A Simple and Efficient Synthesis of Alkyl (2-Nitroaryl)acetates and Alkyl 2-(2-Nitroaryl)propanoates via Vicarious Nucleophilic Substitution of Hydrogen in Nitroarenes by Carbanions or Alkyl Chloroacetates of Alkyl 2-Chloropropanoates[1]

B. Mudryk, M. Mąkosza*

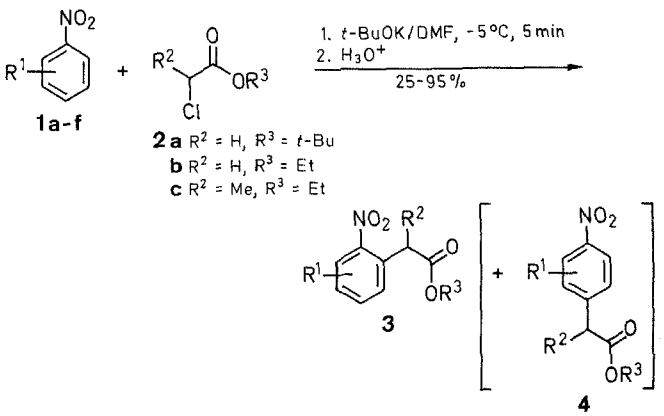
Institute of Organic Chemistry, Polish Academy of Science, ul. Kasprzaka 44/52, PL 01-224 Warsaw, Poland

Alkyl chloroacetates react with nitroarenes and potassium *tert*-butoxide in dimethylformamide according to the Vicarious Nucleophilic Substitution pattern, preferentially in the position *ortho* to the nitro group, giving alkyl (2-nitroaryl)acetates in usually good yields. Alkyl 2-(2-nitroaryl)propanoates are obtained in an analogous manner.

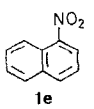
A variety of α-functionalized alkyl substituents can be directly introduced into nitroarenes *ortho* and/or *para* to the nitro group, by reaction with carbanions containing suitable leaving groups. The reaction named Vicarious Nucleophilic Substitution of hydrogen (VNS) proceeds via nucleophilic addition of a carbanion followed by base-induced β-elimination; it is general in character with respect to nitroarenes and carbanions.[2]

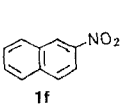
In a previous communication[3] we reported that alkoxycarbonylmethylation of nitroarenes can be effected via reaction with the carbanions of alkyl (phenylthio)acetates and (dimethylaminothiocarbonylthio)acetates (ethoxycarbonylmethyl *N,N*-dimethyldithiocarbamates) in a base-solvent system such as NaOH/DMSO or NaH/DMSO. The reaction proceeded preferentially in the *para* position. Alkyl chloroacetates have been found to react unsatisfactorily under these conditions. On the other hand, use of the tertiary carbanion derived from ethyl 2-chloropropanoate lead to efficient VNS of hydrogen exclusively at the position *para* to the nitro group.[4]

Here we report that under appropriate conditions, namely potassium *tert*-butoxide in dimethylformamide at about −5 °C, alkyl chloroacetates enter easily the VNS reaction, thus offering a simple way of introduction of alkoxycarbonylmethyl substituents into nitroarenes. Since carbanions of alkyl chloroacetates are less bulky than those derived from alkyl (phenylthio)acetates, the substitution occurs preferentially in the position *ortho* to the nitro group, affording alkyl (2-nitroaryl)acetates in usually good yields.



1	R^1	1	R^1
a	4-Cl	c	H
b	4-F	d	3-CF_3


1e


1f

Alkyl (2-nitroaryl)acetates are valuable intermediates in organic synthesis, for example as precursors of oxindoles.[5] They have earlier been obtained either by aromatic nucleophilic substitution of halogen in *o*-halonitrobenzenes by malonic esters followed by hydrolysis and decarboxylation of one of the alkoxycarbonyl groups[6] or by nitration of alkyl arylacetates and isolation of the desired *ortho*-substituted product from the resultant mixture or isomers.[7] These methods either require a few steps or suffer from lack of selectivity. We have found that brief mixing of a nitroarene **1** with ethyl or *tert*-butyl chloroacetate **(2a)** in the presence of a two- or a threefold excess of potassium *tert*-butoxide in dimethylformamide at about −5 °C (these conditions were found to be the best) results in the formation of the desired *tert*-butyl (2-nitroaryl)acetates **3** in good yields (Table). For 4-chloro- and 4-fluoronitrobenzene **(1a, b)**, VNS proceeds at position 2, no traces of halogen-substitution products being observed. This is in accord with our previous results obtained in the reaction with the secondary carbanion of chloromethyl phenyl sulfone and follows the general rule that VNS is a much faster reaction than conventional aromatic nucleophilic substitution.[2] The orientation pattern for nitrobenzene **(1c)** and *tert*-butyl chloroacetate **(2a)** expressed by the *ortho*/*para* ratio of the isomeric products **3ca/4ca** = 1.6 is similar to that obtained in the reaction of chloromethyl phenyl sulfone under comparable conditions (*ortho*/*para* = 2.0),[10] the yields being moderate, however, because of the relatively low electrophilicity of nitrobenzene in comparison with the other nitroarenes tested. Thus, we conclude that the magnitude of the overall steric factor controlling the *ortho*/*para* ratio in the VNS is about the same for both the *tert*-butoxycarbonyl and phenylsulfonyl groups.

The reaction of alkyl chloroacetates **2a, b** with 4-nitroanisole and benzyl 4-nitrophenyl ether failed to produce VNS products, apparently due to insufficient electrophilicity of these nitroarenes.

The electrophilic nitroarenes **1d, e, f** not having substituents at the *para* positions were found to exert a strong tendency for *ortho*-substitution by alkyl chloroacetates. 1-Nitronaphthalene **(1e)** and 2-nitronaphthalene **(1f)** are exclusively substituted at positions 2 and 1 (**3eb** and **3fa**), respectively (same regiochemistry as in the reaction of chloromethyl phenyl sulfone with these nitroarenes[11]). The reaction of 3-trifluoromethylnitrobenzene **(1d)** with *tert*-butyl chloroacetate **(2a)** leads predominantly to hydrogen substitution at position 6 (*ortho* to the nitro group), the ratio 6-: 4-substitution being 2.7 : 1 which resembles the 3.5 : 1 ratio of 6-: 4-substitution observed in the analogous reaction with chloromethyl phenyl sulfone[12]. Finally, we have found that the tertiary carbanion of ethyl 2-chloropropanoate **(2c)** reacts with 4-halonitrobenzenes **1a** and **1b** at the position *ortho* to the nitro group under the same conditions, although the yields of the VNS products are lower than in the reactions with alkyl chloroacetates **2a** and **2b**. When 4-fluoro-1-nitrobenzene **(1b)** was subjected to the reaction with *tert*-butyl 2-chloropropanoate **(2c)** we observed that VNS competed with aromatic nucleophilic substitution of fluorine; VNS being the main reaction, however, and the ratio of products **3bc : 4bc** was 3.3 : 1. This result nicely corresponds to our previous findings regarding the reaction of the tertiary carbanion of 1-chloroethyl phenyl sulfone with **1b**, which lead to an analogous product ratio of 3.6 : 1,[10] and thus again indicates that the rate of VNS at the position *ortho* to the nitro group decreases significantly with increasing size of the carbanion. In such cases, the aromatic nucleophilic substitution of fluorine in 4-fluoronitrobenzene may compete considerably with the VNS of *ortho*-hydrogen.

Ethyl (5-Chloro-2-nitrophenyl)acetate (3ab); Typical Procedure:
To a stirred solution of *t*-BuOK (800 mg, 7 mmol) in dry DMF (15 mL), a solution of 4-chloronitrobenzene (**1a**; 475 mg, 3 mmol) and ethyl chloroacetate (**2b**; 385 mg, 3.15 mmol) in DMF (1 mL) is added dropwise over a period of 2–3 min at −5° ± 2 °C. After additional stirring for 2–3 min at about −5 °C, the dark-blue mixture is poured into

Table. Alkyl (Nitroaryl)acetates and Alkyl 2-(Nitroaryl)propanoates **3** Prepared

Starting Materials	Products		Yield (%)	mp (°C)	Molecular Formula[a] or Lit. Data	^{1}H-NMR ($CDCl_3$/TMS)[b] δ, J(Hz)
	Position of $CH(R^2)CO_2R^3$					
1a + 2a	2–	**3aa**	79	60–61	mp 61–63 °C[3]	1.43 (s, 9H); 3.91 (s, 2H); 7.3–7.6 (m, 2H); 8.08 (d, 1H, J = 8)
1a + 2b	2–	**3ab**	72	oil	bp 90–95 °C/0.001 Torr[8]	1.25 (t, 3H, J = 7.5); 3.96, 4.14 (s + q, 4H, J = 7.5); 7.3–7.6 (m, 2H); 7.95 (m, 1H)
1b + 2a	2–	**3ba**	77	oil	$C_{12}H_{14}FNO_4$ (255.2)	1.44 (s, 9H); 3.91 (s, 2H); 6.9–7.25 (m, 2H); 8.0–8.3 (m, 1H)
1c + 2a	2–	**3ca**	25	oil	bp 180 °C/0.2 Torr[9]	1.43 (s, 9H); 3.94 (s, 2H); 7.3–7.7 (m, 3H); 8.09 (m, 1H)
	4–	**4ca**	16	oil	mp 34–36 °C[3]	1.44 (s, 9H); 3.64 (s, 2H); 7.44 (d, 2H, J = 9); 8.17 (d, 2H, J = 9)
1d + 2a	6–	**3da**	60	59–61	$C_{13}H_{14}F_3NO_4$ (305.3)	1.43 (s, 9H); 3.99 (s, 2H); 7.49, 7.81 (2d, 2H, AB system, J = 8); 8.31 (s, 1H)
	4–	**4da**	22	oil	$C_{13}H_{14}F_3NO_4$ (305.5)	1.43 (s, 9H); 3.84 (s, 2H); 7.3–8.4 (m, 3H)
1e + 2b	2–	**3eb**	86	61–63	$C_{14}H_{13}NO_4$ (259.3)	1.21 (t, 3H, J = 7); 3.78 (s, 2H); 4.13 (q, 2H, J = 7); 7.2–8.0 (m, 6H)
1f + 2a	1–	**3fa**	95	95–96	$C_{16}H_{17}NO_4$ (287.3)	1.41 (s, 9H); 4.34 (s, 2H); 7.6–8.5 (m, 6H)
1a + 2c	2–	**3ac**	45	oil	$C_{11}H_{12}ClNO_4$ (257.7)	1.22 (t, 3H, J = 7); 1.61 (d, 3H, J = 7); 4.14, 4.32 (2q, 3H, J = 7, 7); 7.3–7.6 (m, 2H); 7.93 (d, 1H, J = 8.5)
1b + 2c	2–	**3bc**	33	oil	$C_{11}H_{12}FNO_4$ (241.2)	1.21 (t, 3H, J = 7); 1.61 (d, 3H, J = 7); 4.14, 4.37 (2q, 3H, J = 7, 7); 6.8–7.4 (m, 2H); 7.9–8.3 (m, 1H)
	4–	**4cc**[c]	10	oil	oil[3]	1.22 (t, 3H, J = 7); 1.54 (d, 3H, J = 7); 3.83, 4.13 (2q, 3H J = 7, 7); 7.48 (d, 2H, J = 9); 8.19 (d, 2H, J = 9)

[a] Satisfactory microanalyses: C ± 0.42, H ± 0.19, N ± 0.23.
[b] Recorded at 60 MHz on a Varian EM-360 spectrometer.
[c] Product **4cc** is formed via substitution of fluorine and subsequent dechlorination; such dechlorination occurs often in similar systems.[10]

diluted HCl (200 mL). This mixture is extracted with CH_2Cl_2 (2×20 mL), the extract is washed with H_2O (2×100 mL) to remove DMF and dried ($MgSO_4$), and the solvent is evaporated. Column chromatography of the residue on silica gel (hexane/EtOAc, 20:1, as eluent) affords the pure product **3ab** as a light yellow oil; yield: 525 mg (72%).

This work was supported by the Polish Academy of Sciences Grant CPBP 01.13

Received: 1 June 1988; revised: 10 August 1988

(1) Part 156 in the Series Reactions of Organic Anions.
Part 155: Jończyk, A., Radwan-Pytlewski, T., submitted to *J. Org. Chem.*
(2) Mąkosza, M., Winiarski, J. *Acc. Chem. Res.* **1987**, *20*, 282.
(3) Mąkosza, M., Winiarski, J. *J. Org. Chem.* **1984**, *49*, 1494.
(4) Stahly, G.P., Stahly, B.C., Lilje, K.C. *J. Org. Chem.* **1984**, *49*, 578.
(5) Walker, G.N. *J. Am. Chem. Soc.* **1955**, *77*, 3844.
Simet, L. *J. Org. Chem.* **1963**, *28*, 3580.
(6) Mąkosza, M., Jagusztyn-Grochowska, J., Jawdosiuk, M. *Rocz. Chem.* **1976**, *50*, 1841.
(7) Schofield, K., in: *Aromatic Nitration*, Cambridge University Press, Cambridge, 1980, p. 153.
(8) Hromatka, O., Knollmüller, M., Deschler, H. *Monatsh. Chem.* **1969**, *100*, 469.
(9) Flitsch, W., Russkamp, P. *Liebigs Ann. Chem.* **1985**, 1398.
(10) Mudryk, B., Mąkosza, M. *Tetrahedron* **1988**, *44*, 209.
(11) Mąkosza, M., Danikiewicz, W., Wojciechowski, K. *Liebigs Ann. Chem.* **1987**, 711.
(12) Mąkosza, M., Glinka, T., Kinowski, A. *Tetrahedron* **1984**, *40*, 1863.