

THE METHYLATION OF SOME PHENOLS AND ALCOHOLS WITH
SODIUM HYDRIDE / METHYL IODIDE IN TETRAHYDROFURAN
AT ROOM TEMPERATURE¹

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Alcohols and weakly acidic phenols which do not react with diazomethane can be methylated in the presence of acid catalysts^{2,3}, but certain hindered alcohols^{2,3} and phenols³ react with difficulty or not at all. We describe here the use of sodium hydride / methyl iodide in tetrahydrofuran (THF) at room temperature for the methylation of alcohols and phenols, and include several compounds not readily methylated by other procedures.⁴

We had already shown that in a THF / dimethylformamide mixture at 80°C, sodium hydride / methyl iodide will methylate an N-acyl- or N-alkyloxycarbonyl-amino acid to give the corresponding N-substituted, N-methylamino acid methyl ester.⁵ We confirmed that methylation of N-benzyloxycarbonyl-tyrosine gave the O-methyl ether, established that the methylation of N,O-dibenzyloxycarbonyl-tyrosine gave the same product, due to the lability of the O-benzyloxycarbonyl group, and then sought to obtain selectivity between N- and O-methylation by using milder conditions. We found that both the N- and O-methylation of N-benzyloxycarbonyl-tyrosine still took place in THF at 23°C, but that the product was, surprizingly, the free acid and not the methyl ester.⁶ Several other phenols and alcohols were then methylated, as described in Table I.

The results in Table I show that besides phenol, m-nitrophenol and benzyl alcohol, catechol (1,2-dihydroxybenzene), triphenylcarbinol and the highly hindered⁷ 2,6-di-tert-butyl-p-cresol were

Table I. Methylation of phenols and alcohols

Compound	MeI (mol)	NaH (mol)	Percent yield	
			23 ^o	80 ^o
Phenol	8	2	74	74
Phenol	8 ^b	2	69	72
Phenol	8 ^c	2	22	80
<i>p</i> -Cresol ^d	8	2		51,60 ^e
<i>m</i> -Nitrophenol	4	2	95	
<i>p</i> -Nitrophenol	4	2	0 ^f ,85 ^e	0 ^f
Catechol	8	3	84 ^g	
2,6-Di- <i>t</i> -butyl- <i>p</i> -cresol	8	2	86	97 ^{eh}
<i>n</i> -Heptyl alcohol	4	1.5	40 ⁱ	35 ⁱ
Cyclohexyl alcohol	4	1.5	64 ⁱ	66 ⁱ
Benzyl alcohol	4	1.5	74	90
Triphenylcarbinol	4	1.5	85 ^j	

a) To 0.01 mol of compound in 50 ml of THF, predried with NaH, was added methyl iodide followed by NaH (50% dispersion in oil, washed with dry benzene, and filtered). The mixture, protected from the atmosphere with a drying-tube, was stirred at room temperature (23^oC) or in a wax-bath at 80^oC for 24 hours. The solvent was evaporated, the residue was distributed between 25 ml of water and 100 ml of ether, and the ether layer was washed twice with water, dried (MgSO₄), and evaporated. The residue was weighed and analyzed by NMR spectroscopy (CDCl₃ vs TMS). No starting material remained except for f, i. b) Ethyl iodide. c) Isopropyl iodide. d) Impure starting material. e) Reaction mixture contained 5 ml of dimethylformamide. f) Starting material recovered. g) δ : 3.91 (6H,s), 6.95 (4H,s). h) Reaction time of 1 hour. δ : 1.43 (18H,s), 2.30 (3H,s,CH₃), 3.60 (3H,s,OCH₃), 7.09 (2H,s). i) Yield calculated from NMR spectrum. j) Product was crystallized from methanol, m.p. 82^o, lit m.p. 82-83^o.⁸ δ : 7.32 (15H,m), 3.03 (3H,s).

readily methylated by sodium hydride / methyl iodide in THF at room temperature. Phenol could also be satisfactorily ethylated and isopropylated by this procedure, but the latter required the use of an elevated temperature. Methylation of the two aliphatic alcohols was incomplete even at 80°.

It should be noted that *p*-nitrophenol was not methylated, even at 80°, by the present procedure, but that the reaction took place at 23° when dimethylformamide was added. This behaviour at 23° is the same as that observed for a carboxyl group under the same conditions.⁶ *p*-Nitrophenol is substantially more acidic than the other phenols tested here, having a pK_a (7.15) of 1.1 units below that of *m*-nitrophenol. It therefore transpires that sodium hydride / methyl iodide will methylate (in THF) weakly acidic phenols in preference to more acidic phenols or acids. This is the opposite preference to that shown by diazomethane. Sodium hydride / methyl iodide therefore provides not only an additional reagent for the methylation of phenols and alcohols, but one with different capabilities. As an example, it has been reported that triphenylcarbinol cannot be methylated with diazomethane in the presence of the usual acid catalysts boron trifluoride² and fluoroboric acid.³ The hindered phenol 2,6-di-*tert*-butyl-*p*-cresol is also inert to diazomethane, or sodium in boiling ligroin, recourse to sodium in liquid ammonia having been taken to prepare the sodium salt for subsequent methylation with methyl iodide in a pressure bottle.

Notes and References

1. Supported by a grant from the Medical Research Council of Canada. N.L.B. is an Associate of the MRCC.
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