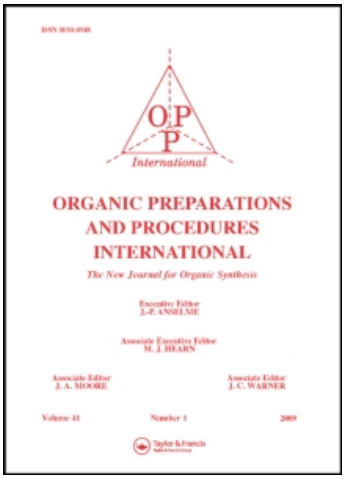

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A NEW AND CONVENIENT PREPARATION OF 3-BROMO-4-CHLORONITROBENZENE

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A NEW AND CONVENIENT PREPARATION OF 3-BROMO-4-CHLORONITROBENZENE

Submitted by (12/12/90
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In the course of our studies on the synthesis of the potent antibacterials "fluoroquinolones",[1] 3-bromo-4-chloronitrobenzene was needed on a large scale. A low yield multi-step synthesis involving exhaustive purification has been described.[2] Although several mild methods are available for bringing about electrophilic bromination of activated aromatic compounds, very few have been reported for deactivated rings. We now describe a simple one-step preparation of 3-bromo-4-chloronitrobenzene by the bromination of easily available p-chloronitrobenzene.

The first method attempted involving the use of liquid bromine, mercuric oxide and sulfuric acid, gave only a 20% conversion after 8 hrs of reflux.[3] The second procedure[4] was modified by changing the mode of addition of potassium bromate and by raising the temperature to 80°. The progress of the reaction was monitored by gas chromatography [OV-1(10%) 6 ft, 110-10-220°]. The results are summarized in the Table. This reaction has been optimized on one mole scale and could easily be carried out on a large scale.

TABLE. Bromination of p-Chloronitrobenzene

Method	Temp. (°C)	Time (hrs	Conversion[a]	Yield[b]
Br_2, HgO	70	3	15%	
H_2SO_4, CCl_4		6	18%	
		8	21%	
$KBrO_3$, H_2SO_4	30	5	0%	
	80	5	94%	85%

a) Based on GC analysis. b) Isolated pure product.

EXPERIMENTAL SECTION

3-Bromo-4-chloronitrobenzene.- To a 3 L three-neck flask, fitted with a mechanical stirrer, a reflux condenser and a thermometer, were added water (800 ml), conc. sulfuric acid (800 ml) and p-chloronitrobenzene (157 g). The well stirred mixture was heated to 80° and potassium bromate (187 g) was added in portions over a period of 3 hrs. Stirring was continued for a further period of 2 hrs

and the reaction mixture was poured onto crushed ice (500 g). The precipitated solid was collected, washed with water and sucked dry. Recrystallization from toluene afforded 200 g (85%) of pure 3-bromo-4-chloronitrobenzene, mp. 62°, lit.[2] 61°.

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A CONVENIENT SYNTHESIS OF (2S)-2-AMINO-3-PHENYLPROPANOL

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(2S)-2-Amino-3-phenylpropanol (**2**) is the precursor to a chiral auxiliary introduced by Evans and co-workers.[1] It is synthesized from L-phenylalanine (**1**) by reduction with borane•dimethyl sulfide.[2] This reaction is exothermic and as Gaze and Evans[2] note "the potential vigor of this exotherm cannot be overemphasized". In addition, dimethyl sulfide (stench) is produced as a side-product. Since we recently had occasion to synthesize the title compound in our studies related to the asymmetric synthesis of unusual amino acids[3] and needed rather large amounts of it, we sought a safer alternative procedure. We have adopted a procedure developed by Giannis and Sanhoff[4] for the reduction of valine and proline and found that reduction of L-phenylalanine (**1**) with lithium borohydride in the presence of chlorotrimethylsilane[4] provides the desired compound **2** in 83% yield. The merits of this procedure are its relative ease of execution and safety. In view of the immense utility of chiral auxiliaries of Evans and co-workers in organic synthesis,[5] we expect our procedure to be very useful.