



Chloro- and Bromo-demethoxylation of Methoxypolynitroaryl Systems

Anthony J. Bellamy* and P. Nick Hudson

Environmental and Chemical Systems Dept., School of Engineering and Applied Science, Royal Military College of Science,
Cranfield University, Shrivenham, Swindon, Wilts SN6 8LA, UK

Abstract. Various reagents for effecting halogenodemethoxylation of methoxy substituted polynitro-phenyl and -biphenyl systems have been investigated, and the preferred procedures for achieving chloro- and bromo-demethoxylation in high yield have been identified.
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Our recently reported¹ strategy for the synthesis of polynitro bi-, ter-, and quater-phenyl systems is dependent upon efficient replacement of aryl methoxy groups by halogen. Although chloro- and bromo-demethoxylation of activated aryl systems is well known,² it was essential to ascertain which were the best halogenating agents and conditions to effect these transformations, and what selectivity was possible in systems which possessed both activated and non-activated methoxy groups.

RESULTS AND DISCUSSION

Our study of the chloro- and bromo-demethoxylation of polynitro-phenyl and -biphenyl systems focused on three basic halogenodemethoxylation procedures:

- (1) treatment with pyridine and a halogenating agent in a co-solvent,³
- (2) treatment with DMF and a halogenating agent in a co-solvent (Vilsmeier-type reagents),^{4,5} and
- (3) treatment with KI in ethanol to effect demethoxylation, followed by treatment of the potassium phenolate salt with a halogenating agent.⁶

The halogenating agents investigated were PCl_5 , POCl_3 and SOCl_2 for chlorodemethoxylation, and PBr_3 and SOBr_2 for bromodemethoxylation, whilst the co-solvents were either toluene or 1,2-dichloroethane.

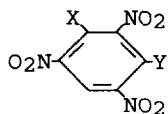
The results obtained with substrates **1**, **2**, **3** and **4** are presented in the Table. From these results we are able to conclude that, in general, the use of a halogenating agent in the presence of DMF and a co-solvent gives consistently better yields than when a halogenating agent is used either alone or in conjunction with pyridine and a co-solvent. For direct chlorodemethoxylation (method 1 or 2), POCl_3 and SOCl_2 with DMF/toluene gave the best yields (76-95 and 83-88% respectively), whilst for direct bromodemethoxylation, PBr_3 and SOBr_2 with DMF, in toluene or 1,2-dichloroethane, are preferred (70-91 and 95% respectively). As has been reported earlier,⁶ demethoxylation of methoxy groups activated by three nitro groups (**1**, X = OMe, Y = H, Cl, Br; **2**, X = OMe, Y = H, OMe; **3**, X = Y = OMe) using KI/ethanol gives the corresponding potassium phenolate salts in high yield. When only two nitro groups are present (**4**, X = OMe), the methoxy group is unreactive under our mild conditions; more forcing conditions

Table 1 - Halogenodemethoxylation of 1, 2, 3 and 4

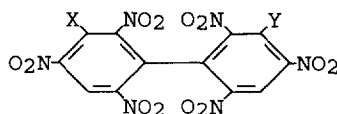
Reactant		Product		Reagent*	Yield (%)
X	Y	X	Y		
1					
OMe	H	O ⁻ K ⁺	H	11	95
O ⁻ K ⁺	H	Br	H	8	100
OMe	Cl	Cl	Cl	1	unchanged
				2	63
				3	impure product
				4	impure product
				5	unchanged
				6	95
				7	88
OMe	Cl	Br	Cl	8	70
OMe	Cl	O ⁻ K ⁺	Cl	11	99
O ⁻ K ⁺	Cl	Cl	Cl	1	73
O ⁻ K ⁺	Cl	Br	Cl	8	83
OMe	Br	Cl	Cl	6	76
OMe	Br	Br	Br	8	84
				9	45
OMe	Br	O ⁻ K ⁺	Br	11	83
O ⁻ K ⁺	Br	Cl	Cl+Br	6	93 (1:1 mixture)
2					
OMe	H	Cl	H	3	78
				6	91
				7	83
OMe	H	Br	H	8	82
				10	95
OMe	H	O ⁻ K ⁺	H	11	98
O ⁻ K ⁺	H	Cl	H	1	100
				7	63
O ⁻ K ⁺	H	Br	H	8	100
OMe	OMe	Cl	Cl	6	90
OMe	OMe	Br	Br	8	90
OMe	OMe	O ⁻ K ⁺	O ⁻ K ⁺	11	95
O ⁻ K ⁺	O ⁻ K ⁺	Br	Br	8	90
3					
OMe	OMe	Cl	OMe	2	49
				6	91
				7	95
OMe	OMe	Br	OMe	8	91
				9	35
4					
OMe	-	O ⁻ K ⁺	-	11	unchanged

* Reagents (further details may be found in the Experimental):

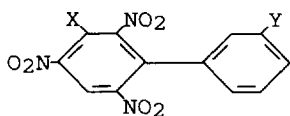
1	POCl ₃	5	SOCl ₂ /toluene	9	SOBr ₂ /DMF/toluene
2	POCl ₃ /pyridine	6	POCl ₃ /DMF/toluene	10	SOBr ₂ /DMF/CICH ₂ CH ₂ Cl
3	POCl ₃ /pyridine/toluene	7	SOCl ₂ /DMF/toluene	11	KI/ethanol
4	PCl ₅ /pyridine/toluene	8	PBr ₃ /DMF/toluene		



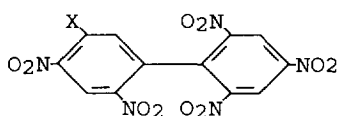
(1)



(2)



(3)



(4)

eg KI/DMF/110°C, may effect demethoxylation in these cases however.⁷ The potassium phenolate salt generated using KI/ethanol may subsequently be halogenated to give overall halogenodemethoxylation (method 3). Chlorodemethoxylation by this route was best achieved using POCl₃ alone (essentially quantitative yield; chlorinating agents in the presence of DMF gave markedly inferior yields). By contrast, bromodemethoxylation by this route was best effected with PBr₃ in the presence of DMF and toluene (83-100%).

Substrates possessing both methoxy and chloro substituents in the same fully activated ring (1, X = OMe, Y = Cl) may be bromodemethoxylated, by either method 2 or 3, with retention of the chloro substituent (1, X = Br, Y = Cl). However chlorodemethoxylation, by either method 2 or 3, of a similar substrate but with bromine instead of chlorine (1, X = OMe, Y = Br) is accompanied by partial or complete replacement of the bromo substituent by chlorine (chlorobromination; 1, X = Y = Cl). Thus the only halogeno-demethoxylation route to the mixed dihalogeno compound 1, X = Br, Y = Cl, is via bromodemethoxylation of the chlorinated precursor.

Halogenodemethoxylation by any of the above methods cleanly differentiates between methoxy groups activated by three nitro groups, and less activated methoxy groups (see substrates 3 and 4). That the latter may be activated towards halogenodemethoxylation at a later stage by further nitration of that particular ring, is an integral part of our strategy for the synthesis of polynitro bi-, ter-, and quater-phenyl systems.¹ We anticipate that those reagents which have been shown to be the best for achieving halogenodemethoxylation in polynitro-phenyl and -biphenyl systems, will also perform well with higher polynitro polyphenyl systems.

EXPERIMENTAL

The general experimental procedures used for the various halogenodemethoxylation reagents are outlined below. For each substrate, the reaction time was determined by following the reaction by TLC, the quantity of halogenating agent and solvent was dictated by the number of methoxy groups to be reacted and by the solubility respectively, and the workup was dictated by the physical properties of the product. When reagents 6, 7 and 8 were used with the potassium phenolate salts (generated by using reagent 11), the

quantity of solvent (toluene) was increased (2-3x), but the proportions of the other reactants remained unchanged. The yields given in the Table are isolated yields. The products were identified and/or characterised by their physical (m.p., TLC, HPLC) and spectroscopic (^1H and ^{13}C NMR) properties, and, where appropriate, elemental analysis. **Warning: many of the compounds involved in this work are potentially explosive, particularly the potassium phenolate salts, and appropriate precautions should be taken.**

Reagent 1 - POCl_3 : 5-20 equivalents of POCl_3 , 100-120°C/30-45min.

Reagent 2 - POCl_3 /pyridine (with or without isolation of the pyridine salt): 4-10 equivalents of pyridine, with POCl_3 equimolar with pyridine, 80-100°C/30-45min.

Reagent 3 - POCl_3 /pyridine/toluene (with or without isolation of the pyridine salt): 4-8ml toluene/mmol, 3-9 equivalents of pyridine, 9-14 equivalents of POCl_3 , 80-100°C/1h.

Reagent 4 - PCl_5 /pyridine/toluene (with isolation of the pyridine salt): toluene 6-7ml/mmol, excess pyridine, 3 equivalents of PCl_5 , 100°C/1h.

Reagent 5 - SOCl_2 /toluene: solution in toluene, 4.5 equivalents of SOCl_2 , reflux.

Reagent 6 - POCl_3 /DMF/toluene: toluene 1-5ml/mmol, 2-3 equivalents of DMF, POCl_3 equimolar with DMF, reflux/1-2h.

Reagent 7 - SOCl_2 /DMF/toluene: toluene 1-3ml/mmol, 2-3 equivalents of DMF, SOCl_2 equimolar with DMF, reflux/1-2h.

Reagent 8 - PBr_3 /DMF/toluene: toluene 1-10ml/mmol, 1-3 equivalents of DMF, PBr_3 equimolar with DMF, reflux 1-2h.

Reagent 9 - SOBr_2 /DMF/toluene: toluene 2-4ml/mmol, 1-2 equivalents of DMF, SOBr_2 equimolar with DMF, 75-95°C/1.5h.

Reagent 10 - SOBr_2 /DMF/ $\text{ClCH}_2\text{CH}_2\text{Cl}$: $\text{ClCH}_2\text{CH}_2\text{Cl}$ 5ml/mmol, 2.8 equivalents of DMF, SOBr_2 equimolar with DMF, reflux/2h.

Reagent 11 - KI/ethanol: ethanol 1.5-10ml/mmol, 1.1-1.5 equivalents of KI, reflux/0.25-3h.

Acknowledgments

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