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A convenient method for the syntheses of tetrahydrofuran moiety from furan by catalytic transfer of hydrogenation with ammonium formate

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Abstract

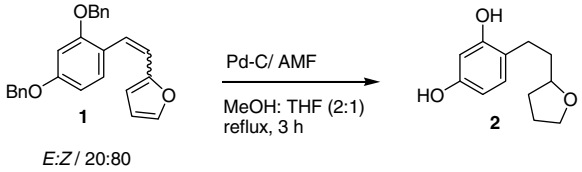
Pd–C/ammonium formate efficiently and selectively reduces hetero-aromatic furan ring to the corresponding tetrahydrofuran moiety. Under this reaction condition, carbon–carbon double bond and α,β-unsaturated ketones also reduced to the corresponding alkanes and saturated ketones.

A large number of biologically active natural products possess substituted tetrahydrofuran moiety[1] such as acetogenins,[2a,b] polyether antibiotics,[3a,b] lignans,[4] and C-glycosides.[5a,b] Many of which contain substituents at the 2- and 5-positions of the ring. Due to the medicinal importance of these compounds, there has been a long-standing interest in the development of simple and stereo-selective methods to synthesize the tetrahydrofuran ring efficiently.[1–6] Several reports have also been recorded for the construction of tetrahydrofuran moiety, most of them involve metal catalyzed oxycarbonylation reactions on ali-cyclic precursor.[7] Surprisingly, there are no direct methods or systematic study for the synthesis of tetrahydrofuran moiety from the readily available hetero-aromatic furan ring by catalytic transfer hydrogenation (CTH). This CTH method has recently received considerable attention to the researchers as the total process is safe, simple, and ecologically friendly.[8]

Herein, we describe a new, simple, and efficient method for the synthesis of substituted tetrahydrofuran ring from hetero-aromatic furan by using ammonium formate as a hydrogen donor with catalytic amount of 10% Pd–C in methanol/THF at reflux. Application of ammonium formate in organic synthesis has been reviewed by Ram and Ehrenkaufer.[9] This versatile, inexpensive, and nontoxic reagent already was employed in the reduction of various functional groups such as azide, nitrile, nitro, aldehyde and ketone, and carbon–carbon double bonds.[10]

In the course of our studies aiming toward the synthesis of polyphenol compounds, we employed CTH method for the reduction of **1** (Scheme 1).

Although the reduction of carbon–carbon double bond and debenzylation was unexpected, the complete reduction of hetero-aromatic furan ring to tetrahydrofuran moiety appeared most intriguing. To the best of our knowledge, there had been three reports where the authors had observed the reduction of furan ring to tetrahydrofuran derivatives by CTH,[11] but not systematically investigated.



Scheme 1.

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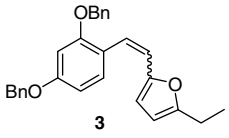
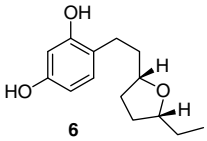
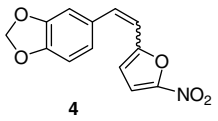
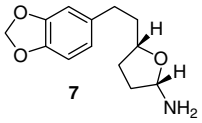
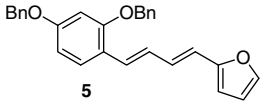
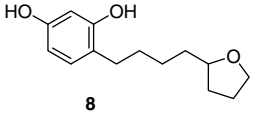
Table 1
Tetrahydrofuran synthesis

Substrate[a]	Product	Yield[b] (%)
 3	 6	69
 4	 7	65
 5	 8	72

[a] Substrates, **3** and **4**, were synthesized by Wittig reactions from the corresponding triphenylphosphonium salts with aldehydes. In all cases, we found 80:20 (*E*:*Z*) isomer.
[b] Isolated yield after column purifications.

These observations prompted us to begun a systematic study of the CTH method of a series of unsaturated furan derivatives. Our previous interest in the synthesis of substituted biaryl compounds allowed access to a series of unsaturated furan derivatives. These compounds were synthesized using common procedures from the corresponding triphenyl phosphonium salt by Wittig reactions with commercially available furan aldehydes. In a typical experiment, the substrates (**3**–**5**) (Table 1) were hydrogenated in refluxing methanol/THF (2:1) in the presence of 10% Pd–C catalyst and excess amount of ammonium formate.

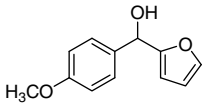
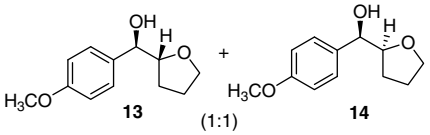
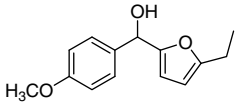
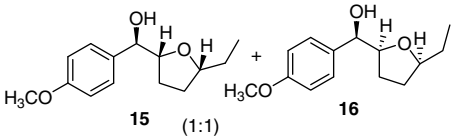
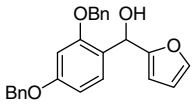
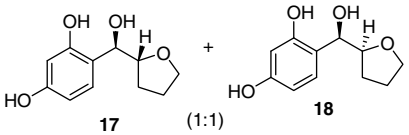
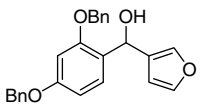
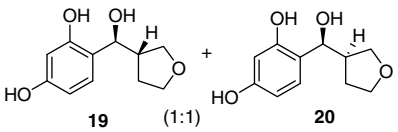
In all cases, we noticed that the reduction of carbon–carbon double bond and debenzylation was accompanied by the complete reduction of the hetero-aromatic furan to tetrahydrofuran ring. In the case of **4**, nitro group also reduced to corresponding amine.

Then, we extended our newly observed methodology to the reduction of substrates, **9**–**12,** which were obtained through Grignard addition reactions on the corresponding furaldehydes (Table 2).

As in the previous cases, the second series of compounds (Table 2, **9**–**12**) underwent smooth reductions, when exposed to 10% Pd–C catalyst and excess amount of ammonium formate at reflux. In all the cases, two diastereoisomers were obtained with the same ratio. The mixtures of diastereoisomers[12] (Table 2, **13** and **14**) were separated by careful column chromatography and the structure and stereochemistry was determined by a combination of high-field 1D and 2D NMR experiments. It is noteworthy that no dehydroxylation was observed in this condition.

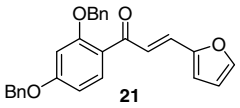
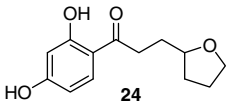
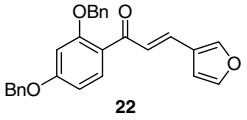
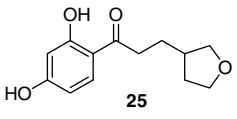
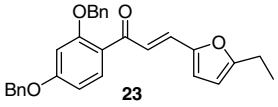
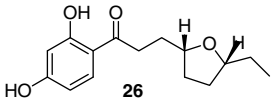
Furthermore, we extended the scope of this reagent to achieve the chemoselective reduction of α,β-unsaturated ketones. Different chalcone derivatives were selected as substrates (Table 3). Remarkable chemoselective carbon–

Table 2
Tetrahydrofuran synthesis

Substrate[a]	Product	Yield[b] (%)
 9	 13 (1:1) 14	85
 10	 15 (1:1) 16	78
 11	 17 (1:1) 18	79
 12	 19 (1:1) 20	75

[a] Substrates, **9**–**12**, were synthesized by Grignard addition reactions with the corresponding commercially available furaldehydes.
[b] Isolated yield after column purifications.

Table 3
Tetrahydrofuran synthesis

Substrate[a]	Product	Yield[b] (%)
 **21**	 **24**	83
 **22**	 **25**	88
 **23**	 **26**	79

Conditions: [a] Chalcone derivatives were synthesized by aldol condensation reaction following the known procedures with benzyl protected acetophenone and corresponding substituted furaldehyde.
[b] In all cases, yield was obtained after column purifications.

carbon double bond reductions along with complete reduction of furan ring were observed in all cases and sensitive functionalities like ketones were unaffected under this condition.[13]

In summary, the ammonium formate/Pd–C system proved to be very efficient and versatile for the one-step reduction of unsaturated furan derivatives to saturated tetrahydrofuran derivatives wherein the sensitive functional group such as the keto group remains intact. The reaction workup procedure was very simple and the products were easily obtained in excellent yield without the need for high pressure equipment and explosive hydrogen gas. Application of this newly developed methodology and the asymmetric version of this reaction are under active investigations.

Acknowledgments

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12. All the compounds gave satisfactory spectroscopic data. Data for the selected compounds are given below: **9**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.39–7.32 (m, 3H), 6.92–6.87 (m, 2H), 6.31 (dd, $J_1 = 2.1$ Hz, $J_2 = 3.3$ Hz, 1H), 6.11 (dt, $J_1 = 2.4$ Hz, $J_2 = 0.6$ Hz, 1H), 5.76 (s, 1H), 3.80 (s, 3H); **13**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.27 (d, $J = 8.1$ Hz, 2H), 6.86 (d, $J = 9.0$ Hz, 2H), 4.81 (d, $J = 2.1$ Hz, 1H), 4.05–3.95 (m, 1H), 3.91–3.83 (m, 1H), 3.82–3.71 (m, 4H), 2.85 (s, 1H), 1.90–1.70 (m, 3H), 1.70–1.51 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.128 (1C), 133.156 (1C), 127.519 (2C), 113.873 (2C), 83.418 (1C), 74.091(1C), 69.157 (1C), 55.446 (1C), 26.212 (1C), 25.338 (1C), **14**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.28 (d, $J = 8.7$ Hz, 2H), 6.86 (d, $J = 9.0$ Hz, 2H), 4.37 (d, $J = 7.5$ Hz, 1H), 4.03–3.92 (m, 1H), 3.92–3.81 (m, 1H), 3.81–3.71 (m, 4H), 3.17 (s, 1H), 1.92–1.70 (m, 2H), 1.70–1.49 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.524 (1C), 133.102 (1C), 128.420 (2C), 113.988 (2C), 83.780 (1C), 76.820 (1C), 68.619 (1C), 55.465 (1C), 28.154 (1C), 26.261 (1C).
13. Reduction of chalcone to saturated alcohol, see: (a) Andrade, C. K. Z.; Silvia, W. A. *Lett. Org. Chem.* **2006**, *3*, 39–41. Reduction of α,β-unsaturated ketones to saturated ketones, see: (b) Ahamed, N.; Lier, J. E. V. *J. Chem. Res.* **2006**, 584–585; (c) Berthold, H.; Schotten, T.; Hong, H. *Synthesis* **2002**, 1607–1610.