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A Simple and Clean Method for Methoxymethylation of Phenols

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Key words: Methoxymethyl ethers of phenols.

ABSTRAK

Satu kaedah mudah dan bersih, untuk penyediaan metoksimetil eter (MOM = CH_2 OMe) bagi fenol yang membawa ikatan hidrogen kumpulan hidroksi dalam molekulnya akan dibincangkan. Tindakbalas 2,5-dihidroksibenzaldehid (1) dengan metoksimetilklorida - metil asetat dalam pelarut eter pada suhu bilik, menghasilkan 57% 2,5- bis(metoksimetoksi) benzaldehid (2). Dalam keadaan tindakbalas yang sama 75% metoksimetil eter (6) telah dihasilkan daripada salisilaldehid. Penghasilan sebanyak 61-81%, tidak dibaiki, bagi metoksimetil eter untuk beberapa fenol yang tidak mempunyai ikatan hidrogen di atas telah juga dihasilkan.

ABSTRACT

A simple and clean procedure for the preparation of methoxymethyl ethers (MOM = CH_2 OMe) of phenols having internally hydrogen bonded hydroxy groups is described. Thus treatment of 2,5-dihydroxybenzaldehyde (1) with a 1:1 mixture of methoxymethyl chloride-methyl acetate in ether at room temperature gives 2.5-bis-(methoxymethoxy)benzaldehyde (2) in 57% yield; under similar conditions, the methoxymethyl ether (6) of salicylaldehyde was isolated in 75% yield. Yields of 61-81%, not optimised, of methoxymethyl ethers of several phenols lacking internal hydrogen bonding were also obtained.

INTRODUCTION

The methoxymethyl ether moiety is a useful hydroxy protecting group for phenols, alcohols, and carboxylic acids. Methoxymethylation is sometimes superior to tetrahydropyranylation, since the latter results in the formation of new assymmetric center(s); with diols and optically active alcohols, a mixture of diastereomers is formed, complicating both purification and spectroscopic analysis (Fuji *et al.* 1975). Preparations of methoxymethyl ethers are based mostly on the reaction of a phenoxide anion with methoxymethyl chloride (Greene 1981). However, such a procedure was not suitable for our purpose, the preparation of bis(methoxymethoxy)benzaldehyde (2) from 2,5-dihydroxybenzaldehyde (1).

Several alternative methods for methoxymethylation which avoid the use of methoxymethyl chloride present some difficulties. The use of methylal and a large molar excess of phosphorus pentoxide (Fuji *et al.* 1975) causes difficulties in work-up, particularly of methoxymethyl ethers of small molecular weight. Based on Fuji's procedure, Yardley and Fletcher, (1976) reported that 3.5 g of (3) required 85 g of phosphorus pentoxide and a final neutralisation volume of 4 litres. They then reported on the use of methylal and 4-toluenesulfonic acid in the presence of molecular sieves (to remove methanol) to facilitate the preparation of some methoxymethyl ethers. However, their procedure failed to afford either the methoxymethyl ether of 2-acetylphenol (4) or the bis-

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methoxymethyl ether of 2,2-dihydroxybenzophenone (5). The difficulty may be due to the internally hydrogen bonded hydroxy groups in these compounds. Recently, the use of methylal and phosphorus oxychloride in toluene at 65°C was reported to give the methoxymethyl ether (6) of salicylaldehyde in 90% yield (Schouten 1985).

We herein report a clean and simple preparation of methoxymethyl ethers, particularly from substrates having internally hydrogen bonded hydroxy groups, such as that in aldehyde (1), which illustrates the importance of correct choice of a solvent. The procedure was found to be superior to that generally used.

MATERIALS AND METHODS

Proton magnetic resonance spectra, in p.p.m. with respect to internal tetramethylsilane, were measured on a Perkin-Elmer R34 instrument at 220 MHz, and a Varian SC300 instrument at 300 MHz as stated. Coupling constants for the aromatic protons were in the normal ranges. Resonances assigned to hydroxyl groups were removed by addition of D_2O.

Mass spectra were recorded on Kratos MS25 and MS30 instruments. Melting points were recorded on a Kofler block and were uncorrected.

Infrared spectra were recorded on a Perkin-Elmer FTIR 1710 spectrometer as Nujol mulls, films or solutions as stated.

Methoxymethylation of Phenolic Hydroxy Groups: A General Procedure for Preparation of Compounds (13 a-i) and (14 a-f).

To a stirred solution of the hydroxy compound (hydroxybenzene, hydroxyaldehyde, hydroxyketone, or hydroxycarboxylic acid) (1.0 mmole) in ether (5 ml) (Note 1) under a nitrogen atmosphere was added methoxymethyl chloride (1.5 mmole), as a 1:1 mixture with methyl acetate (Note 2), and triethylamine (2.0 mmole) (Note 3). The mixture was stirred at room temperature for about 24 h. and the white precipitate was then removed by filtration. Removal of the solvent gave the methoxymethyl ether, usually as a liquid, which was purified either by washing with aqueous 5% sodium hydroxide or by distillation.

Note 1. Ether (5 ml) was used as the solvent for every 1.0 mmole of the hydroxy compound, except for those hydroxy compounds which were not very soluble in ether when more ether was used.

Note 2. Methoxymethyl chloride (1.5 mmole) (Amato *et. al.* 1979) was used for each hydroxy group present in the starting material.

Note 3. Triethylamine (2.0 mmole) was used for every 1.5 mmole of methoxymethyl chloride used in the reaction mixture. Excess of amine ensured that the reaction mixture remained basic throughout.

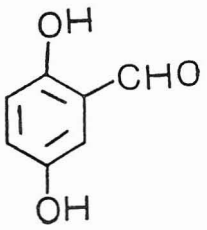
The compounds prepared are listed in Tables 1 and 2. Their analytical and spectrostopic data are shown in Tables 3 and 4, respectively.

RESULTS AND DISCUSSION

In connection with our interest (Ahmad and Bruce, 1986) in developing a new synthetic route to the aglycones of the anticancer anthracyclines, we required the hydroxy protected aldehyde (2). However, treatment of 2,5-dihydroxybenzaldehyde (1) with a 1:1 mixture of methoxymethyl chloride-methyl acetate (Amato *et al.* 1979) in dichloromethane* (Khan and Bruce 1985) in the presence of triethylamine, either at room temperature or at reflux, gave only 5% of the desired aldehyde (2), the major product being the mono-methoxymethyl ether (7). Similar reactions using pyridine as the base in either dichloromethane, tetrahydrofuran or ether failed to give the desired aldehyde (2): only starting material (1) was isolated. Attempted methoxymethylation of aldehyde (1) in the presence of powdered 4A molecular sieves to absorb hydrogen chloride (c,f. Yardley and Fletcher 1975) again gave the mono-methoxymethylation product (7). The difficulty in preparation of (2) may be due to internal hydrogen bonding [as (7a)] in the starting material (1).

1,4-Bis(methoxymethoxy)benzene (8) has previously been obtained by *heating* hydroqui-

* 3-Methoxymethoxy-2-cyclohexen-1-one was obtained in 75% yield from the corresponding hydroxy compound on treatment with methoxymethyl chloride-methyl acetate in the presence of triethylamine in *dichloromethane* at 0°C.



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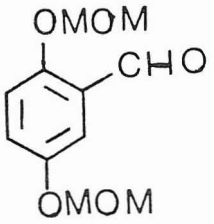

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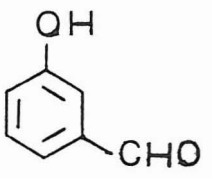

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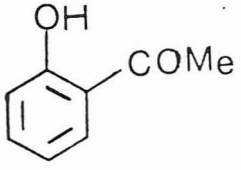

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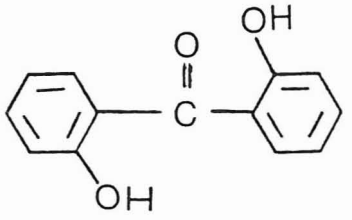

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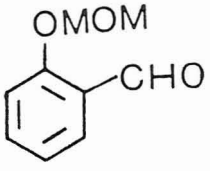

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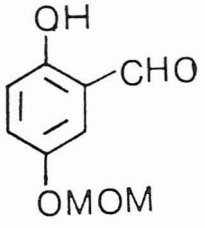
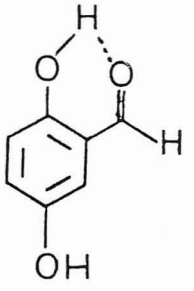


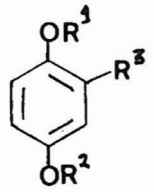
(7)



(7a)

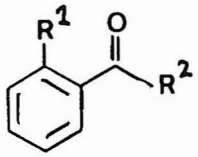
MOM = CH_2OMe

TABLE 1
Methoxymethyl (MOM) ethers of some 1,2,4-trisubstituted benzenes 13[a].

(13) 		Isolated, Yield(%)	b.p. (°C/mmHg)
(a)	$R^1 = R^2 = MOM$, $R^3 = H$	61	76-80/0.1[b]
(b)	$R^1 = R^2 = MOM$, $R^3 = OMe$	76	80-86/0.1
(c)	$R^1 = R^2 = MOM$, $R^3 = CHO$	57	56-60/0.05
(d)	$R^1 = R^2 = MOM$, $R^3 = COPh$	23	96-100/0/0.1
(e)	$R^1 = R^2 = MOM$, $R^3 = CO_2Me$	18	Not determined
(f)	$R^1 = R^2 = MOM$, $R^3 = CO2MOM$	17	Not determined
(g)	$R^1 = H$, $R^2 = MOM$, $R^3 = CHO$	80[c]	50-56/0.1
(h)	$R^1 = H$, $R^2 = MOM$, $R^3 = CO_2H$	82	[m.p 104-106°C] Decomposed on attempted sublimation.
(i)	$R^1 = H$, $R^2 = MOM$, $R^3 = COMe$	10	Not determined

[a] Prepared from the corresponding hydroxy compounds. Except for entry (c), yields were not optimised.
[b] Mamedov and Mamedova (1962), b.p. 136-137°C/5 mmHg.
[c] The compound was prepared in refluxing dichloromethane using powdered 4A molecular sieves.

TABLE 2
Methoxymethyl (MOM) ethers of some 1,2-disubstituted benzenes (14)[a]

(14) 		Isolated	b.p.(°C/mmHg) Yield(%)
(a)	$R^1 = Br$; $R^2 = OMOM$	81	60-64/0.1
(b)	$R^1 = OMOM$; $R^2 = H$	75[b]	60-66/0.1
(c)	$R^1 = OMOM$; $R^2 = OH$	82	60-64/0.1[c]
(d)	$R^1 = OMOM$; $R^2 = OMe$	16	Not determined[d]
(e)	$R^1 = OMOM$; $R^2 = OMOM$	10	Not determined
(f)	$R^1 = OMOM$; $R^2 = Me$	10	Not determined

[a] Prepared from the corresponding hydroxy compounds. Yields were not optimised.
[b] This compound is known; prepared in 90% yield by treatment of the corresponding aldehyde with methylal and phosphorus oxychloride in toluene at 65°C (Schouten, 1985).
[c] Dunn and Bruice (1970), white solid, m.p. 63-64°C.
[d] Dunn and Bruice (1970), b.p. 72-73°C/0.025 mmHg.

TABLE 3
Characteristics of methoxymethyl ethers of some 1,2,4-trisubstituted benzenes (13).

Compound	Elemental analysis or $\underline{M}^+$	P.m.r (220 MHz, CDC13)[a]				I.r/cm^{-1}
		OMe	OCH_2	ArH	Other	(film)[b]
13(a)	$\underline{M}^+$;198.0892	3.42 (s,6H)	5.04 (s,4H)	6.92(s,4H)		15000s
13(b)	C,57.6, H,7.2%	3.46 3.50 3.85	5.12 5.14	6.55(dd,1H) 6.65(d,1H) 7.05(d,1H)		1511m 1153m 1009m
13(c)	C,58.6; H,6.3%	3.46 3.50	5.16 5.21	7.02(d,1H) 7.26(dd,1H) 7.52(d,1H)	0.28 (s,CHO)	1680s 1490m 1385m
13(d)	C,68.1; H,6.0%	3.28 3.46	4.96 5.13	7.06(m,1H) 7.04(s,1H) 7.05(s,1H) 7.44(m,2H) 7.53(m,2H) 7.86(d,2H)		1669s 1597m 1493s
13(e)	$\underline{M}^+$;256.0947	3.44 3.48	5.12 5.16	7.13(m,2H) 7.46(m,1H)	3.86 (s,Co_2 Me)	1720s 1490m
13(f)	C,54.1; H;6.4%	3.47 3.52 3.54	5.02 5.17 5.42	7.08(s,1H) 7.10(s,1H) 7.42(d,1H)		1736s 1498s
13(g)	C,59.6; H,5.7%	3.43	5.12	6.92(d,1H) 7.22(m,2H)	9.29 (s,CHO) 10.65 (s,OH)	3100–3600b 1660s
13(h)	C,54.9; H,5.6%	3.50	5.16 6.96	6.96(d,1H) 7.25(dd,1H) 7.60(d,1H) 1489m	10.10 (bs,20H)	3100–3600b 1682s 1618s
13(i)	$\underline{M}^+$;196.0731	3.50	5.12	6.88(d,1H) 7.80(dd,1H) 7.42(d,1H)	11.92 (s,OH) 2.62 (s,COMe)	3150b 1640s

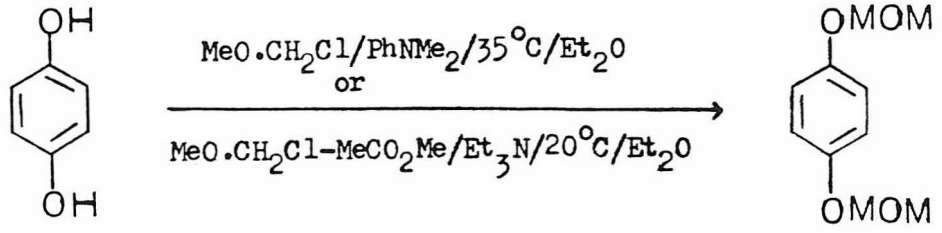
[a] P.m.r. spectra of 13(c,e,j) were recorded at 300 MHz; those of 13(a,f) were recorded at 60 MHz. Signals due to OMe and OCH_2 are singlets.
[b] I.r. spectrum of 13(i) in $CDCl_3$; of 13(h) in Nujol.

none in ether with methoxymethyl chloride and dimethylaniline, in about 60% yield (Mamedov and Mamedova 1962). In our hands, compound (8) was more easily prepared by treatment of hydroquinone with a 1:1 mixture of methoxymethyl chloride - methyl acetate in the presence of triethylamine *at room temperature, in ether,* also in about 60% yield (Scheme 1). Therefore the mono-methoxymethylation product (7), which was obtained previously as described above, was treated with a 1:1 mixture of methoxymethyl chloride-methyl acetate in the same man-

TABLE 4
Characteristics of methoxymethyl ethers of some 1,2-disubstituted benzenes (14).

Compound	Elemental analysis	P.m.r. (220 MHz, $CDCl_3$)[a] OMe	OCH_2	ArH	Other	I.r./cm^{-1} (film)
14(a)	C,44.2;H,3.7; Br, 32.4%	3.50	5.42	7.29(m,2H) 7.60(m,1H) 7.80(m,1H)		1740s
14(b)	C,65.3;H,6.1%	3.42	5.22	7.02(t,1H) 7.16(d,1H) 7.48(td,1H) 7.78(dd,1H)	10.42 (s,CHO)	1690s 1600s
14(c)	C,59.3;H,5.9%	3.56	5.51	6.90(t,1H) 7.00(d,1H) 7.48(td,1H) 7.93(td,1H)	8.66 (s,OH)	3210–3004b 1630s 1615s 1486m
14(d)	C,61.2;H,6.4%	3.54	5.29	7.08(td,1H) 7.20(d,1H) 7.46(td,1H) 7.80(dd,1H)	3.90 (s,CO Me)	 1731s 1755m
14(e)	C,59.0;H,6.4%	3.35 3.39	5.10 5.30	6.93(td,1H) 7.09(d,1H) 7.32(td,1H) 7.70(dd,1H)		1734s 1602s 1488s
14(f)	C,66.5;H,6.7%	3.50	5.28	7.05(td,1H) 7.18(d,1H) 7.45(d,1H) 7.45(td,1H) 7.72(dd,1H)	2.62 (s,COMe)	 1677s 1598m 1483m 1454m

[a] Signals due to OMe and OCH_2 are singlets.



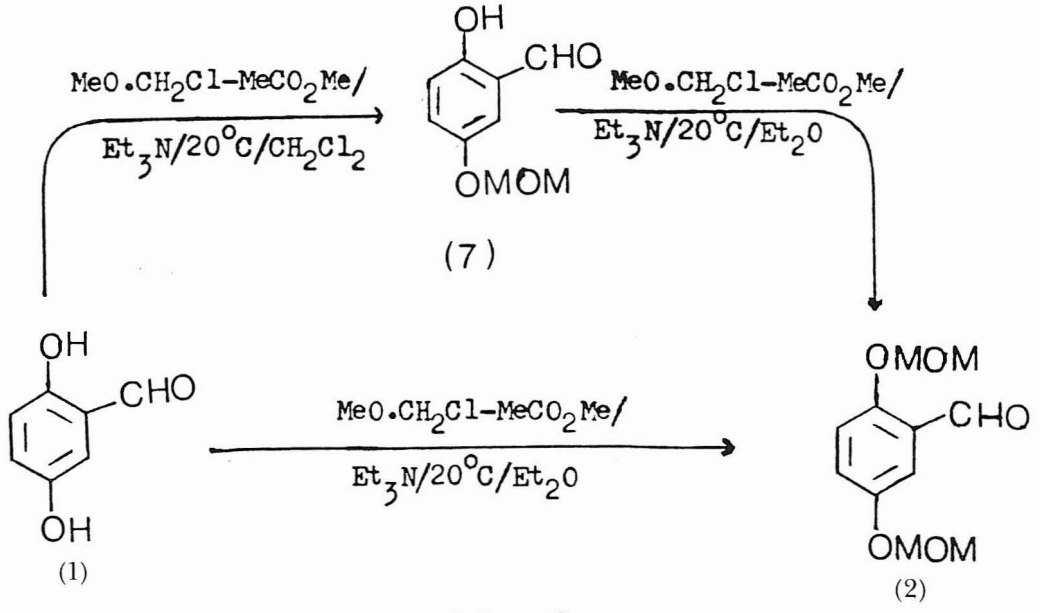
(8)

Scheme 1

ner as outlined for the preparation of (8): this afforded the required bis(methoxymethoxy)-benzaldehyde (2) in 60% yield. Hence, treatment of 2,5-dihydroxybenzaldehyde (1) with 2-3 mol of methoxymethyl chloride-methyl acetate in the presence of triethylamine *in ether* (ins-tead of dichloromethane as before), gave the desired methoxymethyl ether (2) in 57% yield. The latter route reduces to one step the preparation of (2) from the corresponding aldehyde (1) (Scheme 2). This procedure is clean and simple, and illustrates the importance of correct choice of solvent.

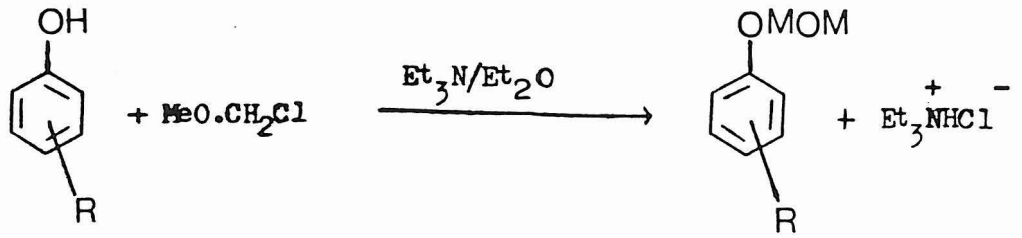
To our knowledge, the use of ether as solvent for preparation of this type of methoxymethyl ether has not been previously reported on. Therefore, it was of interest to explore the use of the method for the preparation of other methoxymethyl ethers, particularly from substrates having internally hydrogen bonded hydroxy groups similar to that in aldehyde (1). Models of general structures (9) and (10) were used. The progress of reaction was easily followed by observing the formation of triethylammonium chloride which precipitated from solution (Scheme 3).

Details of the methoxymethyl ethers which were prepared are summarised in Tables 1 and 2. These show that the substrates without an internal hydrogen bond gave 60-81% of the corresponding methoxymethyl ethers ['a' and 'b' (Table 1) and 'a' (Table 2)].Also, the methoxymethyl ester (11)* was prepared from the corresponding acid (12) in 81% yield. It is worth noting that for the trisubstituted benzenes (9) (Table 1), the yield of bismethoxymethyl ether decreases in the order R = H, Ph, OMe, OH. In contrast, for the disubstituted benzenes (10) the yield of bismethoxymethyl ether decreases in the order R = OH, H, OMe, Me. This order may be due to the solubility of the starting materials. As expected, the monomethoxymethyl ethers of the trisubstituted benzenes (9) were isolated in high yield [entries 'g' and 'h' (Table 1)]. In contrast, it was difficult to prepare the bismethoxymethyl ether of 2',5'-dihydroxyacetophenone: only its 5'-monomethoxymethyl ether was obtained, in 10% yield (entry 'i', Table 1).

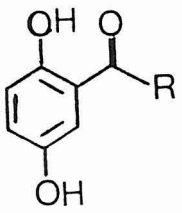


Scheme 2

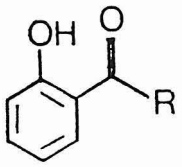
* Compound (11), oil, b.p. 100-106°C/0.1 mmHg: (Found M$^+$, 330.1103); $C_{18}H_{18}O_6$ requires M, 330.1116. It had δ (220MHz,$CDCl_3$), 3.35(3H,s,OMe), 3.48(3H,s,OMe), 3.62(3H,s,OMe), 5.26(3H,s,OCH_2),6.85(1H,d,H-3'), 7.08(1H,dd,H-4'), 7.32(1H,dd,H-3), 7.42(1H,d,H-6'), 7.52(1H,td,H-5), 7.58(1H,dt,H-4), 8.01(1H,dd,H-6); δ_{max}(film) 1658s, 1727s cm^{-1}.



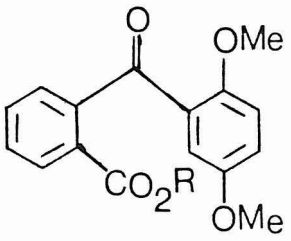
Scheme 3



(9)



(10)



(11) R = MOM

(12) R = H

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