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Regioselective demethylation of 2,6-dimethoxybenzaldehydes with magnesium iodide etherate

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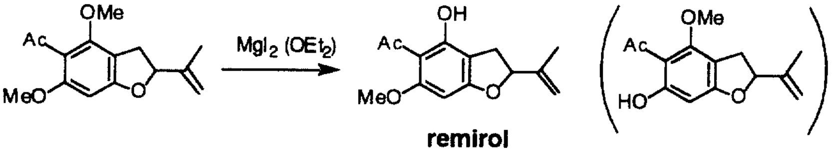
Abstract

Demethylation of asymmetically substituted 2,6-dimethoxybenzaldehydes with magnesium iodide etherate regioselectively single 6-methoxysalicylaldehydes derived from the more unstable chelation. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: deblocking; magnesium; magnesium compounds; phenols; regiocontrol.

Magnesium iodide etherate is a mild reagent for the demethylation on a phenolic *O*-methyl group especially at the position *ortho* to the carbonyl group.[1] In our previous paper,[2] demethylation of 5-acetyl-4,6-dimethoxy-2-isopropenyl-2,3-dihydrobenzofuran, having two *O*-methyl groups at both *ortho* positions to the carbonyl, gave a single mono-demethylated product (racemic remirol). Herein, we discuss this regioselective demethylation.



remirol

Demethylation of two symmetric 2,6-dimethoxybenzaldehydes (**1a**,**b**) and four asymmetric 2,6-dimethoxybenzaldehydes (**1c**–**e**) with magnesium iodide etherate effectively gave single 6-methoxysalicylaldehydes (**2a**–**e**), these results are summarized in Table 1. Interestingly, in NOE measurements of the products, irradiation on the methoxy signal caused some increases (+13% in **2c**, +7% in **2d**, +13% in **2e**) in the aromatic proton signals, and these showed the regioselective demethylation on the more hindered *O*-methyl groups.

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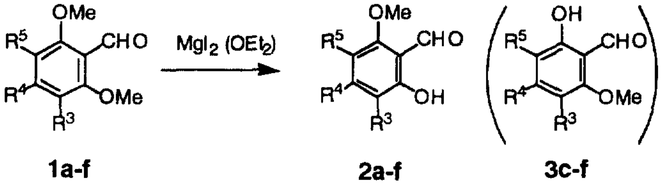
Table 1
Demethylation of 2,6-dimethoxybenzaldehydes **1** with magnesium iodide etherate[5]

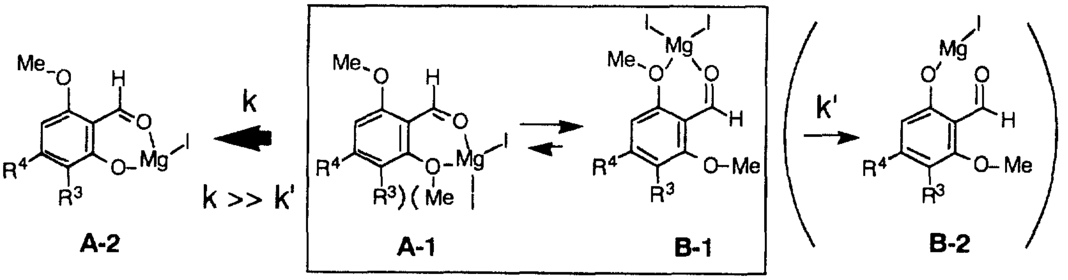
2,6-Dimethoxybenzaldehyde **1**	Reaction Time (h)	Yield of 6-Methoxysalicylaldehyde (%)
1a	1.5	**2a** (70)[6]
1b	1.5	**2b** (63)[7]
1c	4.5	**2c** (84)[4]
1d	3.5	**2d** (94)
1e	4.5	**2e** (68)[6]
1f	3.0	**2f** (90)



a) R^3 = H, R^4 = Me, R^5 = H
b) R^3 = H, R^4 = Pent, R^5 = H
c) R^3 = Me, R^4 = H, R^5 = H
d) R^3 = Cl, R^4 = H, R^5 = H
e) R^3 = Cl, R^4 = Me, R^5 = H
f) R^3 = Cl, R^4 = H, R^5 = Me

Demethylation of asymmetric 3-chloro-2,6-dimethoxy-5-methylbenzaldehyde (**1f**) also gave a single salicylaldehyde, 3-chloro-6-methoxy-5-methylsalicylaldehyde (**2f**), derived from the demethylation on the chloro-side, not 5-chloro-6-methoxy-3-methylsalicylaldehyde (**3f**) derived from the demethylation on the methyl-side. The structure of **2f** was determined by comparing it with the authentic samples **2f** and **3f**.[3]

This regioselectivity might be explained as follows. Each 2,6-dimethoxybenzaldehyde can form an equilibrium of two chelation isomers, unstable A-1 and stable B-1. In the subsequent thermal elimination of methyl iodide (might be a rate-determining step), the elimination may be kinetically more favored from the unstable isomer A-1 than from the stable B-1, via the lower activation. In any case, the demethylation from the isomer, destabilized by steric or electrostatic repulsion, might be kinetically favored.



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2. Yamaguchi, S.; Takai, M.; Hanazome, I.; Okada, Y.; Kawase, Y. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 3603.
3. Compounds **2g** and **3g** were prepared by chlorination of corresponding salicylaldehydes with sulfuryl chloride, and these details will be reported soon in our synthetic study on mycochromenic acid.
4. Details will be reported soon in our synthetic study on mycochromenic acid.

5. General procedure for demethylation: To a benzene solution of magnesium iodide etherate, prepared from magnesium metal (102 mg, 3.99 mmol), iodine (936 mg, 3.62 mmol), ether (6 ml), and benzene (10 ml), was added a solution of 2,6-dimethoxybenzaldehyde (3 mmol) in benzene (30 ml); the mixture was refluxed, treated with 10% hydrochloric acid, and extracted with benzene, and the product was purified on a silica gel column.
6. Details will be reported soon in our synthetic study on cannabiorcichromenic acid.
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