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Expedient Preparation of Trifluoromethyl-Substituted Benzofuranols

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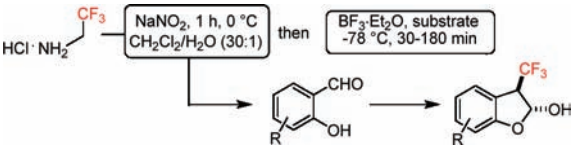
ABSTRACT



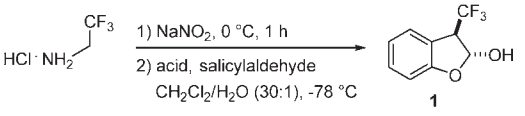
Direct access to 3-trifluoromethyl-substituted benzofuranols is presented. The products are obtained in good yields from commercially available salicylaldehydes by using in situ generated trifluoromethyl diazomethane and boron trifluoride as an activator. As shown in a representative example, the products can be transformed into the corresponding trifluoromethyl-substituted benzofurans.

Trifluoromethyl-substituted heterocycles have found widespread use in the drug industry due to the ability of fluorinated groups to alter essential physical properties of active pharmaceutical ingredients.[1] Among them, benzofuran derivatives bearing a trifluoromethyl group at the C3-position have been surprisingly poorly investigated, probably due to the few synthetic methods available for their preparation.[2]

We recently described reactions in which we used trifluoromethyl diazomethane (F_3CCHN_2) generated in situ in a range of transformations, including cyclopropanation, cyclopropenation, and homologation of aldehydes and cyclohexanones to form trifluoroethyl-substituted ketones.[3] Herein we report our results dealing with the use of in situ generated F_3CCHN_2 in the homologation reaction of salicylaldehyde derivatives,[4] affording direct access to dihydrobenzofuranols bearing a trifluoromethyl group at C3.

Our investigations aimed at the synthesis of benzofuranols started with salicylaldehyde as a test substrate under

Table 1. Optimization Studies[a]



entry	acid	equiv	yield[b]
1	$ZrCl_4$	1.8	18%
2	$AlCl_3$	1.8	traces
3	$TiCl_4$	1.8	10%
4	$SnCl_4$	1.8	nr
5	$SbCl_5$	1.8	25%
6	$BF_3 \cdot OEt_2$	1.8	74%
7	$BF_3 \cdot OEt_2$	0.3	13%
8	$HBF_4 \cdot OEt_2$	1.8	nr

[a] General procedure: $F_3CCH_2NH_3Cl$ (3.0 equiv) and $NaNO_2$ (3.6 equiv) are stirred for 1 h at 0 °C in CH_2Cl_2/H_2O (30:1), followed by addition of Lewis acid and salicylaldehyde (0.22 mmol, 1 equiv) at −78 °C. [b] Yield based on NMR analysis.

(1) For general reviews on fluorine chemistry, see: (a) Kirsch, P. *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*; WILEY-VCH: Weinheim, 2004. (b) Schlosser, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 5432. (c) Isanbor, C.; O'Hagan, D. *J. Fluorine Chem.* **2006**, *127*, 303. (d) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881. (e) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320.

(2) (a) Kobatake, T.; Fujino, D.; Yoshida, S.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2010**, *132*, 11838. (b) Konno, T.; Chae, J.; Ishihara, T.; Yamanaka, H. *Tetrahedron* **2004**, *60*, 11695. (c) Jiang, Z.-X.; Qing, F.-L. *J. Fluorine Chem.* **2003**, *123*, 57.

(3) (a) Morandi, B.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 938. (b) Morandi, B.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 4294. (c) Morandi, B.; Mariampillai, B.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 1101. (d) Morandi, B.; Cheang, J.; Carreira, E. M. *Org. Lett.* **2011**, *13*, 3080. (e) Morandi, B.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 9085.

(4) For the preparation of benzofurans from salicylaldehyde and other diazocompounds, see: (a) Dudley, M. E.; Morshed, M. M.; Hossain, M. M. *Synthesis* **2006**, 1711. (b) Dudley, M. E.; Morshed, M. M.; Brennan, C. L.; Islam, M. S.; Ahmad, M. S.; Atuu, M.-R.; Branstetter, B.; Hossain, M. M. *J. Org. Chem.* **2004**, *69*, 7599.

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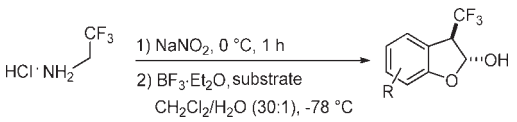
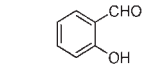
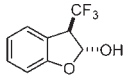
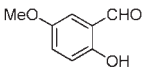
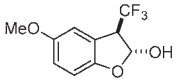
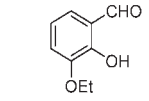
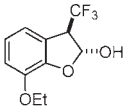
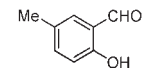
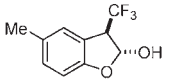
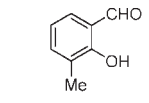
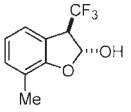
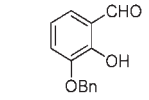
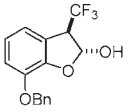
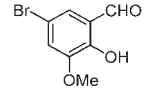
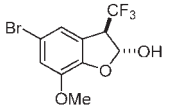
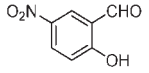
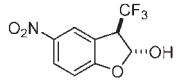
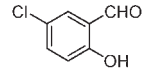
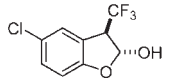
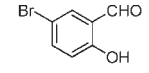
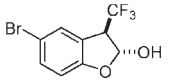
Table 2. Reaction Scope[a]



substrate	product	number	yield[b]
		**1**	74%
		**2**	70%
		**3**	68%
		**4**	71%
		**5**	67%
		**6**	73%
		**7**	54%
		**8**	57%
		**9**	72%
		**10**	69%

[a] General procedure: $F_3CCH_2NH_3Cl$ (3.0 equiv) and $NaNO_2$ (3.6 equiv) are stirred for 1 h at 0 °C in CH_2Cl_2/H_2O (30:1), followed by addition of BF_3•OEt_2 (1.8 equiv) and substrate (0.22 mmol, 1 equiv) at −78 °C. [b] Isolated yield.

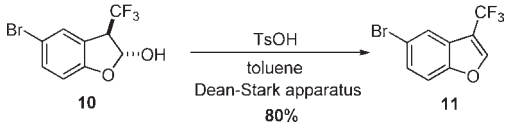
conditions previously reported by us[3e] for the homologation of aldehydes to trifluoroethyl-substituted ketones. In the initial screening experiments, $F_3CCH_2NH_2$•HCl and $NaNO_2$ were stirred at 0 °C over 1 h in a mixture of 30:1 CH_2Cl_2/H_2O, which was then cooled over 10 min to −78 °C; the test substrate (salicylaldehyde) and $ZrCl_4$ were then added. After stirring for 45 min, we obtained (3-trifluoromethyl-2,3-dihydrobenzofuran-2-ol) in 18% yield and low conversion (Table 1, entry 1). We then screened a variety of Lewis acids, including $AlCl_3$, $TiCl_4$, $SnCl_4$, $SbCl_5$, and BF_3•OEt_2. To our delight BF_3•OEt_2 proved to be suitable to mediate the conversion of salicylaldehyde to **1** in 74% yield (entry 6). However, its use in a substoichiometric quantity was deleterious to the reaction, affording product in low yield (entry 7). To exclude the possibility of Brønsted acid catalysis (HBF_4), a control reaction was performed with HBF_4, which failed to give product under otherwise standard conditions.

Having identified suitable reaction conditions for the conversion of salicylaldehyde to the corresponding trifluoromethyl-substituted benzofuranol, we examined the scope of the reaction. Electron-rich substrates worked well, affording products **2**–**6** (Table 2) in good yields. More surprisingly, salicylaldehydes bearing electron-withdrawing groups also furnished products **8**–**10** (Table 2) in moderate to good yields. Overall, the method tolerates a broad range of functional groups and allows quick access to products with potential for further elaboration. The configuration of the hemiacetal was unambiguously assigned as trans by X-ray crystallographic analysis for product **3** and assigned by analogy to the other benzofuranols produced.

Finally, we were interested in examining the dehydration of these products, since the corresponding trifluoromethyl-substituted benzofurans have been poorly described in the literature and might serve as useful heterocyclic building blocks for drug discovery. Satisfyingly with **10** as a test substrate, benzofuran **11** was obtained in 80% yield by refluxing the starting material in toluene with *p*-toluenesulfonic acid and azeotropic removal of water (Scheme 1).

In conclusion, we have described the conversion of salicylaldehydes to trifluoromethyl-substituted dihydrobenzofuranols using a protocol that utilizes trifluoromethyl diazomethane generated in situ.[5] The heterocyclic products were obtained in good yields following a protocol that is experimentally practical.[6] As shown for a prototypical case, the furanols may be subjected to dehydration to furnish the corresponding C3 substituted trifluoromethyl benzofurans.

Scheme 1. Preparation of a Trifluoromethylated Benzofuran



Acknowledgment. We are grateful to the SSCI for a fellowship to B.M. and the ETH-Zurich for generous support through grant 0-20744-11.

Supporting Information Available. Full experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

(5) We believe the mechansim involves the following steps: coordination of BF_3, attack of the diazocompound onto the activated aldehyde, migration of the phenyl ring, and hemiacetal formation.

(6) Safety Precaution: trifluoromethyl diazomethane is a potentially explosive compound, and although we never experienced any problem while performing reactions with dilute solutions of this reagent, we recommend the use of a blast shield.