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# $Fe^{3+}$-Catalyzed transacetalization of 2-alkoxytetrahydrofurans with alcohols

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This work is dedicated to the memory of Professor Yoshihiko Ito

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**Abstract**—The transacetalization of 2-alkoxy-4-benzylidenetetrahydrofurans with alcohols proceeds smoothly with the aid of $Fe(ClO_4)_3$ catalyst. The catalyst reactivity is ordered as $Fe(ClO_4)_3 > Zn(ClO_4)_2 > Mg(ClO_4)_2$. The present transacetalization provides an entry for various 2-alkoxytetrahydrofurans, which have potential as anticancer agents.

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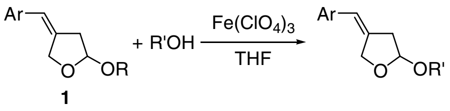
Iron catalysts in organic reactions have recently received much attention in view of their inexpensiveness and environmental friendliness.[1] Among iron salts such as $FeCl_3$, which are readily available as commercial sources, $Fe(ClO_4)_3$ is ranked as a powerful Lewis acid.[2] As for metallic perchlorates as catalysts or reagents, an explosive hazard with heating appears to be a common understanding. In spite of such a reputation,[3] these compounds are not explosive in solution, and frequently used in synthetic chemistry. For instance, not only $Fe(ClO_4)_3$ but also $Zn(ClO_4)_2$ and $Mg(ClO_4)_2$ have been shown to serve as Lewis acid catalysts in various organic transformations such as acylation of alcohols,[4] decarboxylative esterification of carboxylic acids,[5] condensation of β-ketoesters with amines,[6] and pyranylation and depyranylation of alcohols,[7] and protection of alcohols with $Boc_2O$ (*tert*-butyl dicarbonate).[8] Under such backgrounds, we report here the first systematic study of $Fe^{3+}$-catalyzed transacetalization with alcohols using 2-alkoxytetrahydrofurans **1** as the substrate (Scheme 1).

Recently, we have shown that 2-alkoxy-4-benzylidenetetrahydrofurans **1** can be readily prepared from vinyl ethers and cinnamyl alcohols with the aid of palladium(II) catalyst.[9] The 2-butoxy-4-benzylidenetetrahydrofuran (Ar = Ph, R = *n*-Bu) obtained has been found to exhibit apoptosis-inducing activity toward U937 human leukemia cell.[10] Thus, to survey their structure–activity relationship, we are engaged in the preparation of a series of 4-benzylidenetetrahydrofurans **1** bearing various 2-alkoxy groups. In line with such studies, we have found that $Fe(ClO_4)_3{\cdot}6H_2O$ serves as an effective catalyst for the transacetalization of 2-alkoxytetrahydrofurans **1** with alcohols (Scheme 1). Reported herein are the characteristics of this reaction. Undoubtedly, the present reaction provides an entry for various 2-alkoxytetrahydrofurans **1**, which have potential as anticancer agents.



**Scheme 1.**

For a survey of the reaction shown in Scheme 1, 2-ethoxy-4-benzylidenetetrahydrofuran (**1a**) was firstly allowed to react with benzyl alcohol in THF. The representative results are given in Table 1. Since the transacetalization is an equilibrium process, the use of excess benzyl alcohol (10-fold excess per **1a**) afforded **1b** in a relatively higher yield (81%) for 1 h (entries 1 and 2). However, we were pleased to find that the amount of benzyl alcohol was decreased down to 5-fold excess

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*Keywords*: Transacetalization; Ferric perchlorate; Tetrahydrofuran derivatives.

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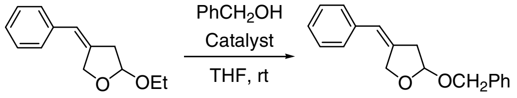
**Table 1.** Transacetalization of 2-ethoxy-4-benzylidenetetrahydrofuran (1a) with benzyl alcohol[a]



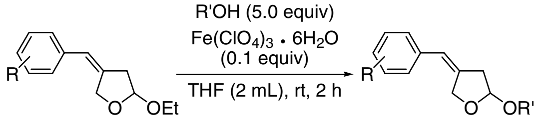
**1a** **1b**

| Entry | Catalyst |  | PhCH$_2$OH |  | Time (h) | Yield[b] (%) |
|---|---|---|---|---|---|---|
|  | (mmol) | (equiv) | (mmol) | (equiv) |  |  |
| *Fe(ClO$_4$)$_3$·6H$_2$O* |  |  |  |  |  |  |
| 1 | 0.05 | 0.1 | 0.5 | 1.0 | 1 | 47 |
| 2 | 0.05 | 0.1 | 5.0 | 10.0 | 1 | 81 |
| 3 | 0.05 | 0.1 | 2.5 | 5.0 | 0.5 | 68 |
| 4 | 0.05 | 0.1 | 2.5 | 5.0 | 1 | 69 |
| 5 | 0.05 | 0.1 | 2.5 | 5.0 | 2 | 79 |
| 6 | 0.05 | 0.1 | 2.5 | 5.0 | 3 | 63 |
| 7 | 0.10 | 0.2 | 2.5 | 5.0 | 1 | 77 |
| *Zn(ClO$_4$)$_2$·6H$_2$O* |  |  |  |  |  |  |
| 8 | 0.05 | 0.1 | 2.5 | 5.0 | 2 | 12 |
| *Mg(ClO$_4$)$_2$* |  |  |  |  |  |  |
| 9 | 0.05 | 0.1 | 2.5 | 5.0 | 2 | 0 |
| *PPTS (pyridinium p-toluenesulfonate)* |  |  |  |  |  |  |
| 10 | 0.05 | 0.1 | 2.5 | 5.0 | 2 | 0 |

[a] A solution of substrate **1a** (0.5 mmol) and benzyl alcohol in THF (2 ml) was added into 25 mL round bottomed flask containing catalyst, and the solution was stirred for 1–2 h.

[b] NMR yield with internal standard.

**Table 2.** Transacetalization of 2-ethoxytetrahydrofuran **1a** with various alcohols



**1a** R= H
(0.5 mmol)

**1c-l**
**2a, b**

| Entry | Product | R | R′ | Yield[a] (%) |
|---|---|---|---|---|
| 1 | **1c** | H | Me | 84 |
| 2 | **1d** | H | Oct | 68 |
| 3 | **1e** | H | *i*-Pr | 66 |
| 4 | **1f** | H | *t*-Bu | 0 |
| 5 | **1g** | H | CH$_2$CH$_2$OH | 73 |
| 6 | **1h** | NO$_2$ | CH$_2$CH$_2$Br | 85 |
| 7 | **1i** | H | Ph | 0 |
| 8 | **1j** | 4-NO$_2$ | Me | 80 |
| 9 | **1k** | 4-NO$_2$ | Oct | 71 |
| 10 | **1l** | 4-NO$_2$ | PhCH$_2$ | 64 |
| 11 | **2a** | H | H | 20 |
| 12 | **2a** | H | H | 40[c] |
| 13 | **2b** | 4-NO$_2$ | H | 38[c] |
| 14 | **2a** | H | H | 0[b] |
| 15[d] | **2a** | H | H | 55 |
| 16[d] | **2a** | H | H | 71[c] |

[a] NMR yield with internal standard.

[b] FeCl$_3$ (0.05 mmol) was used in place of Fe(ClO$_4$)$_3$·6H$_2$O.

[c] 1.0 equiv of Fe(ClO$_4$)$_3$·6H$_2$O and 20 equiv of H$_2$O were used.

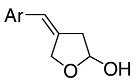
[d] (2*R**,2′*R**)-**3** was used as the substrate.

per **1a**, if the reaction time was prolonged to 2 h (entries 3–6). Namely, a 79% yield of **1b** was formed with 10 mol % catalyst and 5 equiv of benzyl alcohol in 2 h (entry 5). We have thus set these conditions as our standard.[11] Note that increasing the amount of catalyst from 10 to 20 mol % did not profoundly improve the yield of **1b** (entries 4 and 7).

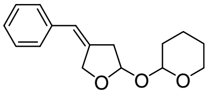
Under our standard condition, Zn(ClO$_4$)$_2$ afforded only 12% yield of **1b**, but no transacetalization took place with Mg(ClO$_4$)$_2$ catalyst (entries 8 and 9). These facts indicate that the Lewis acidity of M(ClO$_4$)$_n$ is ordered as shown below. Note that no reaction occurred with PPTS catalyst (entry 10).

$$\mathrm{Fe(ClO_4)_3} > \mathrm{Zn(ClO_4)_2} > \mathrm{Mg(ClO_4)_2}$$

Under our standard condition, the transacetalization proceeds smoothly with a wide range of alcohols such as methyl, octyl, and isopropyl alcohol (Table 2, entries 1–3), but no reaction occurred with bulky *t*-butyl alcohol (entry 4). Ethylene glycol and bromoethanol gave the corresponding hydroxyl and bromoethyl furanoacetal in good yields (entries 5 and 6). Unfortunately, no reaction took place with phenol (entry 7), probably because of its less nucleophilcity. The NO$_2$ substituent on the benzylic moiety gave no effect on the reaction (entries 8–10).

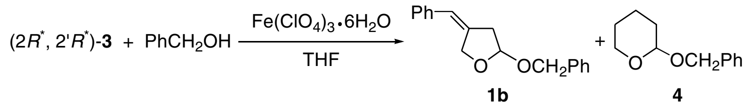


**2a**: Ar= Ph
**2b**: Ar= 4-NO$_2$-C$_6$H$_4$

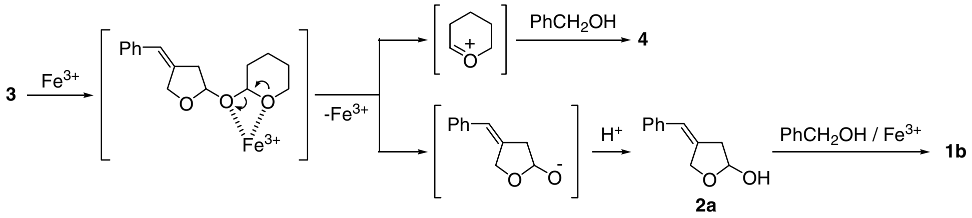


**3**

When H$_2$O was used as a nucleophile, 2-hydoxytetrahydrofuran **2a** or **b** was formed, but in lower yield (20%) (entry 11). The use of a large amount of Fe(ClO$_4$)$_3$ (100 mol %) and H$_2$O (20 equiv per **1a**) increased its yield up to 40% (entry 12). No reaction occurred with FeCl$_3$ catalyst (entry 14), probably because hydroscopic FeCl$_3$ is deactivated by water. For the preparation of 2-hydroxytetrahydrofuran **2a**, 2-pyranyloxytetrahydrofuran **3** was found to be a preferable substrate. Thus, treatment of (2*R**,2′*R**)-**3**[12] with H$_2$O under usual conditions produced **2a**[13] in 55% yield (entry 15). The use of a large amount of Fe(ClO$_4$)$_3$ (100 mol %) and water (20 equiv per **3**) increased its yield up to 71% (entry 16). Such susceptibility of **3** was also indicated by the transacetalization of (2*R**,2′*R**)-**3** with PhCH$_2$OH (5 equiv) which gave **1b** in higher yield (97% yield) under usual conditions (Scheme 2).[14] In this reaction, the pyranyl moiety was transformed into 2-benzyloxypyran **4** (~90%).[15,16] Since DFT calculation unambiguously shows that Fe$^{3+}$ preferably coordinates to the pyranyl acetal,[17] product **4** must be formed via pyranoxocarbenium ion as shown in Scheme 3. The process affords 2-hydroxytetrahydrofuran **2a**,[18] but the OH group in **2a** is then exchanged with PhCH$_2$OH to afford **1b**. A higher reactivity of the OH group in **2a** for the exchange was shown by a separate experiment.[19]



Scheme 2.



Scheme 3.

Morken and Dueñes have recently shown that 2-alkoxy-4-vinyl-tetrahydrofurans undergo facile Lewis acid catalyzed diastereoselective transacetalization with other nucleophiles such as allylsilane.[20] Combined with their success, our present results prove a synthetic mobility of acetal unit in **1**. In addition, we believe that the present method must contribute to the synthetic chemistry of furanoside and pyranoside acetals related to carbohydrates.

In summary, $Fe(ClO_4)_3$ serves as an effective catalyst for the transacetalization of 2-alkoxy-4-benzylidene-tetrahydrofurans **1** with various alcohols under mild conditions. In this reaction, water can be used as a nucleophile to give the corresponding 2-hydroxy-tetrahydrofurans **2**.

## References and notes

1. (a) Bolm, C.; Legros, J.; Le Paih, J.; Zani, L. *Chem. Rev.* **2004**, *104*, 6217–6254; (b) Diaz, D. D.; Miranda, P. O.; Padron, J. I.; Martin, V. S. *Curr. Org. Chem.* **2006**, *10*, 457–476.
2. (a) Salehi, P.; Iranpoor, N.; Behbahani, F. K. *Tetrahedron* **1998**, *54*, 943–948; (b) Pelzer, S.; Kauf, T.; van Wüllen, C.; Christoffers, J. *J. Organomet. Chem.* **2003**, *684*, 308–314.
3. It is reported that such a reputation is due to the mistaken association of metallic perchlorates with the oxidizing potential of perchloric acid and the pyrotechnic performances of $NH_4ClO_4$ (Bartoli, G.; Locatelli, M.; Melchiorre, P.; Sambri, L. *Eur. J. Org. Chem.* **2007**, 2037–2049, and also see: Bartoli, G.; Sambri, L.; Locatelli, M. *J. Fudan University, Natl. Sci.* **2005**, *44*, 650–651).
4. Bartoli, G.; Bosco, M.; Dalpozzo, R.; Marcantoni, E.; Massaccesi, M.; Sambri, L. *Eur. J. Org. Chem.* **2003**, 4611–4617.
5. (a) Gooßen, L.; Döhring, A. *Adv. Synth. Catal.* **2003**, *345*, 943–947; As for simple esterification of carboxylic acids, see: (b) Bartoli, G.; Boeglin, J.; Bosco, M.; Locatelli, M.; Massaccesi, M.; Melchiorre, P.; Sambri, L. *Adv. Synth. Catal.* **2005**, *347*, 33–38.
6. Bartoli, G.; Bosco, M.; Locatelli, M.; Marcantoni, E.; Melchiorre, P.; Sambri, L. *Synlett* **2004**, 239–242.
7. Heravi, M. M.; Behbahani, F. K.; Oskooie, H. A.; Shoar, R. H. *Tetrahedron Lett.* **2005**, *46*, 2543–2545.
8. Bartoli, G.; Bosco, M.; Locatelli, M.; Marcantoni, E.; Melchiorre, P.; Sambri, L. *Org. Lett.* **2005**, *7*, 427–430.
9. (a) Minami, K.; Kawamura, Y.; Koga, K.; Hosokawa, T. *Org. Lett.* **2005**, *7*, 5689–5692; (b) Kawamura, Y.; Imai, T.; Hosokawa, T. *Synlett* **2006**, 3110–3114.
10. Hosokawa, T.; Sazuka, M.; Minami, K.; Kawamura, Y. Unpublished result.
11. $Fe(ClO_4)_3 \cdot 6H_2O$ (22.8 mg, 0.05 mmol) was placed in a 25 mL side-armed round bottomed flask under Ar, and a solution of (*Z*)-4-benzylidene-2-ethoxytetrahydrofuran (**1a**) (102 mg, 0.5 mmol) and benzyl alcohol (0.25 mL, 2.5 mmol) in THF (2.0 mL) was added. After the reaction mixture was stirred for 2 h at room temperature, the mixture was filtered through silica gel column (15 mm × 60 mm 5 g, diethyl ether 100 mL), and the solvent was evaporated under reduced pressure to give **1b** with unreacted benzyl alcohol and **1a**. The yield of **1b** was determined to be 79% by NMR from this mixture. In a separate experiment, isolation of **1b** was performed by Kugelrohr distillation (40–80 °C/5 mm Hg), which afforded pure **1b** (80 mg, 0.3 mmol) in 60% yield. **1b**: $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 2.78 (dm, $J = 16.4$ Hz, 1H), 2.95 (dm, $J = 16.4$ Hz, 1H), 4.54 (d, $J = 12.0$ Hz, 1H), 4.72–4.74 (m, 2H), 4.75 (d, $J = 12.0$ Hz, 1H), 5.31 (d, $J = 4.8$ Hz, 1H), 6.41–6.44 (m, 1H), 7.13 (d, $J = 7.5$ Hz, 2H), 7.21 (t, $J = 7.5$ Hz, 1H), 7.26–7.36 (m, 5H), 7.33 (t, $J = 7.5$ Hz, 2 H); $^{13}C$ NMR (101 MHz, $CDCl_3$): $\delta$ 41.06, 68.08, 68.69, 101.34, 121.69, 126.48, 127.58, 127.81, 127.92, 128.37, 128.44, 137.33, 137.94, 138.81; FTIR (KBr, $cm^{-1}$): 3048, 2913, 2863, 1595, 1491, 1448, 1421, 1364, 1258, 1199, 1166, 1076, 1037, 1008, 993, 969, 755; GCMS *m/z*: 266 ($M^+$).
12. 2-Pyranoxytetrahydrofurans **3** were prepared from commercially available 2-vinyloxytetrahydropyran and cinnamyl alcohol by using palladium(II) catalyst, and the diastereomers of ($2R^*,2'R^*$) and ($2R^*,2'S^*$)-**3** were separated by TLC, as reported previously see: Ref. 9a.
13. Compound **2a**: $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 2.73 (dm, $J = 16.3$ Hz, 1 H), 2.81 (br s, 1H), 2.96 (dm, $J = 16.3$ Hz, 1H), 4.71 (dq, $J = 13.8$, 2.1 Hz, 1H), 4.82 (dm, $J = 13.8$ Hz, 1H), 5.63 (dd, $J = 4.8$, 2.5 Hz, 1H), 6.45–6.49 (m, 1H), 7.13 (d, $J = 7.5$ Hz, 2H), 7.21 (t, $J = 7.5$ Hz, 1H), 7.34 (t, $J = 7.5$ Hz, 2H); $^{13}C$ NMR (101 MHz, $CDCl_3$): $\delta$ 41.84, 68.18, 96.93, 122.31, 126.64, 127.86, 128.48, 137.15, 138.17; GCMS *m/z*: 190 ($M^+$).
14. The essentially same result was obtained even by using a mixture of ($2R^*,2'R^*$) and ($2R^*,2'S^*$)-**3** (87:13).

15. Examples for cleavage of pyranyl ethers see: (a) Habibi, M. H.; Tangestaninejad, S.; Mohammadpoor-Baltork, I.; Mirkhani, V.; Yadollahi, B. *Tetrahedron Lett.* **2001**, *42*, 2851–2853; (b) Khan, A. T.; Choudhury, L. H.; Ghosh, S. *Tetrahedron Lett.* **2004**, *45*, 7891–7894; (c) Davis, K. J.; Bhalerao, U. T.; Rao, B. V. *Synthetic Commun.* **2000**, *30*, 2301–2308.
16. The use of other solvents such as toluene gave **1b** in comparable yields, indicating that the reaction is not affected by solvent polarity.
17. Since X-ray structure of (2$R^*$, 2′$R^*$)-**3** was already revealed by us (Ref. 9a), its geometrical optimization by 6-31G*/B3LYP was done on the basis of its geometry. Toward the optimized structure deduced, $Fe^{3+}$ was allowed to coordinate at either the pyranyl or furanyl acetal moiety, and further optimization was made by 3-21G/B3LYP. As a result, only the former case led to the optimization of the stabilized conformer.
18. At the early stage of the reaction, the formation of a small amount of **2a** was observed by NMR.
19. The reaction of **2a** with $PhCH_2OH$ (5 equiv) in the presence of $Fe(ClO_4)_3$ (10 mol %) in THF for 10 min gave **1b** in ~90% yield.
20. Dueñes, R. A.; Morken, J. P. *Synlett* **2007**, 587–590.