Synlett A. Hauser, R. Bohlmann Letter

Preparation of Aldehydes by Oxidation of Benzylic Amines with Selectfluor™ (F-TEDA-BF4)

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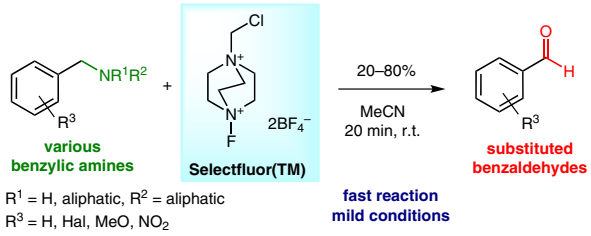

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Abstract Aldehydes are obtained by mild oxidation of benzylic amines with Selectfluor™. The results are compared favorably with the Polonovski-like process using hypervalent iodine.

Key words Selectfluor™, amines, oxidation, aromatic aldehydes

A key transformation occurring during many metabolic pathways is the oxidation of amines to aldehydes or ketones.[1] It is an important source for the incorporation of carbon- and nitrogen-containing building blocks by biogenesis. Specialized amine oxidases perform this vital function for instance in the liver. In addition, it plays a vital part in the metabolism of drugs. The toolbox of organic chemistry includes numerous processes for this oxidation. However, they often require either heavy metals or multiple steps. Therefore, two recent papers report mild oxidations of amines into aldehydes by hypervalent iodine in chloroform.[2]

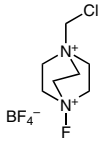
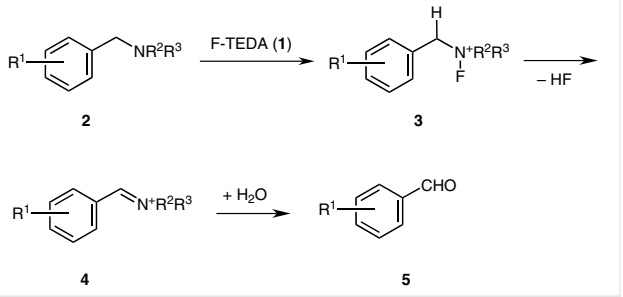


Figure 1 Selectfluor™ (**1**, F-TEDA-BF4)

We were investigating the reaction of benzylic amines **2** with Selectfluor™ (**1**, Figure 1, F-TEDA-BF4) for the preparation of fluorinated derivatives as part of the late-stage derivatization strategy. Analysis of our reaction mixtures indicated the formation of aldehydes **5** instead (Scheme 1). To the best of our knowledge the observed reaction with **1** has not been reported before. There are several reports and reviews[3] on fluorination reactions employing **1**, but despite early reports of the slow oxidation of benzylic alcohols with **1** they were not extended to the oxidation of amines.[4] Consequently, the newly observed reaction of **1** was investigated in detail comparing also the conditions and yields with those of the more frequently applied oxidation strategy using hypervalent iodine.[2]

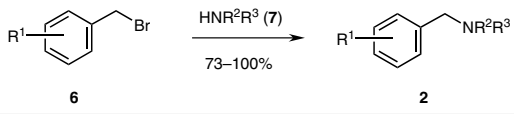


Scheme 1 Proposed mechanism of the reaction

Regarding the reaction mechanism, the first step of the new transformation might be the nucleophilic attack of **2** at the fluorine atom in **1**, analogous to the S_N2 reaction on carbon.[5] Elimination of hydrofluoric acid would intermediately give an imine **4** which in turn could be hydrolyzed to the isolated aldehyde **5**.

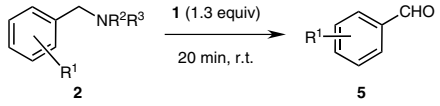
To find the most practical conditions different equivalents of **1** were reacted with **2f** along with **2d** and **2e** (Table 1, entry 4–6) at different temperatures in acetonitrile as well as in chloroform, and the conversion of **2f** was determined *via* UPLC at distinct time points (Table S1). Formation of product **5b** was observed in each experiment even though to different extent, hence, for best results and convenience the reaction conditions were chosen as follows:

1.3 equivalents of **1** in acetonitrile at 25 °C for 20 minutes. Subsequently, a complete set of differently substituted tertiary amines each with three differently substituted benzyl moieties was investigated under these conditions (Table 1, entries 1–9). In addition to that, the reactivities of (1) a secondary along with a tertiary amine (Table 1, entries 10, 11) and (2) a steric unrestricted together with a constraint amine (Table 1, entries 12, 13) were compared to illustrate the scope of the reaction. Therefore, the reported substrates **2a**–**m** were either purchased commercially or derived from the corresponding benzylic bromides **6** by amination with amines **7** (Scheme 2).[6] The subsequent reaction of **1** with these **2a**–**m** resulted in the formation of the corresponding aldehydes **5a**–**f** in all cases, though showing varying conversions from poor to excellent (see Table S2, Figures S2 and S3). These results indicate that the chemical environment of the amines has a larger impact on the product formation than the aromatic substituents. In case of the diisopropylamine derivatives good to excellent yields were observed, surpassing the reported results obtained when using hypervalent iodine in chloroform over two hours at 60 °C.[2a] Due to different volatility of the products, not all purified fractions could be fully dried under high vacuum resulting partially in decreased purity (see Table S1).



Scheme 2 Synthesis of benzylic amines **2** from bromides **6**

Table 1 Synthesis of Benzylic Aldehydes **5** from Amines **2** with **1**



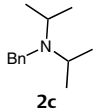
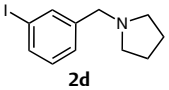
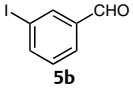
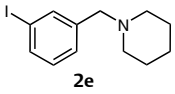
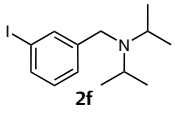
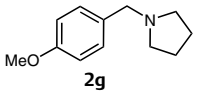
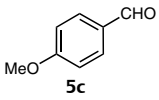
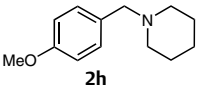
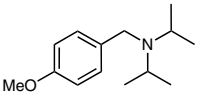
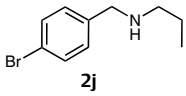
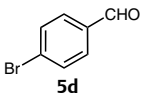
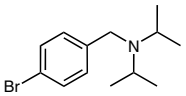
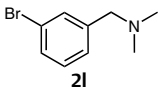
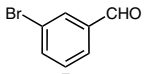
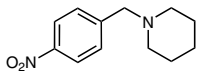
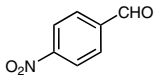
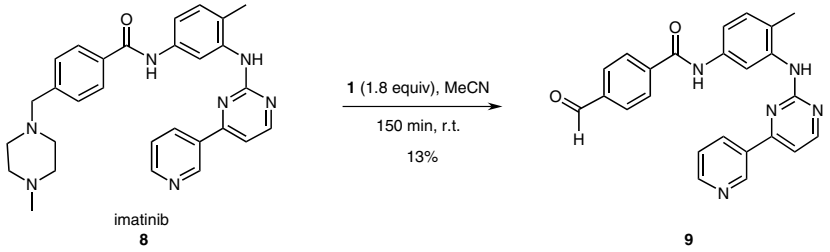
Entry	Substrate	Product **5**	Yield (%)	Yield (%)[a]
1	 **2a**	PhCHO **5a**	83	–[b]
2	 **2b**	**5a**	25	–[b]
3	 **2c**	**5a**	90	95
4	 **2d**	 **5b**	88	55

Table 1 (continued)

Entry	Substrate	Product **5**	Yield (%)	Yield (%)[a]
5	 **2e**	**5b**	45	–[b]
6	 **2f**	**5b**	92	75
7	 **2g**	 **5c**	49	–[b]
8	 **2h**	**5c**	20	–[b]
9	 **2i**	**5c**	72	69
10	 **2j**	 **5d**	21	50
11	 **2k**	**5d**	93	82
12	 **2l**	 **5e**	90	42
13	 **2m**	 **5f**	30	42

[a] Yields obtained by Desjardins et al.[2a]
[b] Reactions were not performed by Desjardins et al.[2a]

To test the applicability of our developed protocol for more complex substrates the commercially available compound imatinib (**8**) in which various different amine functionalities are present was reacted with **1** under similar conditions as described before (Scheme 3). We were delighted to observe the distinct conversion of the benzylic amine into the corresponding aldehyde **9** (Figure S1) which is known to be an in vivo metabolite of imatinib.[7] By this model transformation the generality of our novel developed synthesis strategy was demonstrated.[8]



Scheme 3 Reaction of imatinib (**8**) with **1**

In conclusion, we report the discovery of a rapid, mild, convenient method for the straightforward preparation of benzylic aldehydes from amines by the use of Selectfluor™ (**1**).[9,10] The efficacy, selectivity, and easy handling of **1** far outweigh its higher risk and slightly higher price than hypervalent iodine. The reaction can be carried out without metals or detours *via* protecting group manipulations. This transformation should be kept in mind while reacting benzylic amines with **1**. Apart from being a side reaction during the fluorination protocol, this strategy provided smooth access to different metabolic intermediates of diverse drugs. In future experiments, this approach together with a larger scope of substrates and the influence of different solvents shall be investigated more in detail.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1561642.

References and Notes

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(7) Genovino, J.; Lütz, S.; Sames, D.; Touré, B. *J. Am. Chem. Soc.* **2013**, *135*, 12346.
(8) Since our work for this manuscript was finished, two novel approaches for the oxidative deamination of benzylic amines have been published which should be mentioned here despite of the smaller reaction scope they cover. See: (a) Ling, Z.; Yun, L.; Liu, L.; Wu, B.; Fu, X. *Chem. Commun.* **2013**, *49*, 4214. (b) Gong, J. L.; Qi, X.; Wei, D.; Feng, J.-B.; Wu, X.-F. *Org. Biomol. Chem.* **2014**, *12*, 7486.
(9) **Experimental Procedure**
To a suspension of 1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane ditetrafluoroborate (**1**, 0.975 mmol) in MeCN (3 mL) the amine (**2**, 0.75 mmol) dissolved in MeCN (3 mL) was added dropwise at r.t. The reaction was stirred at r.t. for another 20 min. The solvent was evaporated, and the obtained residue was purified via flash column chromatography using silica gel as stationary phase.
(10) **Benzaldehyde (5a)**
^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.05 (s, 1 H), 7.89–7.95 (m, 2 H), 7.63–7.69 (m, 1 H), 7.54–7.60 (m, 2 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 192.4, 136.5, 134.5, 129.8, 129.0 ppm. IR: ν = 3070 (m), 2837 (m), 2678 (w), 1559 (w), 1686 (vs) cm^{-1}.
3-Iodobenzaldehyde (5b)
^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.95 (s, 1 H), 8.23 (t, *J* = 1.5 Hz, 1 H), 7.98 (dt, *J* = 7.6, 1.6 Hz, 1 H), 7.87 (dt, *J* = 7.8, 1.3 Hz, 1 H), 7.31 (t, *J* = 7.8 Hz, 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 190.7, 143.2, 138.5, 138.1, 130.8, 128.9, 94.7 ppm. IR: ν = 3377 (w), 3057 (w), 2825 (m), 2727 (m), 1699 (vs) cm^{-1}.
4-Methoxybenzaldehyde (5c)
^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.92 (s, 1 H), 7.87 (d, *J* = 8.8 Hz, 2 H), 7.01–7.06 (m, 2 H), 3.92 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 190.8, 164.7, 132.0, 130.1, 114.4, 55.6 ppm.
4-Bromobenzaldehyde (5d)
^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.00 (s, 1 H), 7.77 (dd, *J* = 6.4, 2.1 Hz, 2 H), 7.71 (dd, *J* = 6.8, 1.8 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 191.0, 135.1, 132.4, 131.0, 129.8 ppm. IR: ν = 3350 (w), 3086 (m), 2860 (s), 1699 (vs), 1585 (vs), 1383 (vs), 835 (vs), 814 (s) cm^{-1}.
3-Bromobenzaldehyde (5d)
^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.99 (s, 1 H), 8.04 (t, *J* = 1.8 Hz, 1 H), 7.83 (dt, *J* = 7.7, 1.2 Hz, 1 H), 7.78 (ddd, *J* = 7.9, 2.0, 1.0 Hz, 1 H), 7.45 (t, *J* = 7.8 Hz, 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 190.7, 138.1, 137.3, 132.4, 130.7, 128.4, 123.4 ppm. IR: ν = 1695 (s), 1556 (s), 1252 (m), 754 (vs) cm^{-1}.
4-Nitrobenzaldehyde (5f)
^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.18 (s, 1 H), 8.41 (d, *J* = 8.6 Hz, 2 H), 8.10 (d, *J* = 8.8 Hz, 2 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 190.3, 151.2, 140.1, 130.5, 124.3 ppm. IR: ν = 3107 (*w*), 2850 (m), 1709 (vs), 1605 (m), 1539 (s), 1381 (m), 1346 (vs), 1327 (s), 1288 (m), 1105 (m), 1007 (w), 851 (s), 818 (s), 741 (s) cm^{-1}.