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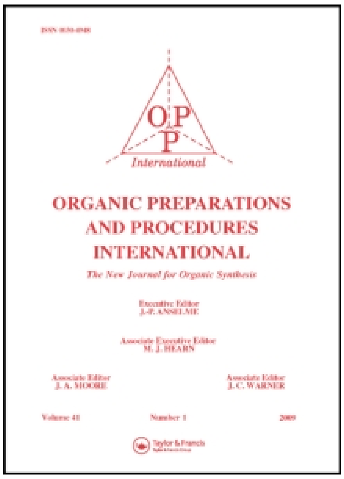

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CHLOROMETHYLATION OF NITROPHENOLS WITH CHLOROMETHYL METHYL ETHER

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CHLOROMETHYLATION OF NITROPHENOLS WITH CHLOROMETHYL METHYL ETHER

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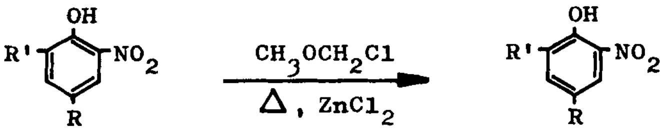

I

II

a)	$R = CH_3$, $R' = H$	a)	$R = CH_3$, $R' = ClCH_2$	(86%)
b)	$R = H$, $R' = CH_3$	b)	$R = ClCH_2$, $R' = CH_3$	(89%)
c)	$R = H$, $R' = H$	c)	$R = ClCH_2$, $R' = ClCH_2$	(65%)

The chloromethylation of aromatic compounds is a well known reaction[1] which can be successfully applied to phenolic compounds, phenol ethers, etc. Nevertheless, there has not been much published on the chloromethylation of nitrophenols. Until recently, only the monochloromethyl derivatives of o, m and p-nitrophenol[2-4] and of 2,4-dinitrophenol[5] had been described. In another connection, we reported that chloromethyl methyl ether (CME) can be used for the preparation of 2-hydroxy-3-nitro-5-methyl benzyl chloride and 2,6-bis-chloromethyl-4-nitrophenol.[6] This procedure has now been found

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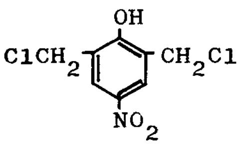
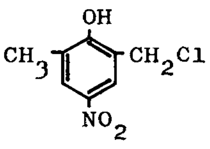
to be generally applicable to *o*-nitrophenols and, in some instances, to *p*-nitrophenols; it failed with dinitrophenols.

CME has already been used by other authors for chloromethylation.[7] The use of a catalyst is necessary for the chloromethylation of nitrophenols. Our procedure consists of refluxing the nitrophenol with zinc chloride and an excess of CME, which serves as solvent. Since CME is readily prepared,[8] this represents a very simple and convenient procedure.

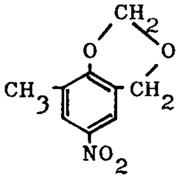
Excellent yields of pure products (IIa and IIb) are obtainable with *o*-nitrophenols; 2-nitrophenol gave the dichloromethylated product (IIc). From 4-nitrophenol the dichloromethylated product (III) is also formed, in contrast with the results obtained using HCl and methylal.[4] However, in this case the purification is more complicated and the yield of pure product is only 40-45%. Under the same conditions, 2-methyl-4-nitrophenol did not give the expected chloromethylated product (IV); only the benzdioxane derivative (V) was obtained.[9] The chloromethylated product (IV) can be prepared by the procedure described for 4-nitrophenol[4] in a less than satisfactory yield of pure product.



III



IV



V

As expected, 2,4-dinitrophenol cannot be chloromethylated with CME and $ZnCl_2$ (other catalysts have not yet been tested). In this case we could only isolate the starting product. This is not very surprising, because the direct

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chloromethylation of 2,4-dinitrophenol requires more vigorous reaction conditions.[10] (An alternative route for the preparation of 2-hydroxy-3,5-dinitro benzyl chloride is the nitration of 2-hydroxy-5-nitro benzyl chloride.[5]) The procedure reported here may also be applicable to dihydroxy-diphenylmethane derivatives of nitrophenols. These results will be the subject of a forthcoming publication.

EXPERIMENTAL

CAUTION! Since bis(chloromethyl) ether has been reported[11] to be carcinogenic, care should be exercised with chloromethyl methyl ether.

General Procedure for Chloromethylation with CME. To 0.1 mole of the nitrophenol and 2.5 g. $ZnCl_2$ were added 100 ml. of CME. The solution was refluxed for 8-9 hrs. Excess CME was removed in vacuo (using finally a bath temperature of 60°C) and the dry solid residue was purified by recrystallization as described for the individual compounds. The entire reaction and purification should be performed with the exclusion of moisture, but no unusual precautions have to be taken.

2-Hydroxy-3-nitro-5-methyl benzyl chloride (IIa) by recrystallization from 200 ml. of petroleum ether (80-100°C), yield 17.4 g. (86%) of bright, yellow plates or needles. mp. 91,6°C (a sublimed sample)[12]

Anal. Calcd. for $C_8H_8ClNO_3$

C, 47,66; H, 4,00; N, 6,95; Cl, 17,59;

Found C, 47,69; H, 3,95; N, 7,05; Cl, 17,59;

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3-Methyl-4-hydroxy-5-nitro benzyl chloride (IIb) by recrystallization from 100 ml. of petroleum ether (80-100°C), yield 17,9 g. (89%) of large, yellow crystals. A sample for elemental analysis was sublimed *in vacuo*, mp. 82,2°C.[12]

Anal. Calcd. for $C_8H_8ClNO_3$
C, 47,66; H, 4,00; N, 6,95; Cl, 17,59; O, 23,81;
Found C, 47,87; H, 4,03; N, 7,22; Cl, 17,60; O, 23,85;

2,4-Bis-chloromethyl-6-nitrophenol (IIc) by boiling the residue with a mixture of 100 ml. of benzene and 50 ml. of petroleum ether (80-100°C), clarification with charcoal and filtration. Addition of 100 ml. of petroleum ether (80-100°C) to the hot, yellow filtrate gave large, yellow crystals, yield 15 g. (63%). A sample for elemental analysis was sublimed *in vacuo*, mp. 100,5°C.[12]

Anal. Calcd. for $C_8H_7Cl_2NO_3$
C, 40,70; H, 2,99; N, 5,93; Cl, 30,04;
Found C, 41,00; H, 3,12; N, 6,12; Cl, 30,22;

2,6-Bis-chloromethyl-4-nitrophenol (III) by boiling the residue with 150 ml. of benzene, clarification with charcoal and filtration. A pale yellow oil was precipitated by adding petroleum ether (80-100°C) to the filtrate. Further recrystallization yielded large, white crystals, 9,4 g. (40%). mp. 134,2°C.[12]

Anal. Calcd. for $C_8H_7Cl_2NO_3$
C, 40,70; H, 2,99; N, 5,93; Cl, 30,04;
Found C, 40,63; H, 3,06; N, 5,83; Cl, 29,67;

6-Nitro-8-methyl-1,3-benzdioxane (V) by recrystallization from 200 ml. of benzene and clarification with charcoal,

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yield 8,1 g. (41,5%) of slightly grey needles. mp. 134,2°C,[12] lit. mp. 131°C.[9]

<u>2-Hydroxy-3-methyl-5-nitro benzyl chloride (IV).</u> A mixture of 5.51 g. (0.036 mole) of 2-methyl-4-nitrophenol, 65 ml. of conc. HCl, 0.5 ml. of conc. H_2SO_4 and 7.6 g. (0.1 mole) of methylal was stirred for 4-5 hrs., while the temperature was maintained at 70°C. During this time, hydrogen chloride was bubbled into the reaction mixture, which was cooled subsequently in ice for 1 hr. The precipitated solid was filtered, dried and recrystallized from benzene to yield 2.4 g. (33%) of a slightly grey product (mp. 115-117°C). Further recrystallization gave a pure product melting at 122,2°C.[12]

<u>Anal.</u> Calcd. for $C_8H_8ClNO_3$

C, 47,66; H, 4,00; N, 6,95; O, 23,81; Cl, 17,59;

Found C, 47,88; H, 4,19; N, 6,99; O, 23,53; Cl, 17,15;

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12. Melting points were determined with a Mettler FP1. The values reported are the average of three values, differing by not more than ± 0.2°.

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