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A convenient synthesis of 5-fluorofuran-2-carboxylic acid

Renhua Song, Weimin Lin, Qin Jiang *

AMRI, 26 Corporate Circle, PO Box 15098, Albany, NY 12212, United States

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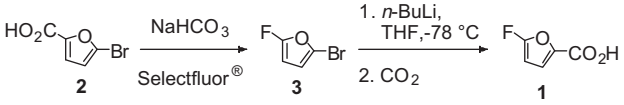
ABSTRACT

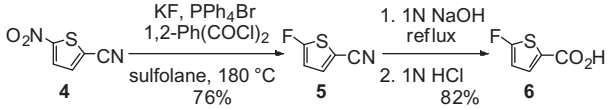
A convenient synthesis of 5-fluorofuran-2-carboxylic acid has been achieved in two steps and 56% total yield. Fluorodenitration of commercially available benzyl 5-nitrofuran-2-carboxylate utilizing potassium fluoride and catalytic tetraphenylphosphonium bromide in sulfolane at 140 °C for 2 h furnished benzyl 5-fluorofuran-2-carboxylate. Hydrogenolysis of benzyl 5-fluorofuran-2-carboxylate gave the title compound.

5-Fluorofuran-2-carboxylic acid (**1**) is a useful building block in pharmaceutical research.[1] The preparation of **1** was described in the literature[1a] as shown in Scheme 1. The authors did not provide a yield, and in our hands following the procedures provided only a 5% yield of **1** from **2**. Fluorodenitration is a practical method for introducing fluorine into the *meta*-position of an activated aromatic ring.[2] Chambers[3] reported a fluorodenitration strategy to convert 5-nitrothiophene-2-carbonitrile (**4**) to 5-fluorothiophene-2-carboxylic acid (**6**) (Scheme 2) in good yield. Therefore, we considered a similar strategy to prepare the furan analogue (**1**) and the results are reported herein.

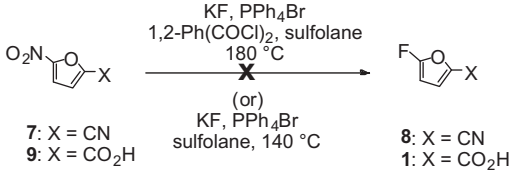
We first investigated Chambers' method (KF, PPh_4Br, 1,2-$Ph(COCl)_2$, sulfolane, 180 °C)[3] to convert 5-nitrofuran-2-carbonitrile (**7**) to 5-fluorofuran-2-carbonitrile (**8**), as well as 5-nitrofuran-2-carboxylic acid (**9**) to **1** (Scheme 3). In both cases, we observed no formation of the desired products. We investigated the fluorodenitration of various esters of **9**. The reactions were carried out with or without phthaloyl chloride at various temperatures (Table 1). Both methyl ester (**10a**) and *tert*-butyl ester (**10b**) gave complex reaction profiles (entries 1 and 2), whereas the benzyl ester (**10c**) gave the desired corresponding fluoride (**11c**) (entries 3–12). Our investigation showed that the addition of phthaloyl chloride is not necessary for the fluorodenitration of an activated furan ring and reaction temperatures from 120 to 140 °C can be tolerated (entries 7–9). A significant reduction in yield was noted when the reaction was conducted at 160 °C (entry 5). Considering the shorter reaction time, we believe 140 °C is the best reaction temperature (entry 7).[4] Different solvents were also investigated (entries 7 and 10–12) with sulfolane providing the best results of those examined. Our



Scheme 1.



Scheme 2.



Scheme 3.

fluorodenitration condition (KF, PPh_4Br, sulfolane, 140 °C) was applied to convert **7** to **8** and **9** to **1**. No desired corresponding fluorides were observed (Scheme 3).

Hydrogenolysis of **11c** gave the title compound (**1**) in 95% yield (Scheme 4).[5] Thus, starting from the commercially available ester **10c**, 5-fluorofuran-2-carboxylic acid (**1**) has been achieved in two steps and 56% total yield.

* Corresponding author. Tel.: +1 518 512 2380; fax: +1 518 512 2079.
E-mail address: qin.jiang@amriglobal.com (Q. Jiang).

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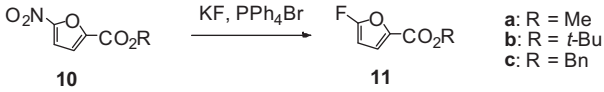
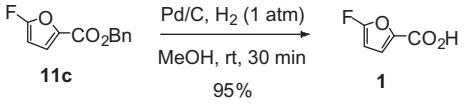
Table 1
Fluorodenitration of 5-nitrofuran-2-carboxylate



10 **11**

Entry	Compound	R	Phthaloyl Chloride	Solvent	*T* (°C)	*t* (h)	Product	Yield (%)[a]
1	**10a**	Me	–	Sulfolane	140	2	**11a**	–
2	**10b**	*t*-Bu	–	Sulfolane	140	2	**11b**	–
3	**10c**	Bn	0.9 equiv	Sulfolane	180	2	**11c**	7
4	**10c**	Bn	–	Sulfolane	180	2	**11c**	11
5	**10c**	Bn	–	Sulfolane	160	2	**11c**	15
6	**10c**	Bn	0.9 equiv	Sulfolane	140	4	**11c**	40
7	**10c**	Bn	–	Sulfolane	140	2	**11c**	59
8	**10c**	Bn	–	Sulfolane	130	5	**11c**	56
9	**10c**	Bn	–	Sulfolane	120	6	**11c**	59
10	**10c**	Bn	–	DMSO	140	1.5	**11c**	20
11	**10c**	Bn	–	DMF	140	2.5	**11c**	42
12	**10c**	Bn	–	NMP	140	2	**11c**	31

[a] Isolated yield.



11c **1**

Scheme 4.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.07.087.

References and notes

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4. *Standard procedure for fluorodenitration:* A suspension of commercially available benzyl 5-nitrofuran-2-carboxylate (**10c**, 0.793 g, 3.21 mmol), spray-dried potassium fluoride (0.932 g, 16.0 mmol), and tetraphenylphosphonium bromide (0.139 g, 0.330 mmol) in anhydrous sulfolane (10 mL) was heated at 140 °C under nitrogen for 2 h (reaction was monitored by TLC). The reaction mixture was cooled to rt and diluted with water (10 mL). The resulting mixture was extracted with diethyl ether (×3). The combined extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash column (5% MTBE/hexanes) to give **11c** (0.416 g, 59%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.34 (m, 5H), 7.15 (t, *J* = 3.5 Hz, 1H), 5.62 (dd, *J* = 7.1, 3.6 Hz, 1H), 5.32 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9 (d, *J* = 284 Hz), 157.7, 135.5, 135.0, 128.6, 128.5, 128.4, 120.6, 85.1 (d, *J* = 13.4 Hz), 66.6; ^{19}F NMR (282 MHz, $CDCl_3$) δ 106.4.
5. Preparation of **1**: To a solution of **11c** (0.220 g, 1.00 mmol) in MeOH (10 mL) was added 10% Pd/C (50% wet, 22 mg). The resulting suspension was stirred at rt under hydrogen atmosphere (balloon, 1 atm) for 30 min (reaction was monitored by TLC; prolonged reaction time resulted in de-fluoronation). The reaction mixture was filtered through a short pad of diatomaceous earth and the filter cake was washed with methanol (10 mL). The filtrate was concentrated under reduced pressure. The residue was triturated with a mixture of hexanes (4 mL) and methylene chloride (2 mL), filtered, and dried under high vacuum to give **1** (0.123 g, 95%) as a white solid: ^{1}H NMR (300 MHz, CD_3OD) δ 7.20 (t, *J* = 3.5 Hz, 1H), 5.81 (dd, *J* = 7.0, 3.5 Hz, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ 160.7, 160.2 (d, *J* = 281 Hz), 137.1, 121.6, 86.0 (d, *J* = 13.6 Hz); ^{19}F NMR (282 MHz, CD_3OD) δ 110.8.