New Procedure for Making 2-(Chloromethyl)-4-nitrotoluene

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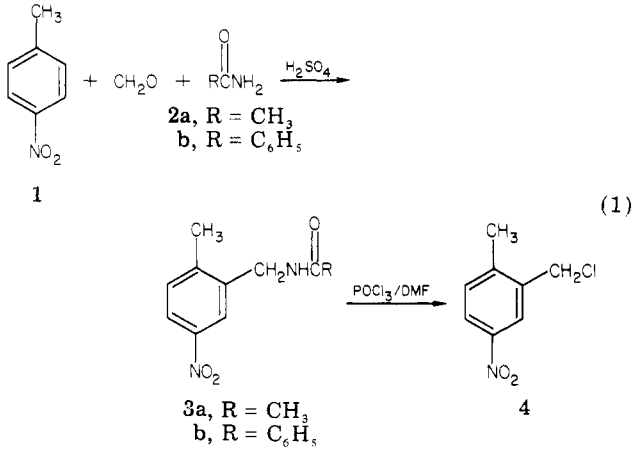
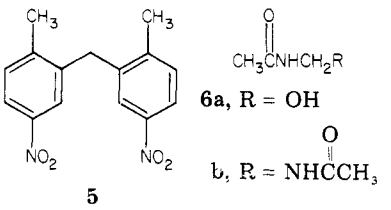
For many years bis(chloromethyl) ether (BCME) has been employed as a chloromethylating agent for various aromatics.[1a] However, the known carcinogenicity[2] of BCME makes it an extremely hazardous material with which to work, especially in reactions with deactivated aromatics where the concentration of BCME is high due to the slow rate of chloromethylation.[1a]

We describe a method of making 2-(chloromethyl)-4-nitrotoluene (**4**) from *p*-nitrotoluene (**1**) in 65% yield that does not require the use of BCME. In earlier reported procedures, **1** was reacted with either preformed BCME or BCME which was generated from the reaction of formaldehyde and acid.[1] Our two-step procedure includes the frequently used amidomethylation reaction[3] and the less familiar von Braun reaction.[4] *p*-Nitrotoluene is first converted to the amidomethylation product **3a** by heating it with acetamide, paraformaldehyde, and H_2SO_4, and the chloromethyl derivative **4** is produced upon treating **3a** with $POCl_3$ and DMF in hot xylene (eq 1).



(1)

As shown in Table I, a 70–75% yield of **3a** can be obtained on reacting **1** with an equimolar quantity of paraformaldehyde and 2–3 mol of acetamide (**2a**) in concentrated H_2SO_4 at 55 °C for 8 h. A competing reaction is the formation of diarylmethane **5**. Formation of **5** becomes significant at lower acetamide concentrations or at higher temperatures. Without acetamide, **5** was isolated



in 79% yield after **1** and paraformaldehyde were heated in H_2SO_4 at 65 °C for 16 h. The importance of *N*-(hydroxymethyl)acetamide (**6a**) as an intermediate in the amidomethylation reaction is indicated by the formation of **3a** from **1** and **6a** in yields of 38% and 65% by using 1 and 2 mol of the methyl alcohol **6a**, respectively. In contrast, **3a** was not detected after heating **1** and methylenebis(acetamide)[5] **6b** at 55 °C for 19 h. The diarylmethane **5** is not formed from product **3a**, since **5** was not detected after heating **3a** with **1** in concentrated H_2SO_4 at 55 °C for 18 h.

In Table II are listed several conditions in which **4** can be obtained from **3a** in good yield. Higher yields were observed with a $POCl_3$/**3a** molar ratio of 2.1. The best yield (85%) was obtained in refluxing xylene which contained 1 equiv of DMF. The use of 2 equiv of LiCl gave no improvement in yield, and a lower yield (24%) of **1** was isolated when **3a** was heated with 1.1 equiv of thionyl chloride in DMF at 100 °C for 2 h.

The chloromethyl derivative **4** was also isolated, along with benzonitrile, when **3b** was heated in refluxing phosphorus oxychloride for 3 h (eq 2). The isolation of benzonitrile supports the suggested pathway through the imidoyl chloride intermediate[4] for the von Braun reaction.

$$\mathrm{ArCH_2NHC(O)R} \xrightarrow{POCl_3} \mathrm{ArCH_2N{=}CCl\text{-}R} \rightarrow \mathrm{ArCH_2Cl + RCN} \quad (2)$$

The use of acetamide, rather than benzamide, offers the advantage of facile isolation of **4**, since acetonitrile is removed with an aqueous wash, while water-insoluble benzonitrile (bp 191 °C) is more difficult to separate.

Experimental Section

***N*-(2-Methyl-5-nitrobenzyl)acetamide (3a). (a) From Acetamide and Paraformaldehyde.** To a solution of 6.85 g (0.05 mol) of *p*-nitrotoluene and 1.5 g (0.05 mol) of paraformaldehyde in 60 mL of concentrated H_2SO_4 was added 8.85 g (0.15 mol) of acetamide in portions. The solution was heated at 55 °C for 8 h and poured over ice and water. The resulting solid was collected and heated in 10–12 parts of butyl acetate at 90 °C and filtered. Cooling the filtrate gave 7.8 g (75%) of **3a** as a colorless solid: mp 141–143 °C; IR, 3275, 1640, 1660 (sh) cm^{-1}; mass spectrum, *m/e* 208 (M^+); ^1H NMR ($CDCl_3$) δ 2.02 (s, 3 H, $COCH_3$), 2.37 (s, 3 H, $ArCH_3$), 4.39 (d, 2 H, CH_2), 6.32 (br s, 1 H, NH), 7.18 (d, 1 H, J = 8 Hz, arom 3-position), 7.86 (d, 2 H, J = 10 Hz, arom 4- and 6-positions). Anal. Calcd for $C_{10}H_{12}N_2O_3$: C, 57.69; H, 5.77; N, 13.46. Found: C, 57.39; H, 5.77; N, 13.50.

The material which was insoluble in butyl acetate was recrystallized from $CHCl_3$–MeOH to give bis(2-methyl-5-nitrophenyl)methane (**5**): mp 153–156.5 °C (lit.[1d] mp 153 °C); ^1H NMR ($CDCl_3$) δ 2.33 (s, 6 H, CH_3), 3.98 (s, 2 H, CH_2), 7.27 (d, 1 H, J = 9 Hz, arom 3-position), 7.61 (d, 1 H, J = 3 Hz, arom 6-position), 7.91 (dd, 1 H, J = 9 Hz, arom 4-position).

(b) From *N*-(Hydroxymethyl)acetamide. A solution of 6.85 g (0.05 mol) of *p*-nitrotoluene in 60 mL of concentrated H_2SO_4 was cooled in an ice bath, and 4.45 g (0.05 mol) of *N*-(hydroxymethyl)acetamide[6] was added. The mixture was stirred to solution and heated at 55 °C for 16 h. Pouring the mixture over ice and water gave a solid which was heated in 85 mL of butyl acetate

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Table I. Preparation of 3a from 1, Acetamide, Paraformaldehyde, and Concentrated H_2SO_4

expt	mol of CH_3CONH_2	reaction conditions		% yield[a]	
		temp, °C	time, h	3a	5
1	1.0	23	24	0	
2	1.0	55	3	26	25
3	1.0	55	24	26	
4	1.0	90	7	0	50
5	2.0	55	10	62	8
6	3.0	23	24	30	1
7	3.0	55	8	75	4

[a] Determined by NMR of crude product.

Table II. Preparation of 4 from 3a and $POCl_3$

expt	molar ratio of $POCl_3$/3a	reaction conditions			% yield of 4
		solvent	time, h	temp, °C	
1	2.1[a]	xylene	1	144	85
2	2.1	chlorobenzene	1.5	135	67
3	1.1	chlorobenzene	5	135	30
4	1.5	*N,N*-dimethylformamide	3	125	58
5	3	$POCl_3$	3	105	50
6	1.1[b]	toluene	16	110	40
7	1.1	ethylene dichloride	6	84	50

[a] DMF (1.0 mol) was used. [b] DMF (1.3 mol) was used.

at 90 °C and filtered. Cooling the solution gave 3.9 g (38%) of **3a**. The insoluble material (2.5 g) was crude diarylmethane **5**.

With 8.90 g (0.10 mol) of *N*-(hydroxymethyl)acetamide, a 65% yield of **3a** was isolated after 8 h at 55 °C.

***N*-(2-Methyl-5-nitrobenzyl)benzamide (3b).** To a solution of 6.85 g (0.05 mol) of *p*-nitrotoluene in 60 mL of concentrated H_2SO_4 was added 7.55 g (0.05 mol) of *N*-(hydroxymethyl)benzamide.[7] The solution was stirred at room temperature for 63 h and poured into ice and water. Recrystallization three times from ethanol gave 4.0 g (30%) of colorless **3b**: mp 134–137 °C; IR, 3300, 1635, 1655 (sh) cm^{-1}; mass spectrum, *m/e* 270 (M^+). Anal. Calcd for $C_{15}H_{14}N_2O_3$: C, 66.67; H, 5.78; N, 10.37. Found: C, 66.54; H, 5.10; N, 10.12.

A reaction time of 7 days gave **3b** in 43% yield.

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2-(Chloromethyl)-4-nitrotoluene (4). (a) From 3a. A solution of 6.24 g (0.03 mol) of **3a**, 9.67 g (0.063 mol) of $POCl_3$, and 2.19 g (0.03 mol) of DMF in 50 mL of xylene was refluxed 1 h. The cooled solution was washed with water and evaporated to give 4.73 g (85%) of **4**, mp 61–62 °C (after recrystallization from hexane) (lit.[1b] mp 63–64 °C).

Caution: **4** is a lachrymator and may be a skin irritant.

(b) From 3b. A solution of 2.70 g (0.01 mol) of **3b** and 6.12 g (0.04 mol) of $POCl_3$ was refluxed for 3 h. The cooled solution was stirred in water for 30 min, and the resulting two layers were extracted with chloroform. Evaporation gave 1.5–2 g of oil; the IR showed a mixture of **4** and benzonitrile (2225 cm^{-1}).

Registry No. 1, 99-99-0; **2a**, 60-35-5; **3a**, 86392-53-2; **3b**, 86392-54-3; **4**, 58966-24-8; **5**, 86409-50-9; **6a**, 625-51-4; *N*-(hydroxymethyl)benzamide, 6282-02-6.

Communications

Mixed Anhydrides in Peptide Synthesis. Reduction of Urethane Formation and Racemization Using *N*-Methylpiperidine as the Tertiary Amine Base

Summary: The side reactions of urethane formation and racemization accompanying couplings by the mixed anhydride method are reduced when *N*-methylpiperidine is used as base, the best results being achieved in dichloromethane.

Sir: One of the popular methods of coupling in peptide synthesis involves activation of the *N*-(alkoxycarbonyl)-amino or protected peptide acid by formation of the anhydride with a carbonic acid monoester.[1,2] This mixed carboxylic acid–carbonic acid anhydride **3** is generated by reaction of the acid **1** with an alkyl chloroformate (**2**) in the presence of a tertiary amine base. Aminolysis by the nucleophile (**4**) produces the peptide **5**. The method is quick and efficient for chain buildup by the successive addition of single residues.[2,3] Conditions for minimizing racemization during the coupling of peptide acids have been defined.[4,5] Unfortunately, a second acylation product (**6**), namely, a urethane formed by attack of the nucleophile at the carbonic acid carbonyl, results from the aminolysis of the mixed anhydride (see ref 2 and 3). More urethane is produced when the activated residue is valyl or isoleucyl,[6] but little else is known about the reaction. This

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