Vicarious Nucleophilic Substitution of Hydrogen in Nitroarenes by Carbanions of Alkyl Dichloroacetates. Some New Transformations of Chloro(nitroaryl)acetates[1]

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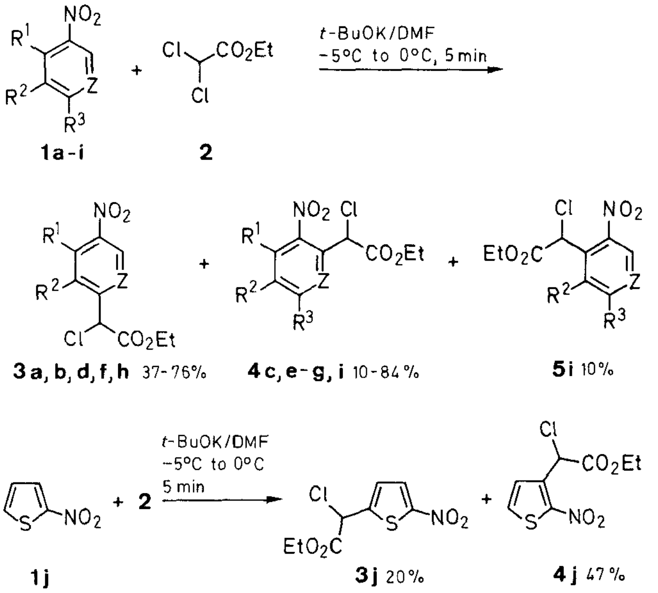
Vicarious Nucleophilic Substitution of Hydrogen in nitroarenes by ethyl dichloroacetate anion provides ethyl chloro(nitroaryl)acetates, which can be transformed into ethyl imino(nitroaryl)acetates and ethyl oxo(nitroaryl)acetates by treatment with sodium azide.

Ring substituted arylglycines, particularly (aminoaryl)-glycines are important intermediates in the synthesis and manufacturing of semisynthetic β-lactam antibiotics, hence there is a great interest in simple and versatile methodology leading from available starting materials to these amino acids.[2] A feasible approach to this problem appeared to be the synthesis of halo(nitroaryl)acetic esters via Vicarious Nucleophilic Substitution of Hydrogen (VNS)[3] followed by exchange of the halogen for an amino group. This is strongly supported by the report that bromo(4-nitrophenyl)acetic acid is transformed into (4-nitrophenyl)glycine by treatment with ammonia.[4] VNS is a general method to introduce α-functionalized alkyl substituents into aromatic nitro compounds by the reaction with carbanions of the general structure $X\text{-}CR\text{-}Y^-$ (where X = Cl, Br, OAr, SAr, etc.; Y = SO_2Ar,[5] CN,[6] CO_2R,[7] $P(O)(OEt)_2$,[8] etc.). The orientation pattern of this reaction is dependant on the structure of both nitroarenes and reacting carbanions. Secondary carbanions such as chloromethyl sulfones,[5,9] alkyl chloroacetates,[7] etc. react in both *ortho* and *para* positions, whereas tertiary carbanions react predominantly at the *para* position.[10] Various dichloro-substituted carbanions such as derived from α,α-dichloromethyl sulfones,[5] sulfoxides,[11] phosphonates[12] and even chloroform[13] and bromoform[13] react satisfactorily according to the VNS scheme.

Since (4-nitrophenyl)glycine is efficiently produced via substitution of bromine in bromo(4-nitrophenyl)acetic acid,[4] synthesis of the corresponding ester was first attempted by the reaction of nitrobenzene with ethyl dibromoacetate. Reaction, in the presence of potassium *tert*-butoxide in dimethylformamide, however, gave the desired product in < 10% yield.

On the other hand, the reaction of ethyl dichloroacetate (**2**) with nitrobenzene (**1a**) performed under similar conditions (potassium *tert*-butoxide in dimethylformamide) gave ethyl chloro(4-nitrophenyl)acetate (**3a**) in 76% yield. Similarly reactions of **2** with other nitro compounds gave the corresponding ethyl α-chloro(nitroaryl)acetates (Table 1). The orientation pattern (predominantly *para* to the nitro group) was analogous to that which has been observed in the cases of other tertiary carbanions. However, when the *para* position was occupied, e.g. 4-chloronitrobenzene (**1c**), the *ortho* product was obtained.

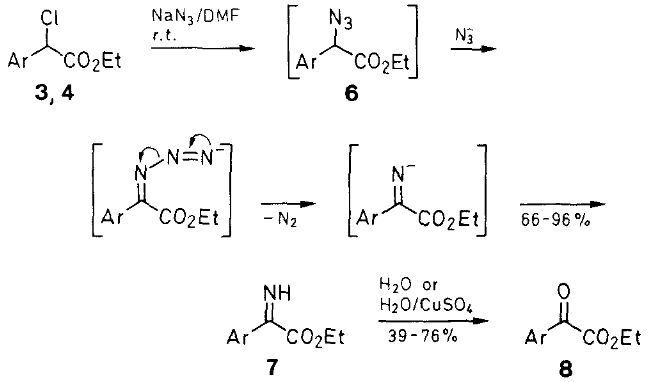
Our particular interest was directed toward the transformation of the obtained chloro(nitroaryl)acetates **3** into (4-aminophenyl)glycines. We intended to employ an approach as described for bromo(4-nitrophenyl)acetic acid,[4] to the chloro analogue and its derivatives. However, our attempts of introduction an amino group via substitution of the chlorine in the reaction of **3** or **4** with ammonia or amino-group equivalents, such as phthalimide or nitrite anions, failed. Reactions of chloro(4-nitrophenyl)acetic acid and the corresponding ester **4a** with these reagents gave unidentified tarry products. These results are probably due to the electron-transfer processes, which lead to complex mixture of unidentified materials. The tendency of 4-nitrobenzyl-type chlorides to undergo such processes is known.[14]



1, 3–5	Z	R¹	R²	R³
a	CH	H	H	H
b	CH	Cl	H	H
c	CH	H	H	Cl
d	CH	H	NO_2	H
e	CH	H	H	CO_2Et
f	CH	benzo		H
g	N	H	H	OMe
h	N	OEt	H	H
i	N	H	H	Cl

Scheme A

Other methodologies for the transformation of α-chloro acids into α-amino acids consist in the substitution of chlorine by the azido group followed by the reduction of the resulting α-azido derivative and also in the reactions of such chloro derivatives with alkali metal cyanates which, after hydrolysis of the obtained urethanes, give amino acid derivatives. Both of these methods gave unexpected results when applied to esters of chloro(nitroaryl)acetic acids **3**, **4**. In the reaction of ethyl chloro(4-nitrophenyl)acetate (**3a**) with sodium azide in dimethylformamide evolution of gas was observed and after few minutes the starting material disappeared. After workup with water, ethyl oxo(4-nitrophenyl)acetate (**8a**) was isolated in 75% yield. This reaction proceeds probably via formation of unstable α-azido compound **6** which is a strong C–H acid. Compound **6** exists in the mixture in the form of the corresponding carbanion which undergoes elimination of nitrogen to result in imine **7a**. The imine **7a** hydrolyzes to oxoacetate **8a** during the aqueous workup. The hydrolysis of imines **7** was accelerated by the addition of copper(II) salts.



Scheme **B**

Table **1.** Reactions of Ethyl Dichloroacetate with Aromatic Nitro Compounds **1**

Substrate	Product[a]	Yield (%)	Molecular Formula[b]
1a	**3a**	75	$C_{10}H_{10}ClNO_4$ (243.6)
1b	**3b**	76	$C_{10}H_9Cl_2NO_4$ (278.1)
1c	**4c**	62	$C_{10}H_9Cl_2NO_4$ (278.1)
1d	**3d**	39	$C_{10}H_9ClN_2O_6$ (288.6)
1e	**4e**	10	$C_{13}H_{14}ClNO_6$ (315.7)
1f	**3f**	37	$C_{14}H_{12}ClNO_4$ (293.7)
	4f	14	$C_{14}H_{12}ClNO_4$ (293.7)
1g	**4g**	84	$C_{10}H_{11}ClNO_5$ (228.7)
1h	**3h**	71	$C_{11}H_{13}ClN_2O_5$ (288.75)
1i	**4i**	59	$C_9H_8Cl_2N_2O_4$ (279.1)
	5i	10	$C_9H_8Cl_2N_2O_4$ (279.1)
1j	**3j**	20	$C_8H_8ClNO_4S$ (249.7)
	4j	47	$C_8H_8ClNO_4S$ (249.7)

[a] All compounds obtained as oils.

[b] Satisfactory microanalyses obtained: C ±0.45, H ±0.22 (exception **3h** +0.43), N ±0.41 (exception **3b** +0.65), Cl ±0.53.

Table **2.** Iminoacetates **7** and Oxo(nitroaryl)acetates **8**

Ester	Product	Yield (%)	mp (°C)	Molecular Formula[a]
3a	**8a**	76[b]	oil	$C_{10}H_9NO_5$ (223.2)
3b	**8b**	39[b]	oil	$C_{10}H_8ClNO_5$ (257.6)
4c	**7c**	66	65–66	$C_{10}H_9ClN_2O_4$ (256.6)
4c	**8c**	60[b]	oil	$C_{10}H_8ClNO_5$ (257.6)
4g	**7g**	70	100–101	$C_{10}H_{11}N_2O_5$ (239.2)
5i	**7i**	96	103–104	$C_9H_8ClN_3O_4$ (257.6)

[a] Satisfactory microanalyses obtained: C ±0.15, H ±0.26, N ±0.38, Cl ±0.34.

[b] Quenching at the presence of Cu salt.

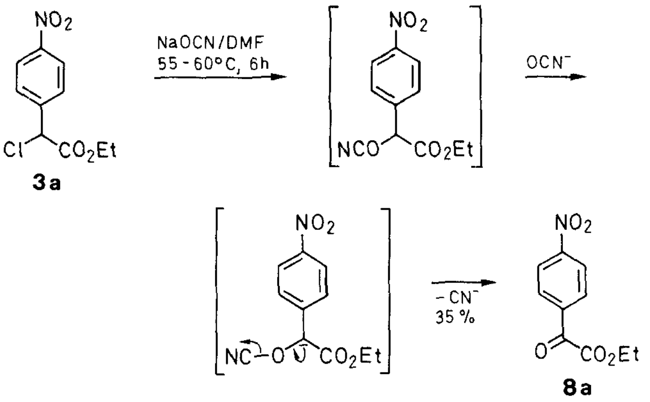
Imines **7c,g,i** were relatively stable and could be isolated. The increased stability of imine was probably due to intramolecular hydrogen bonding between the imine N–H and the neighboring nitro group (**7c,i**), or between the imino N–H and nitro group or pyridine nitrogen **7g**).

The attempts to substitute the chlorine in chloro(4-nitrophenyl)acetate (**3a**) by cyanate anion led to a complex mixture of the products in which oxoacetate **8a** was the major product (TLC control). After the workup ethyl (4-nitrophenyl)oxoacetate (**8a**) was isolated in 35% yield. This reaction proceeds apparently via substitution at the oxygen of the ambident cyanate anion, followed by elimination of hydrogen cyanide.

Table **3.** ^1H-NMR Spectral Data of the Products Prepared

Product	^1H-NMR[a] (solvent/TMS) δ, J(Hz)
3a	(CCl_4) 1.25 (t, 3H, $J = 7.5$), 4.22 (q, 2H, $J = 7.5$), 5.36 (s, 1H), 7.59–8.25 (m, 4H)
3b	(CCl_4) 1.44 (t, 3H, $J = 7.5$), 4.37 (q, 2H, $J = 7.5$), 5.45 (s, 1H), 7.43–8.09 (m, 3H)
3c	(CCl_4) 1.32 (t, 3H, $J = 7.5$), 4.22 (q, 2H, $J = 7.5$), 5.97 (s, 1H), 7.36–8.09 (m, 3H)
3d	(CCl_4) 1.35 (t, 3H, $J = 7.5$), 4.29 (q, 2H, $J = 7.5$), 6.09 (s, 1H), 8.30 (d, 1H, $J = 9.0$), 8.63 (dd, 1H, $J = 9.0, 2.0$), 8.93 (d, 1H, $J = 2.0$)
3e	(CCl_4) 1.04–1.40 (m, 6H), 4.08–4.60 (m, 4H), 8.23 (s, 2H), 8.66 (s, 1H)
3f	(CCl_4) 1.22 (t, 3H, $J = 7.5$), 4.19 (q, 2H, $J = 7.5$), 6.01 (s, 1H), 7.39–8.48 (m, 6H)
3h	(CCl_4) 1.16–1.93 (m, 6H), 4.00–4.77 (m, 4H), 5.43 (s, 1H), 7.50 (s, 1H), 8.93 (s, 1H)
3j	(CCl_4) 1.34 (t, 3H, $J = 7.5$), 4.27 (q, 2H, $J = 7.5$), 5.51 (s, 1H), 7.15 (d, 1H, $J = 4$), 7.74 (d, 1H, $J = 4$)
4f	(CCl_4) 1.25 (t, 3H, $J = 7.5$), 4.19 (q, 2H, $J = 7.5$), 5.48 (s, 1H), 7.33–8.15 (m, 6H)
4g	(CCl_4) 1.30 (t, 3H, $J = 7.5$), 4.07 (s, 1H), 4.30 (q, 2H, $J = 7.5$), 6.30 (s, 1H), 6.93 (d, 1H, $J = 9.5$), 8.47 (d, 1H, $J = 9.5$)
4i	(CCl_4) 1.34 (t, 3H, $J = 7.5$), 4.29 (q, 2H, $J = 7.5$), 6.11 (s, 1H), 7.62 (d, 1H, $J = 8$), 8.48 (d, 1H, $J = 8$)
4j	(CCl_4) 1.32 (t, 3H, $J = 7.5$), 4.22 (q, 2H, $J = 7.5$), 6.16 (s, 1H), 7.36 (d, 1H, $J = 6$), 7.56 (d, 1H, $J = 6$)
5i	(CCl_4) 1.34 (t, 3H, $J = 7.5$), 4.26 (q, 2H, $J = 7.5$), 6.06 (s, 1H), 7.92 (s, 1H), 9.08 (s, 1H)
7c	(CCl_4) 1.23 (t, 3H, $J = 7.5$), 4.16 (q, 2H, $J = 7.5$), 7.51 (d, 1H, $J = 9$), 7.59 (s, 1H), 8.02 (d, 1H, $J = 9$), 11.62 (br s, 1H)
7g	($CDCl_3$) 1.27 (t, 3H, $J = 7.5$), 4.13 (s, 1H), 4.40 (q, 2H, $J = 7.5$), 7.10 (d, 1H, $J = 9.5$), 8.57 (d, 1H, $J = 9.5$), 11.50 (s, 1H)
7i	(CCl_4) 1.25 (t, 3H, $J = 7.5$), 4.11 (q, 2H, $J = 7.5$), 7.51 (s, 1H), 9.21 (s, 1H), 11.70 (br s, 1H)
8a	(CCl_4) 1.45 (t, 3H, $J = 7.5$), 4.46 (q, 2H, $J = 7.5$), 8.12–8.45 (m, 4H)
8b	(CCl_4) 1.45 (t, 3H, $J = 7.5$), 4.46 (q, 2H, $J = 7.5$), 7.76–8.18 (m, 3H)
8c	($CDCl_3$) 1.35 (t, 3H, $J = 7.5$), 4.27 (q, 2H, $J = 7.5$), 7.52–8.15 (m, 3H)

[a] Recorded on Varian EM-360 (60 MHz) spectrometer.



Scheme C

The presented reaction sequence provides a new synthesis of (aryl)oxoacetates and their imines.

Reactions of Nitroarenes with Ethyl Dichloroacetate; General Procedure:

A solution of nitroarene (10 mmol) and ethyl dichloroacetate (**2**; 1.7 g, 11 mmol) in DMF (10 mL) is added dropwise to a stirred solution of *t*-BuOK (3.4 g, 30 mmol) in DMF (30 mL) at −5°C. After complete addition the mixture is stirred for additional 5 min and poured into aq HCl (5%, 200 mL). The product is extracted with CH_2Cl_2 (3 x 50 mL) and dried ($MgSO_4$). After evaporation of the solvent the crude product is purified by column chromatography (silica gel, hexane/EtOAc 5:1).

Transformation of the Esters 3, 4 into Iminoacetates 7 and Oxoacetates 8; General Procedure:

To a stirred solution of an ester **3** or **4** (1 mmol) in DMF (10 mL) NaN_3 (0.13 g, 2 mmol) is added in one portion (gas evolution!). The progress of the reaction was monitored by TLC. After the starting material is disappeared the reaction mixture is poured into H_2O (50 mL). (To complete the decomposition of imine **7** copper sulfate (0.1 g) is added.) Product is extracted with CH_2Cl_2 (4 x 25 mL) and dried ($MgSO_4$). After removing of the solvent the product is purified by column chromatography (silia gel, EtOAc/hexane 1:2).

Reaction of the Ester 3a with Sodium Cyanate:

Ethyl chloro(4-nitrophenyl)acetate (**3a**; 0.25 g, 1 mmol) and NaOCN (85 mg, 1.3 mmol) in DMF (5 mL) are stirred at 55–60°C for 6 h. Then the mixture is poured into H_2O (50 mL), extracted with CH_2Cl_2 (3 x 25 mL) and dried ($MgSO_4$). After removing of the solvent residue is chromatographed (silica gel, EtOAc/hexane 1:4). Product **8a** is isolated in form of yellow oil; yield: 78 mg (35%).

This work was supported by the Polish Academy of Sciences Grant CPBP 01.13.1.

Received: 5 March 1990

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