroscopic data did not match those previously reported for this compound.[19] Therefore, synthetic nerolione was derivatized and a single crystal X-ray diffraction analysis was performed. This study fully confirmed our proposed structure.[20]

When applying the same methodology, benzofurans **33** and **34**, displaying antifungal activities,[21] were synthesized in exquisite overall yields (Scheme 7).

Scheme 7



Using this novel methodology, several biologically active benzofurans have been prepared in yields much

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(18) Markó, I.; Tsukazaki, M.; Giles, P.; Brown, S.; Urch, C. *Angew. Chem., Int. Ed.* **1997**, *36*, 2208.

(19) Nielek, S.; Lesiak, T. *Chem. Ber* **1982**, *115*, 1247.

(20) Full data and details will be available in the forthcoming full paper.

(21) Podea, P.; Tosa, M.; Paizs, C.; Irimie, F. *Tetrahedron: Asymmetry* **2008**, *19*, 500.

(22) **General Procedure for the Synthesis of Benzofuran Carbaldehydes.** To 15 mL of anhydrous THF, cooled to 0 °C, were added sequentially the hydroxyphenone **19** (3 mmol, 1 equiv), ethylene dichloride **8** (0.34 mL, 4.2 mmol, 1.4 equiv), and potassium *tert*-butoxide (1.30 g, 11.4 mmol, 3.8 equiv). After the mixture was stirred for 1−4 h at room temperature, full conversion was observed as indicated by TLC, and 20 mL of water was added. The mixture was neutralized with 1 M sulfuric acid. The aqueous layer was extracted with 3 × 20 mL of dichloromethane. The organic phase was dried, filtered, and concentrated in vacuo. The crude mixture was dissolved in 100 mL of dichloromethane, and 100 mL of a 0.01 M aqueous sulfuric acid solution was added. After 16−120 h under vigorous stirring (at room temperature or reflux, see the Supporting Information), the aqueous layer was extracted with 2 × 60 mL of dichloromethane. The organic layer was dried, filtered, and concentrated. The crude product was further purified by chromatography over silica gel. For full details, see the Supporting Information.

higher than those obtained when the previously described routes to these compounds were followed.

In summary, we have discovered a novel reaction leading to the efficient and connective assembly of highly functionalized benzofurans, in good to excellent yields. Starting from *o*-hydroxyphenones, the corresponding (*Z*)-chloromethylene furans were obtained. These were smoothly rearranged into the corresponding benzofuran carbaldehydes under acid catalysis.[22] Several mechanistic investigations are currently underway and the scope and limitations of this unique procedure, including its transposition to other heterocycles, are being extensively studied in our laboratories.

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Supporting Information Available. Experimental procedures, characterization of new compounds, and references to known compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.