N-(Arylmethyl)-2-(or -4)-cyanopyridinium Hexafluoroantimonates as New Useful Catalysts for Acetalization of Carbonyl Compounds

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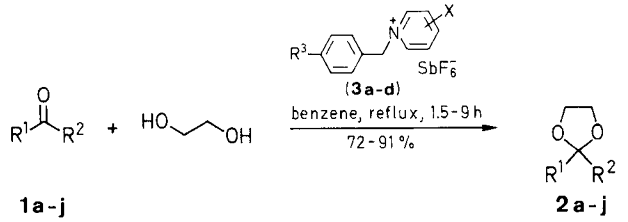
Carbonyl compounds **1** were converted to the corresponding 1,3-dioxolanes **2** and 1,3-dioxanes **4** with ethylene glycol and 2,2-dimethyl-1,3-propandiol, respectively, in the presence of 1-3 mol% of *N*-(benzyl, 4-methylbenzyl or 4-methoxybenzyl)-2(or -4)-cyanopyridinium hexafluoroantimonates **3**. The catalyst **3d** was also effective for the tetrahydropyranylation.

The carbonyl group is one of the most versatile functional groups in organic chemistry and a great deal of synthetic work has been performed on the protection and masking of the carbonyl compounds. The most convenient and practical methods for the syntheses of acetals from aldehydes and ketones are to react carbonyl compounds with diols such as ethylene glycol in the presence of an appropriate acid catalyst with azeotropic removal of water formed.[1] *p*-Toluenesulfonic acid (TsOH) is usually used as an acid catalyst,[2,3] while pyridinium salt type catalysts such as pyridinium *p*-toluenesulfonate is one of the milder catalyst[4] for use with acid-sensitive carbonyl compounds. Generally, the catalysts used for acetalization are not easy to handle due to their hygroscopicity, and therefore must be protected from moisture.

Recently, we have developed a new class of acid catalysts, *N*-benzylpyridinium salts which are characterized by their ease of synthesis and handling due to their reduced hygroscopicity and their chemical stability toward air, water, and organic solvents (e.g. they can be recrystallized from methanol).[5-7] We report here on the use of *N*-benzylpyridinium salts as catalysts for the acetalization of carbonyl compounds with ethylene glycol and 2,2-dimethyl-1,3-propanediol and also for the tetrahydropyranylation of alcohols.



1-2	R^1	R^2	1-2	R^1	R^2
a	Ph	H	**f**	$-(CH_2)_4CH(CH_3)-$	
b	C_5H_{11}	H	**g**	Ph	Me
c	Bu	Me	**h**	Ph	Ph
d	CH_2Ph	CH_2Ph	**i**	CH_2CO_2Me	Me
e	$-(CH_2)_5-$		**j**	$(CH_2)_2CO_2Et$	Me

3	R^3	X
a	H	4-CN
b	Me	4-CN
c	Me	2-CN
d	MeO	2-CN

First, the catalytic activity of some representative *N*-benzylpyridinium salts **3**[5-7] was tested by reacting benzaldehyde with two equivalents ethylene glycol in benzene in the presence of 1 mol% of **3**. All the pyridinium salts **3** used converted benzaldehyde to 2-phenyl-1,3-dioxolane (**2a**) in high yields as shown in Table 1. The order of the activity was **3d** > **3c** > **3b** > **3a**. Thus, **3d** was selected as the most active catalyst and the acetalization of several representative carbonyl compounds by using **3d** was carried out.

As shown in Table 1, aldehydes and ketones were easily converted to the corresponding 1,3-dioxolanes **2** in high yields with 1–3 mol% of **3d**. Sterically hindered 2-methylcyclohexanone also reacted with ethylene glycol to afford the corresponding spirocyclic acetal in high yield. In the cases of alkyl aryl and diaryl ketones, the acetalization was sluggish, although the yield was very good. Benzophenone was also converted to 2,2-diphenyl-1,3-dioxolane (**2h**) in 85% yield. In this case it is demonstrated that the acetalization activity of **3d** is almost the same as that of *p*-toluenesulfonic acid. Acid-sensitive carbonyl compounds, **1i** and **1j**, were also converted to the corresponding 1,3-dioxolanes **2i** and **2j** in 87 and 88% yields, respectively.

Table 1. Acetalization of Carbonyl Compounds **1** with Ethylene Glycol to 1,3-Dioxolanes **2** in the Presence of Catalyst **3**

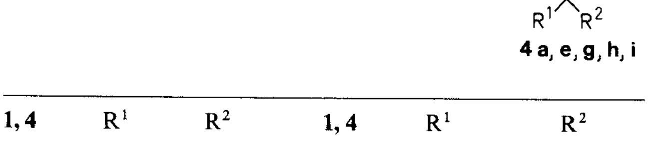
Product	Catalyst[a]	Reaction Time (h)	Yield[b] (%)	mp (°C) or bp (°C)/Torr	
				found	reported
2a	**3a**	5	84	99/8.5	101/10[2]
	3b	5	88	99/8.5	
	3c	2	85	109/15	
	3d	2	89	95/7	
2b	**3d**	3.5	77	83/30	177/760[9]
2c	**3d**	3	72	83/65	62–63/20[10]
2d	**3d**	1.5	83	68	69[2]
2e	**3d**	3.5	82	91/44	65/10[2]
2f	**3d**	7.7	91	98/40	82/15[2]
2g	**3a**	6	0	–	–
	3b	12	0	–	–
	3c	6.6	77	61	61[11]
	3d	4	88	61	
2h[c]	**3d**	9.5	85	100/0.12	168/10[2]
	TsOH	8.5	82	123/1	
2i[d]	**3d**	1.5	88	89/12	36–38/0.75[11]
2j[d]	**3d**	2.5	87	96–97.5/7	106–107/13[12]

[a] 1 Mol % of catalyst based on the carbonyl compounds was used.

[b] Isolated yields by distillation or recrystallization (MeOH).

[c] 3 Mol % of catalyst was used.

[d] Washed with sat. aq $NaHCO_3$ solution in workup.



1, 4	R^1	R^2	1, 4	R^1	R^2
a	Ph	H	**h**	Ph	Ph
e	$-(CH_2)_5-$		**i**	CH_2CO_2Me	Me
g	Ph	Me			

A few carbonyl compounds were also acetalized to the corresponding 5,5-dimethyl-1,3-dioxanes **4** with 2,2-dimethyl-1,3-propanediol in the presence of 1–3 mol% of **3d**. Results of Table 2 demonstrate that **3d** effectively catalyzes the acetalization to give high yields of various 1,3-dioxanes **4** in refluxing toluene.

Table 2. Acetalization of Carbonyl Compound with 2,2-Dimethyl-1,3-propanediol to 5,5-Dimethyl-1,3-dioxanes **5** with **3d** as Catalyst[a]

Product	Reaction Time (h)	Yield[b] (%)	mp (°C) or bp (°C)/Torr	Molecular Formula[c] or Lit. mp (°C) or bp (°C)/Torr
5a	1.5	85	56–58/0.1	
			34–35	34–35[13]
5e	1.5	99	77/4.5	79–80/5[13]
5g	3.7	95	88–89/3	88–89/[13]
5h[d]	3	95	96/0.06	
			79–80	79–80[14]
5i	3	95	96/0.06	$C_{10}H_{18}O_4$ (202.2)

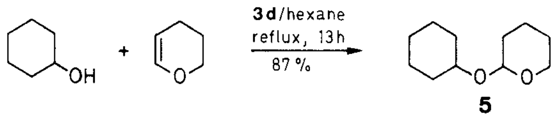
[a] 1 Mol % of catalyst based on the carbonyl compounds was used.

[b] Isolated yields by distillation.

[c] calc. C 59.38 8.97
found 59.20 8.99

[d] 3 Mol% of catalyst was used.

Furthermore, synthesis of an acetal was performed from alcohol and 3,4-dihydro-2*H*-pyran and a catalytic amount of **3d**. Thus, the tetrahyropyranylation of cyclohexanol with 3,4-dihydro-2*H*-pyran was carried out in the presence of 1 mol% of **3d** in hexane under reflux to afford the corresponding acetal **5** in 87% yield.



In conclusion, we have developed a new class of acid catalysts with high activity for the synthesis of various kinds of acetals. The catalysts are easy to use owing to their less hygroscopic nature and chemical stability toward air, water, and organic solvents.

Melting Points were measured with a YANACO micro melting point apparatus and are uncorrected.

***N*-(4-Methoxybenzyl)-2-cyanopyridinium Hexafluoroantimonate (3d):**[7]
A solution of freshly prepared 4-methoxybenzyl bromide[8] (27.8 g, 110 mmol) and 2-cyanopyridine (11.8 g, 113 mmol) in MeCN (60 mL) is stirred at r.t. for 3d. MeCN is evaporated and the residue is partitioned between Et_2O/water (300 mL/100 mL). $KSbF_6$ (27.4 g, 100 mmol) is added to the aqueous layer in one portion. White precipitate formed is collected and recrystallized from MeOH; yield: 10.9 g (21 %); mp 118–120 °C.

$C_{14}H_{13}F_6N_2OSb$ calc. C 36.48 H 2.82 N 6.08
(461.0) found 36.13 2.91 5.92

IR (KBr): ν = 1613, 1257, 1181, 784, 756, 711, 659 cm^{-1}.

^1H-NMR (acetone-d_6/TMS): δ = 3.83 (s, 3 H, CH_3), 6.20 (s, 2 H, CH_2), 7.09 (d, 2 H_{arom}, J = 8.7 Hz), 7.64 (d, 2 H_{arom}, J = 8.7 Hz), 9.50–8.40 (m, 4 $H_{pyridyl}$).

2-Phenyl-1,3-dioxolane (2a); Typical Procedure:

A mixture of benzaldehyde (3.50 g, 33 mmol), ethylene glycol (4.10 g, 66 mmol) and *N*-benzyl-4-cyanopyridinium hexafluoroantimonate (**3a**; 0.143 g, 0.33 mmol) in benzene (30 mL) is heated to reflux. Water formed during the reaction is removed azeotropically (Dean-Stark trap) until the calculated amount of water is formed (~ 5 h). The mixture is cooled to r.t., poured into dil aq NaOH (0.13 g NaOH dissolved in 100 mL water) and extracted with benzene (3 × 100 mL). The benzene extract is dried ($MgSO_4$), evaporated, and the residue is distilled under reduced pressure; colorless oil; yield: 4.16 g (84 %); bp 99/8.5 Torr (Lit.[2] 101/10 Torr).

IR (neat): ν = 3036, 2833, 1459, 1397, 1314, 1220, 1095 cm^{-1}.

^{1}H-NMR (CCl_4/TMS): δ = 3.91 (s, 4 H, CH_2CH_2), 5.70 (s, 1 H, CH), 7.30 (m, 5 H_{arom}).

3,3-Dimethyl-1,5-dioxaspiro[5.5]undecane (4e); Typical Procedure.

A mixture of cyclohexanone (1.08 g, 11 mmol), 2,2-dimethyl-1,3-propanediol (2.29 g, 22 mmol) and *N*-[4-methoxybenzyl]-2-cyanopyridinium hexafluoroantimonate (**3d**; 50.7 mg, 0.11 mmol) in toluene (10 mL) is heated to reflux. Water formed during the reaction is removed azeotropically (Dean-Stark trap) until the calculated amount of water is formed (~ 1.5 h). The cooled (r.t.) mixture is poured into dil aq NaOH (0.07 g NaOH dissolved in 50 mL water) and extracted with benzene 3 × 50 mL. The benzene extract is dried ($MgSO_4$), evaporated, and the residue is distilled under reduced pressure; colorless oil; yield: 1.98 g (99 %); bp 77/4.5 Torr (Lit.[13] 79–80/5 Torr).

^{1}H-NMR (CCl_4): δ = 0.91 (s, 6 H, 2 × CH_3), 1.33–1.75 (br, 10 H, 5 × CH_2), 3.33 (s, 4 H, 2 × CH_2).

2-(Cyclohexyloxy)tetrahydro-2*H*-pyran (5):

A mixture of 3,4-dihydropyran (0.56 g, 6.6 mmol), cyclohexanol (0.55 g, 5.5 mmol) and **3d** (25.4 mg, 0.055 mmol) in hexane is refluxed for 13 h. The cooled (r.t.) mixture is poured into diluted sodium hydroxide solution (0.07 g NaOH dissolved in 50 mL water) and extracted with hexane (3 × 50 mL). The hexane extract is dried ($MgSO_4$), evaporated, and distilled under reduced pressure; colorless oil; yield: 0.87 g (87 %); bp 76–77/3 Torr (Lit.[15] bp 79–80/3 Torr).

^{1}H-NMR (CCl_4): δ = 1.06–2.40 (br, 16 H, 8 × CH_2), 3.20–4.06 (br, 3 H, CH + CH_2), 4.63–4.75 (br, 1 H, CH).

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