Vicarious Substitution of Hydrogen in Aromatic Nitro Compounds with α-Chloro Sulfoxides: A New Synthesis of Nitrobenzyl Sulfoxides[1]

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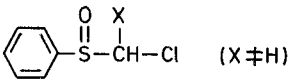
In our previous communications[2a,b], we have shown that some carbanions containing leaving groups in the α-position react with aromatic nitro compounds with replacement of the hydrogen atom in the *para* or *ortho* position to the nitro group. In such nucleophilic substitutions of hydrogen, the leaving group of the carbanion departs as an anion instead of a hydride anion, thus, the term *vicarious substitution* was proposed. This reaction proceeds well with substituted carbanions whose conjugate *C—H* acids do not readily enter S_N2 type substitutions of the leaving group. α-Haloalkylphenyl sulfones, *N,N*-dialkyl-α-haloalkanesulfonamides[2a], α-phenoxy- and α-phenylthioalkanenitriles[2b] belong to this category. Also in the case of α-chloro sulfoxides, the halogen atom is not easily replaced via S_N2 type reactions[3]; therefore, one can expect that these compounds will react via vicarious substitution of hydrogen with nitroarenes. Indeed, α-chlorobenzyl phenyl sulfoxide reacts readily with nitrobenzene in the presence of an excess of powdered sodium hydroxide in dimethyl sulfoxide giving the corresponding 4-nitrobenzhydryl phenyl sulfoxide (yield 53%).

Unlike chloromethyl phenyl sulfone[2a], chloromethyl phenyl sulfoxide (a weaker *C—H* acid) does not react with nitrobenzene under these conditions, however it does react in the presence of an excess of tetrabutylammonium hydroxide in *o*-dichlorobenzene. Instead of using separately prepared tetrabutylammonium hydroxide, the reaction can be carried out in a two-phase system benzene/concentrated aqueous sodium hydroxide solution in the presence of 2 equivalents of tetrabutylammonium hydrogen sulfate (2 equivalents are necessary since the products, nitrobenzylic sulfoxides, are much stronger *C—H* acids than the starting compounds, therefore they remain in the organic phase in the form of anions associated with the tetraalkylammonium cations[4]). On the other hand, dichloromethyl phenyl sulfoxide (a rather strong *C—H* acid) reacts with nitroarenes in the presence of sodium hydroxide in liquid ammonia.

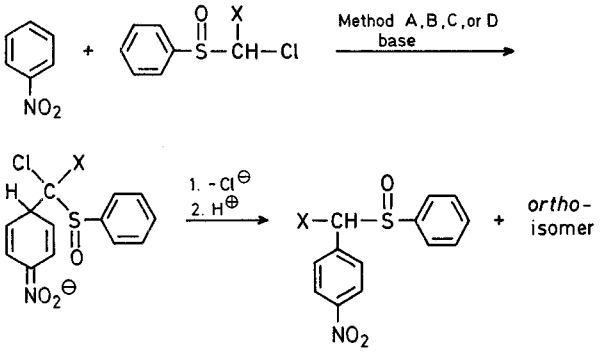
The reaction seems to be highly sensitive to the conditions, however tetrabutylammonium hydroxide in dichlorobenzene appears to be an efficient base in all cases and usually gives higher yields than powdered sodium hydroxide in dimethyl sulfoxide or liquid ammonia. In the reaction of chloromethyl phenyl sulfoxide with nitroarenes, tetrabutylammonium hydroxide was, in our hands, the only effective base.

When starting sulfoxides of the general formula



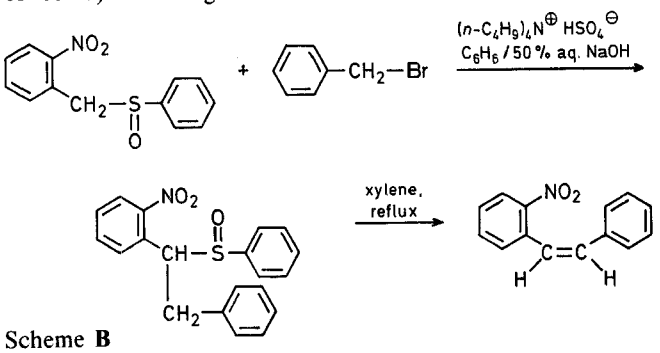
(X≠H)

are used, the products were usually formed as mixtures of two diastereoisomers. In some cases these mixtures were separated by crystallization (Scheme A and Table).



Scheme A

Nitrobenzyl phenyl sulfoxides, easily prepared via the vicarious substitution of hydrogen, appear to be versatile starting materials in the synthesis of a variety of nitroarenes containing a side chain, because the phenylsulfinyl group, unlike the phenylsulfonyl group, is readily removed from a molecule[5]. For example, *o*-nitrobenzyl phenyl sulfoxide, obtained as the major product in the reaction of chloromethyl phenyl sulfoxide with nitrobenzene, was transformed into (*Z*)-2-nitrostilbene in an overall yield of 53% (m.p. 66–67 °C; Ref.[6], m.p. 65–66 °C) according to Scheme B.



Scheme B

The results presented in this paper demonstrate further extensions of the vicarious substitution of hydrogen on a rather large group of *C—H* acids.

α-Chlorobenzyl phenyl sulfoxide and chloromethyl phenyl sulfoxide were prepared according to known methods[8,9]. Dichloromethyl phenyl sulfoxide was prepared by chlorination of chloromethyl phenyl sulfoxide at 10 °C following the general procedure of Ref.[9], since the procedure of Ref.[10] (in the absence of base) gave impure product.

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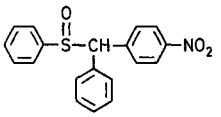
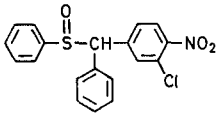
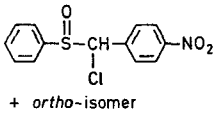
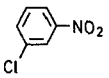
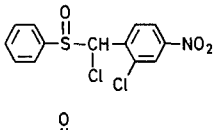
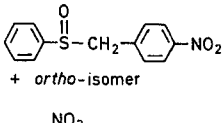
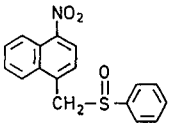
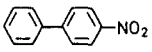
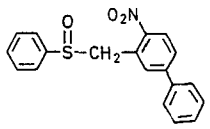
Table. Reactions of Aromatic Nitro Compounds with α-Chloro Sulfoxides

Nitro-arene	X	Product[a]	Yield [%] by Method				Isomer ratio[b]	m.p. [°C]	Molecular formula[c]
			A	B	C	D			
			53	50	66	—	only *p* (Method A)	114–115°[d]	$C_{19}H_{15}NO_3S$ (337.4)
			57	—	—	—	only *p*	112–114°[d]	$C_{19}H_{14}ClNO_3S$ (371.8)
	Cl	 + *ortho*-isomer	trace	57	68	—	*o*:*p* = 1:3 (Method B)	*p*: 105–106°[d] *o*: 112.5–114.5°[d]	$C_{11}H_{16}ClNO_3S$ (295.7)
	Cl		—	68	64	—	only *p* (Method B)	—[e]	$C_{13}H_9Cl_2NO_3S$ (330.2)
	H	 + *ortho*-isomer	0	0	45	54	*o*:*p* = 2:1 (Method D)	*o*: 108–109° *p*: 163–164°[f]	$C_{13}H_{11}NO_3S$ (261.3)
	H	 + 1,2-isomer	—	—	51	58	1,4:1,2 = 1:1 (Method D)	149–152°[g]	$C_{17}H_{13}NO_3S$ (311.4)[h]
	H		—	—	52	59	—	123–124°	$C_{19}H_{15}NO_3S$ (337.4)

[a] Products characterized by I.R. and ^{1}H-N.M.R. spectra and in some cases by oxidation to the corresponding sulfones and nitrobenzoic acids.
[b] Determined from the ^{1}H-N.M.R. spectra.
[c] Satisfactory microanalyses obtained: C ±0.44, H ±0.25, N ±0.15.
[d] m.p. of one isolated diastereoisomer.
[e] m.p. of sulfone: 170–172 °C.
[f] Ref.[7], m.p. 161–162 °C.
[g] m.p. of 1,4-isomer.
[h] Analysis of 1,4-isomer.

Reactions of Aromatic Nitro Compounds with α-Chloro Sulfoxides

Method A, using powdered sodium hydroxide in dimethyl sulfoxide: A solution of the sulfoxide (5 mmol) and the nitroarene (5 mmol) in dimethyl sulfoxide (10 ml) is added dropwise to a stirred suspension of powdered sodium hydroxide (1 g, 25 mmol) in dimethyl sulfoxide (20 ml), while the temperature is kept at ~20 °C. After the addition is completed the mixture is stirred at 20 °C for 1 h, then poured on ice (50 g), neutralized with acetic acid, and extracted with dichloromethane (3 × 50 ml). The combined extracts are washed with water, dried with anhydrous magnesium sulfate, the solvent evaporated, and the residue purified by column chromatography on silica gel eluting with cyclohexane/ethyl acetate.

Method B, using sodium hydroxide in liquid ammonia: A solution of the sulfoxide (10 mmol) and the nitroarene (10 mmol) in tetrahydrofuran (15 ml) is added dropwise to a suspension of powdered sodium hydroxide (2 g, 50 mmol) in liquid ammonia (100 ml). After 1 h of stirring at −30 °C, the ammonia is evaporated, the residue neutralized with dilute sulfuric acid, extracted with dichloromethane (3 × 50 ml), and purified as described for Method A.

Method C, using tetrabutylammonium hydroxide in *o*-dichlorobenzene: A stirred suspension of tetrabutylammonium hydrogen sulfate (2 g, 6 mmol) in *o*-dichlorobenzene (15 ml) is cooled and treated with 50% aqueous sodium hydroxide solution (10 ml) added portionwise (strong exothermic effect). After 15 min, the layers are separated. To the solution of tetrabutylammonium hydroxide in *o*-dichlorobenzene is added first hexamethylphosphoric triamide (1 ml), and then with stirring and cooling (the temperature is kept at ~10 °C) a mixture of the sulfoxide (2.5 mmol) and the nitroarene (2.5 mmol). The mixture is stirred at 10–15 °C for 1 h, then poured on ice (20 g), neutralized with acetic acid, and extracted with dichloromethane (3 × 30 ml). The combined extracts are dried with anhydrous magnesium sulfate, evaporated at room temperature, and the residue purified as described in Method A.

Method D, using 50% aqueous sodium hydroxide and tetrabutylammonium hydrogen sulfate in benzene: To a cooled and stirred mixture of sulfoxide (2.5 mmol), nitroarene (2.5 mmol), tetrabutylammonium hydrogen sulfate (1.7 g, 5 mmol), hexamethylphosphoric triamide (1 ml), and benzene (20 ml), 50% aqueous sodium hydroxide solution (30 ml) is added dropwise. The mixture is stirred at 10 °C for 1 h, then poured on ice (50 g). The product is purified as described in Method A.

(*Z*)-2-Nitrostilbene:

A solution of benzyl bromide (0.85 g, 5 mmol) in benzene (5 ml) is added dropwise to a stirred mixture of 2-nitrobenzyl phenyl sulfoxide (1.3 g, 5 mmol), benzene (20 ml), tetrabutylammonium hydrogen sulfate (0.8 g, 2 mmol), and 50% aqueous sodium hydroxide solution (10

ml). The mixture is stirred at room temperature till the deep blue coloration of the mixture disappears (~6 h). After the typical work-up by Method A, the residue is dissolved in xylene (50 ml) and refluxed for 4 h. The solvent is evaporated and the product is purified from tars by filtration through a layer of silica gel. 2-Nitrostilbene is obtained as a ~10:1 mixture of (*Z*)- and (*E*)-isomers (from G.L.C.; conditions: 5% OV-17 on Chromosorb W, 1.25 m column at 200 °C); yield: 0.6 g (53%); from which (*Z*)-isomer is isolated by crystallization from ethanol; m.p. 66–67 °C (Ref.[6], m.p. 65–66 °C).

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