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ORIGINAL PAPER

Ferric perchlorate as an efficient and useful catalyst for the selective benzylation and methylation of alcohols with benzyl chloride and methyl iodide

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Abstract A mild and efficient method was developed for selective benzylation and methylation of hydroxyl compounds in the presence of a catalytic amount of ferric perchlorate. We showed that ferric perchlorate was very effective in selectively promoting the benzylation and methylation of primary aliphatic and benzylic alcohols versus secondary aliphatic alcohols and phenolic hydroxy groups.

Keywords Benzylation · Hydroxy compounds · Alcohols · Ferric perchlorate · Etherification · Methylation

Introduction

Hydroxyl groups are present in a number of compounds of biological and synthetic interest, including nucleosides, carbohydrates, steroids, macrolides, polyethers, and the side chain of some amino acids. In some oxidation reactions, such as acylation, halogenation with phosphorus, hydrogen halides, or dehydration of these compounds, a hydroxyl group must be protected. In polyfunctional molecules, selective protection becomes an issue that has been addressed by the development of a number of new methods. Ethers are among the most used protective groups in organic synthesis and vary from the simplest, the most stable methyl ether to the more elaborate, substituted trityl ethers developed for use in nucleotide synthesis. Ethers are formed and removed under a wide variety of conditions. There have been many reports on the formation of the ether linkage, but a few are presented from hydroxyl compounds and halides [1]. Numerous methods are available for protecting an alcohol moiety. Conversion into corresponding ethers has been recognized as a common and useful method for the protection of hydroxyl groups. Most commonly used protecting groups are the tetrahydropyranyl (THP), *t*-butyldimethylsilyl (TBDMS), and benzyl (Bn) groups. Benzyl ethers are widely utilized as alcohol protecting groups. They are easily installed, but with poor selectivity between primary and secondary alcohol groups [2, 3], e.g., in carbohydrates, are stable to a wide range of reagents, and are readily removed in the presence of many common functionalities via catalytic hydrogenolysis, dissolving metals, or Lewis/Brønsted acids [4]. In other words, selectivity of reaction pathways is extremely important in organic reactions, such as etherification [5–7].

Recently, we have reported etherification of allylic and benzylic alcohols with aliphatic alcohols in the presence of ferric perchlorate [8] and the ability of ferric perchlorate as a catalyst for some kinds of transformations in organic synthesis [9–12]. In continuation of our works to develop new synthetic methodologies [13–23], we wish to report an effective, inexpensive, and selective benzylation and methylation of hydroxyl groups using ferric perchlorate (Scheme 1).

Results and discussion

Initially, a systematic study was carried out for catalytic evaluation of ferric perchlorate for benzylation and

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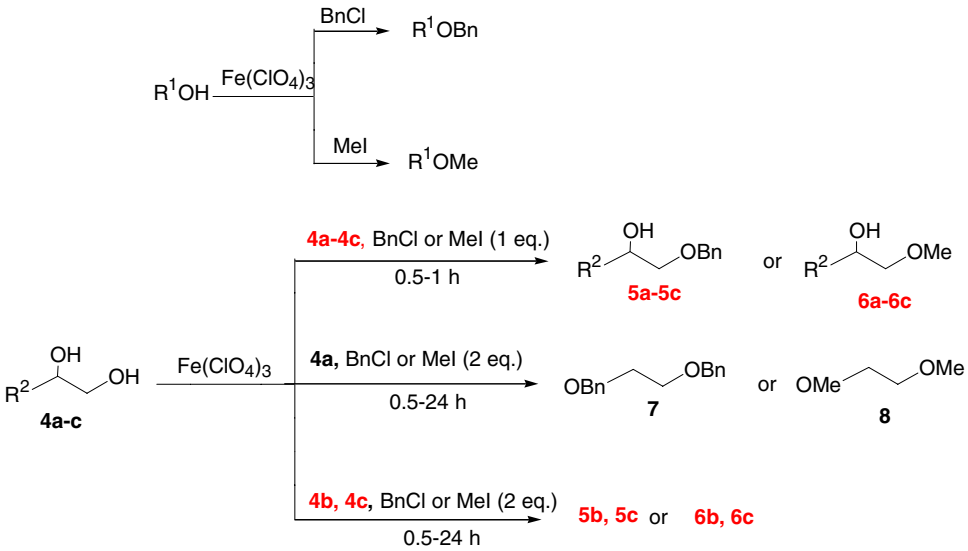
Scheme 1



methylation of benzyl alcohol with benzyl chloride and methyl iodide without catalyst. These reactions did not proceed at all.

When a mixture of the benzyl alcohol and the benzyl chloride is heated at 100 °C in the presence of catalytic amount 5 mol% of ferric perchlorate, evolution of hydrogen halide occurred immediately, and a high yield (90%) of the corresponding ether was obtained (entry 1, Table 1). The high yields of the products, solvent-free and simple reaction procedure make this method attractive for the syntheses of benzylic ethers.

We also found that a catalytic amount of ferric perchlorate (5 mol%) is able to promote quantitative methylation of alcohols using methyl iodide at room temperature, without solvent and in dichloromethane (entries 3, 4, 6; Table 2) in high yields.

However, most of the alcohols studied here were converted into their corresponding alkylation of alcohols in good yields using this catalyst. Etherification was completed within 25–120 min (Tables 1, 2).

In the presence of our system catalyst, phenolic hydroxy groups did not react at all. When cyclic secondary alcohols, such as cyclohexanol, were reacted with benzyl chloride, the expected benzylic ethers were formed. In the end, benzylic ethers on primary alcohol groups were selectively formed from dihydroxy alcohols. It is noteworthy that, when the benzylation and methylation reactions were carried out with an excess of halide, the same ether products were synthesized (Scheme 1, Table 2).

A plausible mechanism for this transformation is shown in Scheme 2. In view of this, ferric perchlorate-activated methyl iodide and then the alcohol oxygen lone pair attack the activated methyl, followed by abstraction of the proton providing the methyl ether (Scheme 2a). The same mechanism is suggested for benzylation of alcohols. In this case, it is possible that the stable benzyl cation is formed, and then the alcohol is collapsed by the benzyl cation yielding the benzyl ether (Scheme 2b).

Conclusion

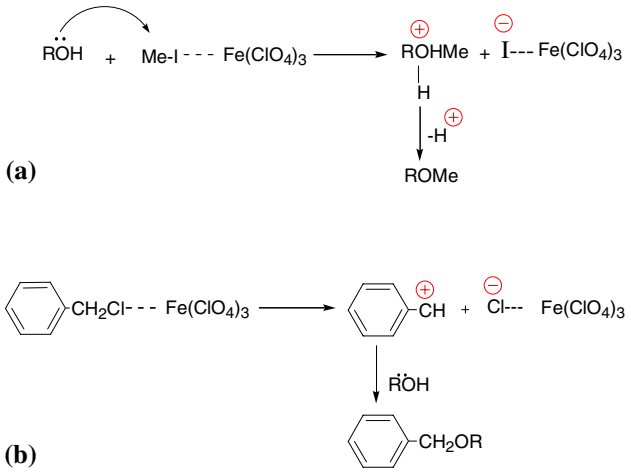
Ferric perchlorate acts as an efficient catalyst for the alkylation of alcohols with benzyl and methyl halides. The significant features of this method include operational simplicity, inexpensive reagents, no need for any additive to promote the reaction, high yields of products, and the use of relatively non-toxic reagents and solvents.

Table 1 Benzylation and methylation of alcohols **1a–j** with benzyl chloride and methyl iodide

Alcohol **1**	Time/min (2x)	BnCl ether (yield%) **2×**	Time/min (2×)	MeI Ether (yield%) **3×**
BnOH (**1a**)	60	BnOBn **2a** (90)	60	BnOMe **3a** (90)
2-$ClC_6H_4CH_2OH$ (**1b**)	60	2-$ClC_6H_4CH_2OBn$ **2b** (91)	120	2-$ClC_6H_4CH_2OMe$ **3b** (91)
4-$MeOC_6H_4CH_2OH$ (**1c**)	30	4-$MeOC_6H_4CH_2OBn$ **2c** (89)	45	4-$MeOC_6H_4CH_2OMe$ **3c** (93)
4-$MeC_6H_4CH_2OH$ (**1d**)	30	4-$MeC_6H_4CH_2OBn$ **2d** (91)	60	4-$MeC_6H_4CH_2OMe$ **3d** (88)
Me_3COH (**1j**)	120	Me_3COBn **2j** (89)	120	Me_3COMe **3j** (82)

Table 2 Benzylation and methylation of glycols **4a–c** with one or two equivalents of benzyl chloride and methyl iodide

Glycol **4**	Time (h)	BnCl ether (yield%) **5**× and **7**×	Time (h)	MeI ether (yield%) 6× and 8×
Using 1 equiv. of BnCl or MeI				
$HO(CH_2)_2OH$ (**4a**)	0.5	$HO(CH_2)_2OBn$ **5a** (92)	1.5	$HO(CH_2)_2OMe$ **6a** (88)
$MeCH(OH)CH_2OH$ (**4b**)	1.0	$MeCH(OH)CH_2OBn$ **5b** (84)	1.2	$MeCH(OH)CH_2OMe$ **6b** (83)
n-$PrCH(OH)CH_2OH$ (**4c**)	0.5	*n*-$PrCH(OH)CH_2OBn$ **4c** (85)	1.2	*n*-$PrCH(OH)CH_2OMe$ **6c** (91)
Using 2 equiv. of BnCl or MeI				
$HO(CH_2)_2OH$ (**4a**)	0.5	$BnO(CH_2)_2OBn$ **7** (90)	1.5	$MeO(CH_2)_2OMe$ **8** (90)
$MeCH(OH)CH_2OH$ (**4b**)	24	$MeCH(OH)CH_2OBn$ **5b** (82)	24	$MeCH(OH)CH_2OMe$ **6b** (85)
n-$PrCH(OH)CH_2OH$ (**4c**)	24	*n*-$PrCH(OH)CH_2OBn$ **4c** (87)	24	*n*-$PrCH(OH)CH_2OMe$ **6c** (90)



Scheme 2

Experimental

Preparation of benzyl ethers with ferric perchlorate: general procedure

Benzyl chloride (1 mmol), 1 mmol alcohol, and 25 mg $Fe(ClO_4)_3$ (0.05 mmol) were mixed in a one neck flask at 100 °C for 0.5–2.0 h (Table 1). The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was diluted with 10 cm^3 H_2O, and 10 cm^3 CH_2Cl_2 was added to the reaction mixture. The organic layer was concentrated, and the product was purified by short-column chromatography to give the benzyl ether in high yield. The identity of the products was consistent with the data reported previously [24].

To document the applicability of ferric perchlorate for large-scale preparations, we set up a reaction with 4.32 g benzyl alcohol (40 mmol), 4.6 cm^3 benzyl chloride (40 mmol), and 1.0 g $Fe(ClO_4)_3$ (2.0 mmol) in a round flask, and then stirred and heated it for 1.0 h under reflux condition. The reaction was carried out without explosion or fire. Thus, $Fe(ClO_4)_3$ could be used for the benzylation of alcohols under solvent-free and reflux conditions, even in large amounts.

Preparation of methyl ethers with ferric perchlorate: general procedure

This was done as in the above procedure, but these reactions were completed at room temperature and entries 3, 4, and 6 were carried out in CH_2Cl_2.

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