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Utilization of 1-Methanesulfonyloxy-6-trifluoromethylbenzotriazole (FMS) as a Coupling Agent for the Esterification of Dihydropyridine-3-Carboxylic Acid

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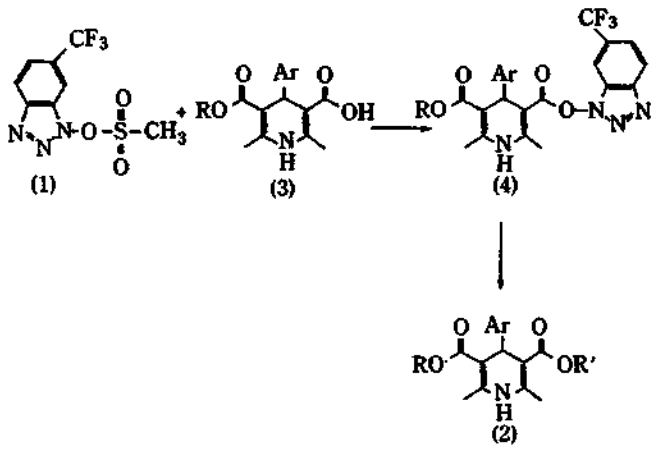
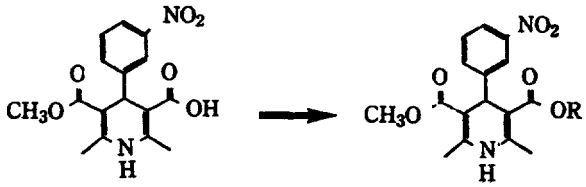
It has been reported that 1-methanesulfonyloxy-6-trifluoromethylbenzotriazole(FMS)(**1**) is the effective coupler for acylation[1]. Now we found that FMS is also effective for esterification of dihydropyridine derivatives(**2**) which are widely used as calcium channel blocker. For the preparation of the dihydropyridine di-ester derivatives the well-known Hantsch reaction is generally applied[2]. On the other hand reactions on the mono-acid intermediate(**3**), which is resolvable, are intensively investigated in order to prepare stereochemically pure compound. In this case the acid chloride[3] and the other acid activating agents were used somewhere[4], but using the FMS instead is not reported yet. We found that this reaction is a neat and economic procedure specially for the industrial purpose. The typical procedure is followed: to the solution of the acid(**3**) and 1 eq. of triethylamine in DMF was added FMS at 0 °C and stirred for 40 min to give the 6-trifluoromethylbenzotriazole(FOBT) intermediate(**4**) in 90% yield. This FOBT intermediate is easily separable if needed by column chromatography (eluted with toluene: ethyl acetate = 7:3) and is very stable in the air at room temperature, no decomposed product was detected over 3 months. The addition of 1.5 eq. of the alcohol to the DMF solution of this intermediate and the subsequent stirring at 60 °C for 2 hr gave the desired product in 80-100% yield (Table 1)[5]. The organic base was not necessary with the simple alkyl alcohols but with the aryl or long chain alcohols 1 eq. of triethylamine or 4-dimethylaminopyridine(DMAP) should be added. DMAP gave the better results compared to triethylamine. The FOBT intermediate can be used with or without isolation and no differences were found in the point of yield. Satisfactory analytical data and NMR spectra were obtained for the compounds.



(1) (3) (4) (2)

Table 1. Reactons with FMS



	R	Yields
1	$-CH_2CH_3$	90%
2	$-CH_2CH_2OCH_3$	95%
3	$-CH(CH_3)_2$	95%
4	$-(CH_2)_9CH_3$[a]	80%
5	$-CH_2CH_2N(CH_3)CH_2Ph$[b]	85%
6	-cyclohexyl[a]	80%
7	$-CH_2Ph$[b]	100%
8	-Ph[b]	95%

[a] 1 eq. of triethylamine added. [b] 1 eq. of DMAP added.

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5. Preparation of Methyl Isopropyl 2,6-dimethyl-4-(3'-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate. 5-Methoxycarbonyl-2,6-dimethyl-4-(3'-nitrophenyl)-1,4-dihydropyridine-3-carboxylic acid (325mg, 1mmol) and triethylamine (0.14m*l*, 1mmol) was stirred in DMF (5ml) for 10 min 1-Methansulfonyloxy-6-trifluoromethylbenzotriazole (FMS) (338mg, 1.2mmol) was added into the solution at 0 °C and stirred. After 30 min isopropyl alcohol (0.12m*l* 1.5mmol) was added and warmed up to 60 °C with stirring for 2hr [FOBT intermediate, m.p. = 189-190 °C, nmr ($CDCl_3$): 2.43(s, 3H), 2.45(s, 3H), 3.67(s, 3H), 5.40(s, 1H), 6.75(b, 1H), 7.05-8.25(m, 7H). The reaction mixture was poured into 100m*l* of water and extracted with methylene chloride. The extract concentrated and the residue was chromatographed on silica gel eluted with toluene: ethyl acetate = 7:3 mixture (87% yield, m.p. = 130-133 °C).

Reducing Characteristics of 4-(Borane-dimethylamino)pyridine. Chemoselective Reduction of Aldehydes in the Presence of Ketones

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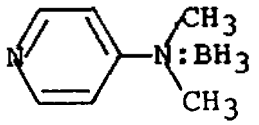
Tertiary amine-borane and pyridine-borane complexes react with aldehydes and ketones sluggishly at an elevated temperature with transferring only one of the three available hydride equivalents.[1] Therefore, they failed to gain widespread use in synthetic applications in spite of their high stability and good solubility in protic and aprotic solvents, although most amine-borane complexes as hydride reducing agents have been known for a long time.[1]

Since 4-dimethylaminopyridine (DMAP),[2] a highly active acylation catalyst, is expected to coordinate less tightly with borane than pyridine, the ability of hydride transfer in 4-(borane-dimethylamino)pyridine would be greater than that in pyridine-borane complex. Although 4-(borane-dimethylamino)pyridine is commercially available,[3] as far as we are aware, there are no reports on the reducing property of the present reagent. Thus, we have briefly investigated its reducing property.

4-(Borane-dimethylamino)pyridine was easily prepared by mixing equimolar amounts of borane-dimethyl sulfide complex and DMAP in ether at room temperature and the desired product was precipitated as white solids. The reagent was soluble in dichloromethane and acetonitrile but insoluble in ether, tetrahydrofuran, ethanol, and water. Furthermore, the reagent was stable under nitrogen at room temperature for several months, whereas it readily decomposed in acidic aqueous solution with evolution of hydrogen gas.



Reduction of acetophenone with equimolar amounts of the reagent in dichloromethane occurred only to an observable extent, yielding 4% of α-methyl benzyl alcohol at room temperature for 24 h, whereas nonyl aldehyde was reduced to nonyl alcohol in 92% yield under the similar condition.

Table 1. Selective Reduction of Aldehydes in the Presence of Ketones with 4-(Borane-dimethylamino)pyridine[a]

Starting mixture	% Reduction[b]
Nonyl aldehyde	95
Acetophenone	3
Nonyl aldehyde	98
Diisopropyl ketone	2
Nonyl aldehyde	98
3-Pentanone	10
Nonyl aldehyde	94
2-Undecanone	8
Nonyl aldehyde	96
Isophorone	0
Nonyl aldehyde	94
Carvone	2
Nonyl aldehyde	95
Mesityl oxide	2
Benzaldehyde	94
2-Undecanone	5
Butyraldehyde	87
Cyclohexanone	48

[a] The reaction was carried out with an equal mixture of the aldehyde, the ketone, and the reagent in dichloromethane at room temperature for 24 h. [b] Determined by GLC using an internal standard.

Therefore, we turned our attention to the possibility of chemoselective reduction of aldehydes in the presence of ketones.[4] The reaction of an equimolar mixture of nonyl aldehyde and acetophenone with 1 equiv of the reagent at room temperature for 24 h afforded a 95% reduction of nonyl aldehyde along with a 3% reduction of acetophenone. The change of solvent to acetonitrile and the use of 2 equiv of the reagent did not show appreciable enhancement of chemoselectivity