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VICARIOUS NUCLEOPHILIC SUBSTITUTION OF NITROBENZENES : APPLICATION OF THE REACTION TO 2-ALKYLNITROBENZENES

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ABSTRACT

Vicarious nucleophilic substitution (VNS) by dichloroacetate and other reagents has been applied in good yield to various ortho-substituted nitrobenzenes including 2-nitrotoluene and 2-nitro ethylbenzene. For alkyl nitrobenzenes, ease of VNS increased para < ortho < meta and methyl < ethyl < iso-propyl. Formation of chlorine-free products upon VNS by methyl dichloroacetate suggests the involvement of radical anions.

INTRODUCTION

Recently, it was reported that nitrobenzenes, variously substituted at the 2 and 4 positions as required for further structural elaboration, were accessible by conjugative addition of Grignard reagents to mono-substituted nitrobenzenes under conditions suitable for large scale operation [1]. The method was well suited to

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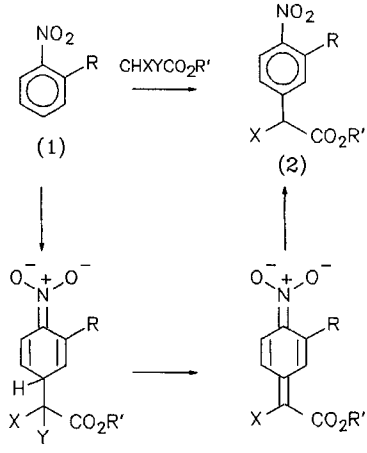
the introduction of primary and secondary alkyl substituents into nitrobenzenes already bearing certain masked functionalities. In contrast, the work of Makosza on vicarious nucleophilic substitution (VNS) offered a complementary synthesis in which the functional group itself could be introduced into nitrobenzenes bearing such groups as halogen, aryl and alkoxy, but not simple alkyl [2]. Thus, each synthesis seemed capable of giving products useful to us but not readily formed by the other method.

Scheme 1.



Unfortunately, for our purposes, the most desirable intermediates (2) (Scheme 1) were those where R was a simple alkyl group and particularly those having a benzylic hydrogen. Under the strongly basic conditions needed for VNS, 2 and 4-alkyl nitrobenzenes can readily lose a benzylic proton so rendering these compounds unsuitable as substrates for VNS. Thus, Mąkosza found that 4-nitrotoluene reacted poorly with chloromethyl-phenylsulphone "because of the high acidity of the methyl group" [3].

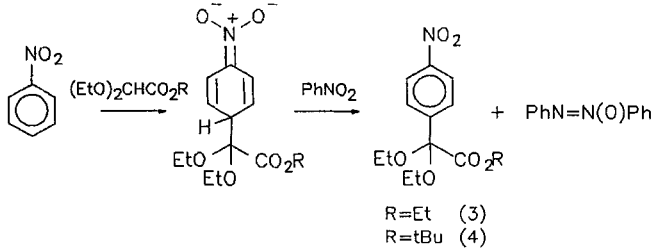
The apparent inapplicability of VNS to nitroderivatives of toluene, ethyl benzene, and the xylenes is

unfortunate because these are the cheapest and most readily available nitroaromatics except for nitrobenzene. Most surprisingly, we have now found that certain of these simple nitro alkylbenzenes can give good yields of VNS products through careful choice of reaction conditions.

RESULTS AND DISCUSSION

As expected, VNS reactions of either ethyl 2-chloropropionate or methyl dihalogenoacetate with nitrobenzenes (1) (Scheme 1) readily gave (2) when R was H, COOMe, Ph, CN, Cl or OMe (Table 1). An unexpected finding was the formation of (3) and (4) (Entry 4 and Scheme 2). This can be attributed to oxidation of an initially formed adduct by nitrobenzene.

Scheme 2.



Reactions with alkyl nitrobenzenes

literature precedence strongly indicates that nitrobenzenes substituted at the 2 or 4 positions by methyl should be totally unsuitable for VNS. Under the strongly basic conditionsneeded for VNS, these methyl nitrobenzenes are expected to react through the methyl

Table 1.

VNS of nitrobenzenes (I) lacking an alkyl substituent (Schemes 1 and 2); reactions in DMF/t-BuOK slurry at -15°C.

N°:	R=	Reagent	Product	% Y	Physical Data (^{1}Hnmr in $CDCl_3$).
1	H	$MeCHClCO_2Et$	4-NO_2PhCHMeCO_2Et	50	m/e 223
2	H	$CHCl_2CO_2Me$	4-NO_2PhCHClCO_2Me	80	m/e 271 (1Cl); δ 3.8s(3.2H),5.5s (1.0H),7.7d(2.0H),8.2d(2.0H).
3	H	$CHBr_2CO_2Et$	4-NO_2PhCHBrCO_2Et	35	m/e 287 (1Br); δ 1.3t(3.1H),4.3m (2.1H),5.4s(0.9H),7.7d(2.0H),8.2d (2.0H).
4	H	$CH(OEt)_2CO_2Et$	4-NO_2PhC$(OEt)_2CO_2$Et, 4-NO_2PhC$(OEt)_2CO_2$tBu & PhN=N(O)Ph	5	m/e 297; δ 1.3m(15H),3.4m(4.0H), 7.8d(2.0H). m/e 198.
5	CO_2Me	$CHCl_2CO_2Me$	4-NO_2-3-MeO_2C-PhCHClCO_2Me	90	m/e 287 (1Cl); δ 3.8s(3.2H),4.0s (2.8H),5.5s(1.0H),7.7-8.1m(3.4H).
6	COMe	$CHCl_2CO_2Me$	4-NO_2-3-MeCO-PhCHClCO_2Me (mixed isomers) & 4-NO_2-3-MeCO-PhCH_2CO_2tBu	10 5	m/e 271 (1Cl). m/e 279 (0Cl).
7	Ph	$CHCl_2CO_2Me$	4-NO_2-3-Ph-PhCHClCO_2Me	80	m/e 305 (1Cl); δ 3.7s(3.1H),5.4s (0.8H),7.2m(1.9H),7.4m(3.1H),7.7m (1.9H),7.9d(1.0H)
8	CN	$CHCl_2CO_2Me$	4-NO_2-3-CN-PhCHClCO_2Me (3:2 ratio of isomers)	80	m/e 254 (1Cl); δ 3.9s(3.0H),5.5s (0.6H),5.7s(0.3H),8.4d(0.8H),7.7-8.2m(3.8H).
9	Cl	$CHCl_2CO_2Me$	4-NO_2-3-Cl-PhCHClCO_2Me	80	m/e 263 (2Cl); δ 3.8s(3.0H),5.4s (1.0H),7.6cd(1.2H),7.75s(1.0H),7.9 d(1.0H),8.0s(0.9H).
10	OMe	$CHCl_2CO_2Me$	4-NO_2-3-MeO-PhCHClCO_2Me & 4-NO_2-3-MeO-PhCHClCO_2tBu	70	m/e 259 (1Cl); δ 1.5s(2.2H),3.8s (2.7H),3.9s(2.7H),5.3s(0.3H),5.4s (0.8H),7.1d(1.0H),7.2s(1.0H),7.8d (1.1H).

group [4]. In a most characteristic reaction, self condensation to give 1,2-diarylethanes is to be expected [5]. Russell and co-workers showed that this condensation and related reactions resulted from the spontaneous formation of radical anions from 2 and 4-nitrotoluenes and alkoxide [6]. Extended reaction periods gave polymers. In accordance with this background, attempts to accomplish the VNS of 2-

Table 2

N°:	R=	Reagents/ media/°C	Product	% Y	Physical Data (^{1}Hnmr in $CDCl_3$).
1	2-Me	$CHCl_2CO_2Me$/ KOtBu/DMF/ -50°C	4-NO_2-3-Me-$PhCHClCO_2Me$ & 4-NO_2-3-Me-$PhCH_2CO_2Me$	50 5	m/e 243 (1Cl); δ 2.6s(3.0H), 3.8s(3.0H),5.4s(1.0H),7.5m (2.1H),8.0d (1.0H). m/e 209 (0Cl).
2	2-Me	$CHCl_2CO_2Me$/ NaOMe/DMF/ -20°C	4-NO_2-3-Me-$PhCHClCO_2Me$ & 4-NO_2-3-Me-$PhCH_2CO_2Me$	70 5	m/e 243 (1Cl); δ 2.6s(3.0H), 3.8s(3.0H),5.4s(1.0H),7.5d (2.1H),8.0d (1.0H). m/e 209 (0Cl).
3	2-Me	$MeCHClCO_2Et$/ KOtBu/DMF/ -40°C	4-NO_2-3-Me-$PhCH(Me)CO_2Et$	60	m/e 237; δ 1.2t(3.1H),1.5d (3.0H),2.6s(3.0H),3.7q (1.0H),4.1m(2.0H),7.3m (2.0H),8.0d(1.0H).
4	2-Me	CH_2ClCO_2Et/ KOtBu/DMF/ -15°C	No VNS products observed		
5	2-Me	$ClCH_2SO_2Ph$/ KOtBu/DMSO/ 20°C	4-NO_2-3-Me-$PhCH_2SO_2Ph$	30	m/e 291.
6	2-Et	$CHCl_2CO_2Me$/ KOtBu/DMF/ -50°C	4-NO_2-3-Et-$PhCHClCO_2Me$ & 4-NO_2-3-Et-$PhCH_2CO_2Me$	50 4	m/e 257 (1Cl); δ 1.3t(3.3H), 2.9m(2.1H),3.8s(3.0H),5.4s (1.0H),7.5m(2.1H),7.9d(1.0H) m/e 223 (0Cl).
7	2-iPr	$CHCl_2CO_2Me$/ NaOMe/DMF/ -5°C	4-NO_2-3-iPr-$PhCHClCO_2Me$	40	m/e 271 (1Cl).
8	3-Me	$ClCH_2SO_2Ph$/ KOtBu/DMSO/ 20°C	4-NO_2-2-Me-$PhCH_2SO_2Ph$ (3:2 ratio mixed isomers)	80	m/e 291.
9	3-Me	$CHCl_2CO_2Me$/ KOtBu/DMF/ -40°C	4-NO_2-2-Me-$PhCHClCO_2Me$ & 4-NO_2-2-Me-$PhCH_2CO_2Me$	60	m/e 243 (1Cl); δ 2.55s (2.9H),3.8s(2.9H),5.6s (0.9H),7.7d(1.0H),8.1m(2.0H) m/e 209 (0Cl).
10	4-Me	$CHCl_2CO_2Me$/ NaOMe/DMF/ -40°C	No VNS products observed		
11	2,5-diMe	$CHCl_2CO_2Me$/ NaOMe/DMF/ -25°C	4-NO_2-2,5-Me_2-$PhCHClCO_2Me$	10	m/e 257 (1Cl).
12	3,5-diMe	$CHCl_2CO_2Me$/ KOtBu/DMF/ -20°C	No VNS products observed		
13	4-Et	$CHCl_2CO_2Me$/ KOtBu/DMF/ -20°C	4-NO_2-2-Et-$PhCH_2CO_2Me$ & 4-NO_2-2-Et-$PhCHClCO_2Me$	10 5	m/e 223 (0Cl). m/e 257 (1Cl).
14	2,6-diMe	$CHCl_2CO_2Me$/ KOtBu/DMF/ -40 to 20°C	No VNS products observed		

nitrotoluene by methyl dichloroacetate or ethyl chloropropionate, under conditions (-5 to 30°C) reported suitable for nitrobenzene [7,8,9] gave 2,2'-dinitrobibenzyl as almost the exclusive volatile product. Most surprisingly, when the reaction temperature was -40°C or less, VNS of 2-nitrotoluene in the presence of potassium t-butoxide became the major pathway (Table 2, Entries 1 and 3). While these reactions were useful for laboratory preparations, the low temperatures needed were not suitable for manufacture. It is known that not all bases capable of removing a proton from the nucleophile precursor will promote VNS [9] and we have been unable to effect the VNS of 2-nitrotoluene by methyl dichloroacetate with potassium carbonate as base. However, use of sodium methoxide gave rise to selective VNS at -20°C, a temperature accessible on the plant (Table 2, Entry 2). High yields of the VNS product resulted only if the reaction was rapidly quenched (Exp.1). The general need for rapid quenching in VNS has been emphasised by Mąkosza [10] and this observation strongly suggests that, on the large scale, the method may be operable only in a continuous mode. Again surprisingly, it was found that the replacement of solid methoxide by a methanolic solution allowed the process to be operated batchwise (Exp.2). Our discovery that 2-nitrotoluene can be selectively functionalised by VNS under conditions

suitable for manufacture is of considerable commercial interest. 2-Nitrotoluene is unavoidably produced as the major but unwanted isomer upon nitration of toluene [11].

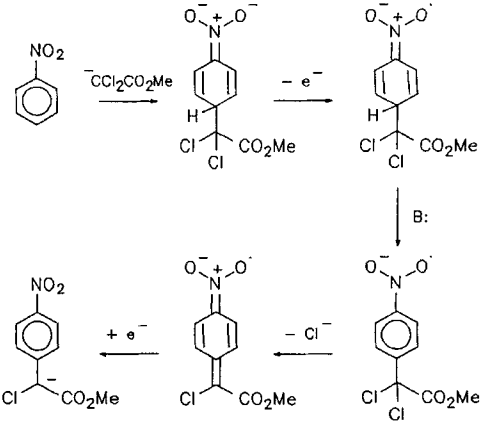
Scope of the reaction

The results of our studies on the scope of VNS of alkyl nitrobenzenes are recorded in Table 2. Briefly, methyl dichloroacetate, ethyl chloropropionate and chloromethylphenylsulphone but not methyl chloroacetate were suitable nucleophile precursors. Among the 2- and 4-alkyl nitrobenzenes studied, ease of VNS, and avoidance of dehydrodimerisation, increased along the series methyl, ethyl, isopropyl. For methylnitrobenzenes, ease of VNS depended on the position of the nitro group and increased in the order para < ortho < meta. This order fits the idea that there is little stabilisation of a benzylic anion by a meta nitro group and that the para-quininoid is more stable than the ortho one [12]. The lack of reactivity of 3,5- and 2,6-dimethylnitrobenzenes was unexpected and may have resulted from steric crowding at the vacant sites (Entry 12) or at the nitro group, preventing co-planarity (Entry 14). Alternatively in both cases, the combined inductive influence of the two methyl substituents (cf Entry 11) and the increased steric requirements may have prevented VNS.

Side products and reaction mechanism

Little is known about the mechanism of VNS, but the sequence of Scheme 1 is usually favoured [2]. The formation of dehydrodimers from alkyl nitrobenzenes during VNS shows that these conditions allow radical anions to be formed and radicals derived from alkyl nitrobenzenes have been detected under conditions suitable for VNS [6]. We have found that a side product often accompanying VNS of nitrobenzenes by methyl dichloroacetate is the nitroarylacetate lacking the expected benzylic chlorine atom (Table 2). These side products may arise from the usual VNS product by dissociative electron capture from an alkoxide anion [13,14]. In collaboration with Prof. Bruce Gilbert and Dr. Adrian Whitworth (University of York) the nitrobenzene radicalanion has been observed during the VNS of nitrobenzene by methyl dichloroacetate in the presence of potassium t-butoxide. The extent to which radical anions lead to VNS has yet to be established, but a plausible sequence by which they might contribute is shown in Scheme 3.

Scheme 3.



CONCLUSIONS

VNS provides a general synthesis of functionalised compounds from simple nitrobenzenes bearing COOR, COR, Ph, CN, Cl, OR or 2-alkyl groups having not more than one benzylic hydrogen. To this list can be added ortho and meta (but not para) methyl or ethyl-nitrobenzenes, provided that the reaction conditions are chosen carefully.

EXPERIMENTAL

Materials

Anhydrous solvents and all other chemicals were purchased from SAF; bulk solvents were purchased from Fisons.

General Procedure (Tables 1 and 2)

The alkoxide (3.0 mol) in DMF or DMSO was stirred at the desired temperature and a mixture of the nitro compound (1.0 mol) and the VNS precursor (1.1 mol) was added dropwise over a few minutes. Samples were withdrawn at intervals, partitioned between dichloromethane and 10% aqueous HCl and the organic phase examined by GC on CP SIL5CB at 80 to 250°C.

Reactions of 2-nitrotoluene with methyl dichloroacetate

Experiment 1: Sodium methoxide (1.7g, 30 mmol) was stirred in DMF (30 ml) at -18°C. Over a period of 1 min there was added dropwise a mixture of 2-nitrotoluene (2.74g, 20 mmol) and methyl dichloroacetate (1.43g, 10 mmol). There was an exotherm (8°C) and the mixture

was quenched rapidly by the addition of 10% aqueous HCl and dichloromethane. GC showed that the extracts contained the VNS product (7 mmol, 70% yield) and 2-nitrotoluene (9 mmol, 45% recovery). The VNS product was isolated by column chromatography on silica with petrol and dichloromethane as eluants.

Experiment 2: 2-Nitrotoluene (54.8g, 0.4 mol), dodecane (1.97g; internal standard), methanol (6 ml) and DMF (40 ml) were charged to a 500 ml jacketted reactor flask. After cooling to -15°C, two solutions (A and B) were added. Solution A was a mixture of methyl dichloroacetate (11.6g, 0.08 mol), 2-nitro-toluene (11.0g, 0.08 mol) and DMF (20 ml). Solution B was a mixture of 30% sodium methoxide in methanol (62 ml) and DMF (138 ml). These solutions were stored at 0°C and pumped into the reaction mixture using peristaltic pumps. The addition of solution B took three hours. The addition of solution A was started 40 mins after that of solution B and took one hour. The optimum yield of VNS was estimated at around two hours after the end of additions, and corresponded to about a 70% yield. After 3 hours, the reaction mixture was drowned into ice cold 5% hydrochloric acid, extracted with dichloromethane, dried (magnesium sulphate), filtered and concentrated under vacuum. The isolated material contained about a 65% yield of VNS. The crude material was purified by high vacuum topping and column

chromatography on silica with ethyl acetate and petrol as eluants. The isolated product (51% yield) was a pale yellow oil of >98% strength by gc and identical to a sample of methyl chloro-(3-methyl-4-nitrophenyl)-acetate prepared [1] by conjugate addition of methyl magnesium bromide to methyl chloro-(4-nitrophenyl)-acetate (Table 1, Entry 2).

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