Vicarious Nucleophilic Substitution of Hydrogen in Nitrobenzoic Acids[1]

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The vicarious nucleophilic substitution of hydrogen in three isomeric nitrobenzoic acids **2**–**4** was studied. The negatively charged carboxylate anion substituent does not disturb the reaction course which proceeds with good to moderate yields to give products **6** and **7**.

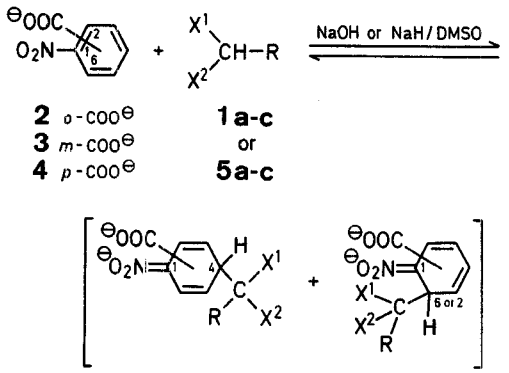
The vicarious nucleophilic substitution of hydrogen is a process by which hydrogen atoms in nitroarenes and some heterocycles can be replaced by functionalized methyl or alkyl substituents[2]. The reaction proceeds via the addition of carbanions containing leaving groups X^1 (e. g. halogen) to nitroarenes followed by base-induced β-elimination of HX^1 from the adducts, known as σ-complexes[3]. Protonation of the resulting nitrobenzylic carbanions during the work up procedure gives the reaction products. The process is of general character with respect to nitroarenes, which can practically contain an unlimited variety of substituents[4]. Here we report that negatively charged carboxylate anion substituents generally do not impede the reaction, although in such cases it proceeds via the addition of carbanions to anions. Since the carboxylate anion substituent does not exhibit a strong electronic effect on the aromatic ring, e.g. $\sigma_{m\text{-}COO^\ominus} = -0.15$[5], these findings are not unexpected.

Results of the reactions of *o*-, *m*-, and *p*-nitrobenzoic acids **2**, **3**, and **4**, respectively (the numbers denote the position of carboxylate anion substituent in relation to the nitro group, this system is used throughout the paper) with 1-chloroalkyl sulfones **1a**–**c** and acetonitrile derivatives **5a**–**c** are given in the Table.

The reaction of the *para*-substituted acid **4** with **1a, b** and **5a**–**c** gave the best results if the product yields are considered. This is also the simplest case since only one product can be formed. On the other hand the tertiary carbanion of **1c** does not react with **4**. It has already been observed that tertiary carbanions do not, as a rule, replace hydrogen *ortho* to the nitro group, apparently due to the steric hindrance in the β-elimination step[4].

The reaction of the *meta*-substituted acid **3** may lead to three isomeric products since there are three positions (2-, 4-, and 6-) available for the nucleophilic attack. Similar to other cases of 3-substituted nitrobenzene derivatives (where the substiuent is electron-withdrawing and bulky) here also the reaction at position 2 was not observed, thus only two isomers (4- and 6-) were formed. We have expected that the negatively charged carboxylate anion group will exert electrostatic repulsion toward carbanionic addition and consequently strong preference for the substitution at position 6 will be observed. This was not, however, the case; in the reaction of **1a** with **3** the ratio of 4-/6- products was 0.67, whereas with the ester, methyl 3-nitrobenzoate, the ratio of 4-/6- products was 0.4. The carboxylate anion group also does not affect relations between the substitution of hydrogen and halogen. In the reaction of **1a** with *meta*-substituted **3** containing a chlorine atom in 4- and 6-positions, substitution of hydrogen at positions 6 and 4, respectively, occurred exclusively, substitution of the halogen was not observed.

A peculiar difference in the orientation pattern was observed in the reaction of *meta*-substituted **3** with **5a** and **5b, c**:



6 **7**

1or5	X^1	X^2	R
1a	Cl	H	$-SO_2-C_6H_5$
1b	Cl	H	$-SO_2-N$(morpholine)
1c	Cl	C_2H_5	$-SO_2-C_6H_5$
5a	C_6H_5-O-	H	$-C\equiv N$
5b	C_6H_5-S-	H	$-C\equiv N$
5c	$(H_3C)_2N-C(=S)-S-$	H	$-C\equiv N$

namely the exclusive substitution at positions 6 and 4, respectively. Although this observation cannot be satisfactorily rationalized, it presents considerable practical value.

Addition of carbanions to *ortho*-substituted **2** can be hindered by the repulsive interaction between the carboxylate anion and the vicinal, negatively charged nitro group, hence the resulting σ-complexes should be destabilized. This can be considered as a secondary stereoelectronic interaction, in analogy to the secondary steric hindrance which is of significant importance in S_NAr reactions and also in the vicarious substitution of hydrogen. This effect does, in fact, operate, **2** is much less active than **3** and **4**, and the ester of **2** gives much better results than the acid **2**, which was not the case for **3** and **4**. On the other hand, only **2** has a sterically unhindered *para*-position, thus it reacted with the tertiary carbanion of **1c**.

We have also found that two isomeric nitrophthalic acids react with **1a** according to the vicarious nucleophilic substitution pathway. In 4-nitrophthalic acid (3,4-dicarboxynitrobenzene according to the system used in this paper) the substitution occurs at position 6 whereas in 2,3-dicarboxynitrobenzene the substitution at positions 4 and 6 was observed. Due to technical difficulties the latter mixture was not separated; it gave, after purification, correct elemental analysis, from the ^{1}H-N.M.R. it was estimated that the 4-/6-isomer ratio is close to 1. Here we have examples of the addition of a carbanion to a dianion with the formation of the intermediate trianion from which hydrogen chloride is eliminated.

Finally the reaction with *p*-nitrophenylacetic acid and its *t*-butyl ester has been studied. A solution of sodium salt of this

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Table. Reactions of Nitrobenzoic Acids **2, 3, 4** with Carbanions of **1a–c** or **5a–c**

Nitrobenzoic Acid (or Ester)	Carbanion Precursor	Position of Substituents in Product **6/7** (Relative to $NO_2 = 1$ in benzene ring)		Yield[a] [%]	m.p. [°C] (solvent)	Molecular Formula[b]	^{1}H-N.M.R. ($CDCl_3$/TMS)[c] δ_{CHRX^2} [ppm]
4	**1a**	4-COOH	$2\text{-}CH_2SO_2C_6H_5$	65	252–254° (C_2H_5OH)	$C_{14}H_{11}NO_6S$ (321.3)	5.27
4	**1b**	4-COOH	$2\text{-}CH_2SO_2$ morpholine	60	230–232° (i-C_3H_7OH)	$C_{12}H_{14}N_2O_7S$ (330.3)	5.08
4	**5b**	4-COOH	$2\text{-}CH_2CN$	77	181–184° (c-$C_6H_{12}/CHCl_3$)	$C_9H_6N_2O_4$ (206.2)	4.50
4	**5c**	4-COOH	$2\text{-}CH_2CN$	45	as above		
4	**1c**	no reaction		–	–	–	–
4 (t-C_4H_9 ester)	**1a**	$4\text{-}COOC_4H_9\text{-}t$	$2\text{-}CH_2SO_2C_6H_5$	62	115–118° (C_2H_5OH)	$C_{18}H_{19}NO_6S$ (377.4)	5.31
3	**1a**	3-COOH	$4\text{-}CH_2SO_2C_6H_5$	23	257–260° (C_2H_5OH/H_2O)	$C_{14}H_{11}NO_6S$ (321.3)	5.32
		3-COOH	$6\text{-}CH_2SO_2C_6H_5$	34	203–206° (C_2H_5OH)	$C_{14}H_{11}NO_6S$ (321.3)	5.50
3	**1c**	no reaction		–	–	–	–
3	**5a**	3-COOH	$6\text{-}CH_2CN$	28	143–144° ($CHCl_3/CH_3OH$)	$C_9H_6N_2O_4$ (206.2)	4.45
3	**5b**	3-COOH	$4\text{-}CH_2CN$	74	158–160° (CH_3OH)	$C_9H_6O_4$ (206.2)	4.56
3	**5c**	3-COOH	$4\text{-}CH_2CN$	37	as above		
4-Cl-**3**	**1a**	3-COOH 4-Cl	$6\text{-}CH_2SO_2C_6H_5$	42	208–210° (CH_3OH)	$C_{14}H_{10}ClNO_6S$ (355.7)	5.21
6-Cl-**3**	**1a**	3-COOH 6-Cl	$4\text{-}CH_2SO_2C_6H_5$	39	206–209° (CH_3OH)	$C_{14}H_{10}ClNO_6S$ (355.7)	5.33
3 (CH_3 ester)	**1a**	$3\text{-}COOCH_3$	$4\text{-}CH_2SO_2C_6H_5$	22	127–130° (C_2H_5OH)	$C_{15}H_{13}NO_6S$ (335.2)	5.40
		$3\text{-}COOCH_3$	$6\text{-}CH_2SO_2C_6H_5$	55	114–116° (C_2H_5OH)	$C_{15}H_{13}NO_6S$ (335.2)	5.32
2	**1a**	2-COOH	$4\text{-}CH_2SO_2C_6H_5$	14[d]	–	–	4.85; 4.94
		2-COOH	$6\text{-}CH_2SO_2C_6H_5$				
2	**1c**	2-COOH	$4\text{-}CH(C_2H_5)SO_2C_6H_5$	18	202–204° (C_2H_5OH)	$C_{16}H_{15}NO_6S$ (349.4)	4.95 (t)
2	**5b**	2-COOH	$4\text{-}CH_2CN$	12	162–164° (CH_3OH)	$C_9H_6N_2O_4$ (206.2)	4.35
		2-COOH	$6\text{-}CH_2CN$	16	132–135° ($CHCl_3/CH_3OH$)	$C_9H_6N_2O_4$ (206.2)	4.23
2 (t-C_4H_9 ester)	**1a**	$2\text{-}COOC_4H_9\text{-}t$	$4\text{-}CH_2SO_2C_6H_5$	29	166–168° (C_2H_5OH)	$C_{18}H_{19}NO_6S$ (377.4)	4.98
		$2\text{-}COOC_4H_9\text{-}t$	$6\text{-}CH_2SO_2C_6H_9$	26	160–162° (C_2H_5OH)		4.90
4-HOOC-**3**	**1a**	3,4-di-COOH	$6\text{-}CH_2SO_2C_6H_5$	15	252–255° (H_2O)	$C_{15}H_{11}NO_8S$ (365.4)	5.32
2-HOOC-**3**	**1a**	2,3-di-COOH	$4\text{-}CH_2SO_2C_6H_5$	52[d]	–	–	5.03; 5.16
		2,3-di-COOH	$6\text{-}CH_2SO_2C_6H_5$				
4-nitrophenyl-acetic acid	**1a**	$4\text{-}CH_2COOH$	$2\text{-}CH_2SO_2C_6H_5$	32	227–230° (CH_3OH)	$C_{15}H_{13}NO_6S$ (335.3)	5.12

[a] Not optimized yields as determined by ^{1}H-N.M.R. spectrometry.

[b] Satisfactory microanalyses obtained: C ±0.35, H ±0.25, N ±0.30.

[c] The position of the entering substituents were determined on the basis of the ^{1}H-N.M.R. spectra of aromatic proton region, here only signals of methylene group protons $—C\underline{H}_2—X^2$ or $—C\underline{H}R—X^2$ are given.

[d] Mixture of isomers not separated.

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acid in dimethyl sulfoxide is pale yellow, but it turns to deep red upon addition of powdered sodium hydroxide, obviously due to the formation of the dianion. Nevertheless the substitution of hydrogen *ortho* to the nitro group takes place under these conditions, although with only moderate yield.

On the other hand, *t*-butyl nitrophenylacetate does not react with **1a** under similar conditions. Thus, we can conclude that in the case of the acid, an equilibrium exists between the mono- and dianion, the former being reactive toward carbanions, whereas the *t*-butyl ester, being a much stronger *C—H* acid, is completely deprotonated under these conditions and therefore unreactive. For the same reason the disubstitution of hydrogen in mononitroarenes and also reactions with mononitrophenols do not occur[6].

From these results it can be concluded that the vicarious nucleophilic substitution is not impeded by the negatively charged substituents in which the negative charge is not conjugated with the ring and thus, the method offers interesting possibilities for the synthesis of substituted nitrobenzoic acids.

Melting points are uncorrected. The ^{1}H-N.M.R. spectra were recorded on a JEOL-INH-MW-100 spectrometer at 100 MHz. Column chromatography was performed using silica gel (Merck 100–200 mesh or 70–230 mesh). All yields were determined on the basis of ^{1}H-N.M.R. spectra of the crude reaction mixtures, recorded in the presence of a known amount of internal standard, α-phenylthio-4-nitrobenzyl methyl sulfone.

Reactions of Nitrobenzoic Acids and their Esters, 3- and 4-Nitrophthalic Acids and 4-Nitrophenylacetic Acid with Carbanions of 1a–c, 5a–c; General Procedure:

To an intensively stirred suspension of powdered sodium hydroxide (1 g, 25 mmol; sodium hydride for the reaction of **3** with **5a** or potassium *t*-butoxide for the reaction of the ester **3** with **1a**) in dimethyl sulfoxide (10 ml), the nitro compound (5 mmol) is added while the temperature is kept at 18 °C. After 5 min a *C—H* acid (5 mmol) in dimethyl sulfoxide (10 ml) is added dropwise. The mixture is stirred for 50 min at the above temperature, poured into a mixture of ice (50 g) and dilute hydrochloric acid (100 ml) and extracted with ethyl acetate or dichloromethane (3 × 50). The products are isolated by one of the following procedures:

(1) For reactions of the nitrobenzoic acids, the organic layer is shaken with aqueous potassium carbonate (2 × 50 ml). The combined aqueous layer is extracted with dichloromethane (3 × 20 ml), acidified and extracted with ethyl acetate (3 × 50 ml). The extract is washed with water (100 ml), dried with magnesium sulfate, evaporated and afterwards:

(a) In the case of the reactions of 4-chloro- **3**, 6-chloro- **3**, and *p*-nitrophenylacetic acid with **1a**, the crude products are recrystallized.

(b) In the case of the reaction of **2** with **5b**, the residue is treated with warm benzene (50 ml). The part which does not dissolve is the crude 5-cyanomethyl-2-nitrobenzoic acid. It is purified by recrystallization. Evaporation of the benzene solution yields 3-cyanomethyl-2-nitrobenzoic acid which is purified by recrystallization.

(c) In the case of the reaction of 4-nitrophthalic acid with **1a**, the residue is treated with warm chloroform (100 ml) and the product is isolated by recrystallization of the undissolved solid.

(d) In the remaining cases, the residue is extracted with warm water (100 ml) in order to remove the substrates; recrystallization of the undissolved part gives products.

(2) For the reaction of the esters with **1a**, the dichloromethane solution is washed with water (100 ml) and dried with magnesium sulfate. Products are isolated by means of column chromatography using the following solvents: ester of **4**; 1:4 ethyl acetate/chloroform; ester of **3**; 1:5 dichloromethane/benzene; ester of **2** 1:1:1 ethyl acetate/chloroform/cyclohexane, and recrystallized.

(3) For the reaction of ester of **3** with **1a**, the extract is washed with water and dried. The solvent is removed under vacuum and the residue crystallized.

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[2] Goliński, J., Mąkosza, M. *Tetrahedron Lett.* **1978**, 3495. Mąkosza, M., Winiarski, J. *J. Org. Chem.* **1980**, *45*, 1534.
[3] Mąkosza, M., Glinka, T. *J. Org. Chem.* **1983**, *48*, 3860.
[4] Mąkosza, M., Goliński, J., Baran, J. *J. Org. Chem.* **1984**, *49*, 1488.
[5] Taft, R.W., Lewis, I.C. *J. Am. Chem. Soc.* **1984**, *81*, 5343.
[6] Mąkosza, M., Ludwiczak, S. *J. Org. Chem.* **1984**, *49*, 4562.

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