Direct Isocyanomethylation of Nitroarenes via the Vicarious Nucleophilic Substitution of Hydrogen with Phenylthiomethyl Isocyanide Carbanion

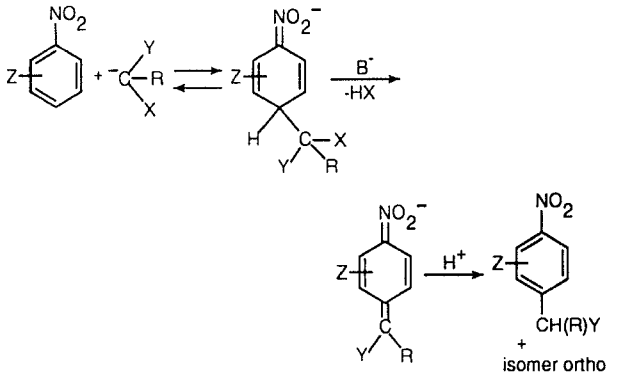
Mieczysław Mąkosza,* Andrzej Kinowski, Stanisław Ostrowski
Institute of Organic Chemistry, Polish Academy of Sciences, ul. Kasprzaka 44/52, PL-01-224 Warszawa, Poland
Received 13 April 1993

Reaction of nitroarenes with phenylthiomethyl isocyanide in the presence of potassium *tert*-butoxide results in the introduction of the isocyanomethyl substituent into positions ortho or para to the nitro group. The products of the reaction when subjected to mild hydrolysis can be converted into nitrobenzylic amines or their formyl derivatives.

Aminomethyl derivatives of arenes are usually prepared by reduction of aromatic nitriles,[1] substitution of the halogen in benzylic halides,[2] or direct electrophilic amidomethylation of arenes with hydroxy- or halomethylamides, followed by hydrolysis.[3]

The majority of these methods are inapplicable for the synthesis of aminomethyl derivatives of nitroarenes. Selective reduction of the cyano group in cyanonitroarenes is rather a difficult task, whereas amidomethylation, being a variant of the Friedel–Crafts reaction, does not proceed satisfactorily with nitroarenes.[4] Aminomethyl derivatives of nitroarenes can also be prepared via substitution of the halogen in nitrobenzyl halides, but the latter are not easily accessible and under basic conditions often undergo side reactions.[5,6]

In this paper we describe the application of the vicarious nucleophilic substitution (VNS) of hydrogen to the synthesis of isocyanomethyl nitroarenes, which are interesting starting materials for further synthesis, and can be readily converted into aminomethyl derivatives. The VNS process consists of the reaction of carbanions bearing a leaving group X at the carbanion center with nitroarenes to form anionic σ-adducts followed by base induced β-elimination of HX (Scheme 1).[7]



Scheme 1

This reaction was shown to be of general character with respect to electrophilic arenes and carbanions and provides an efficient way of introducing α-functionalized alkyl substituents into nitroaromatic rings.

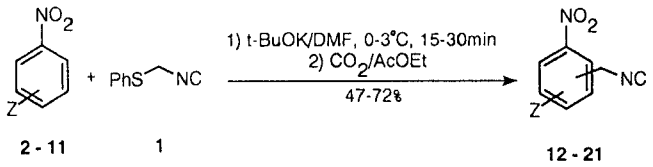
Carbanions of isonitriles are valuable intermediates in organic synthesis, their reactions with a wide variety of electrophiles alkylating agents, aldehydes, Michael acceptors etc. have found considerable applications.[8] On the other hand very little is known concerning reactions of such carbanions with nitroarenes.[9]

The isocyano group possesses the ability to be eliminated by E2 or E1 type processes,[6,10] therefore in the reactions of carbanions of isonitriles with nitroarenes it can act as the leaving group promoting VNS. Such a process was indeed observed,[9b] it is however of minor interest, since substituents introduced into the nitroaromatic rings do not contain the isocyano functionality.

Introduction of the isocyanomethyl substituent into an aromatic ring via the VNS reaction could be carried out by reacting with isocyanomethyl carbanions containing leaving groups better than the NC substituent. Unfortunately α-haloalkaneisonitriles are not sufficiently stable, therefore we have attempted the VNS reaction with the carbanion of phenylthiomethane isocyanide (**1**).[11] Although SPh is a much less efficient leaving group than a halogen and the possibility of competition between the leaving group ability of NC and SPh groups exist, it is the latter, which undergoes elimination from the σ-adduct, when the carbanion of **1** was subjected to the reaction with nitroarenes. Alternative elimination of NC was not observed – no nitrobenzyl phenyl sulfides were found in the reaction mixtures. The VNS process is often sensitive to the conditions,[12] this is also the case of the reaction involving the carbanion of **1**. Standard conditions: potassium *tert*-butoxide in dimethylformamide at 0 to 3 °C assured usually good yields of the VNS products, often some unchanged starting materials were recovered, giving satisfactory overall material balance (Scheme 2). Some difficulties were encountered during the workup procedure. Due to the instability of the nitrobenzylic isonitriles toward acids, acidification of the reaction mixture with aqueous hydrochloric acid, ammonium chloride, and even acetic acid resulted in a partial hydrolysis of the NC group. The best results were obtained when the reaction mixture was poured onto crushed dry ice and treated with ethyl acetate.

Results of the reaction of **1** with nitroarenes are given in the Table. Since the conditions were only tentatively optimized and the same procedure was used in every case, some improvements of yields are possible, particulary taking into account that often unchanged materials were recovered.

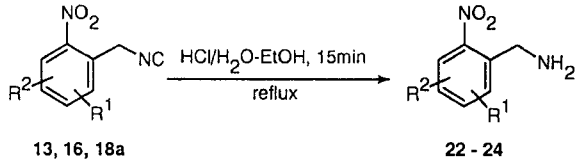
The nitrobenzyl isocyanides obtained via the VNS reaction can be easily converted into the corresponding nitrobenzyl formamides or amines. To exemplify such facile conversion **13**, **16**, and **18a** were treated for a short time with boiling 80% ethanol containing hydrochloric acid as catalyst, giving nitrobenzylamines **22**, **23**, and **24** (Scheme 3).



2 - 11 1 12 - 21

	Z	Position of CH_2NC (in product)		Z	Position of CH_2NC (in product)
2,12	H	2-	1-NO_2-naphthalene (**8**)		
3,13	4-Cl	2-	and **18a**	H	2-
4,14a	3-Cl	2-	and **18b**	H	4-
14b	3-Cl	6-	2-OMe,5-NO_2-pyridine (**9**)		
14c	3-Cl	4-	and **19**	2-OMe	6-
5,15a	2-Cl	6-	2-NO_2-thiophene (**10**)		
15b	2-Cl	4-	and **20**	H	3-
6,16	3-NO_2	4-	5-NO_2-quinoline (**11**)		
7,17a	3-CN	2-	and **21**	H	6-
17b	3-CN	6-			
17c	3-CN	4-			

Scheme 2

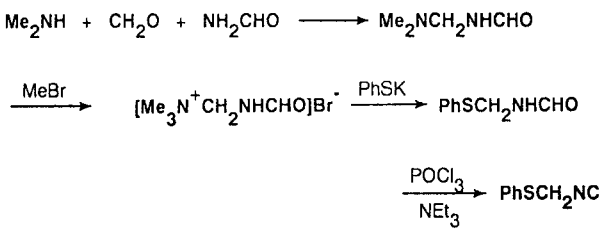


13, 16, 18a 22 - 24

	R^1	R^2
13, 22	4-Cl	H
16, 23	3-NO_2	H
18a, 24	5,6- –CH=CH–CH=CH–	

Scheme 3

Nitroarenes used were of commercial quality, phenylthiomethyl isocyanide **1**, was prepared via modified procedure of Schöllkopf,[11] according to Scheme 4.



Scheme 4

Formylaminomethyldimethylamine:
To a stirred cold (ca. 0 °C) 40% aq solution of Me_2NH (950 mL, 7.57 mol) was added dropwise formamide (360 g, 8 mol), the resulting solution was kept at r.t. for 1 h, and cooled to 0 °C. Formaldehyde (37% aq solution, 640 mL, ca. 8.5 mol) was then added dropwise keeping the temperature below + 5 °C. After the addition was complete, the mixture was kept at r.t. for 2 h and subjected to evaporation at reduced pressure. After removal of H_2O the residue was distilled, yield 620 g (80%); bp 87–92 °C/2 Torr.

Formylaminomethyl Trimethylammonium Bromide:
To a stirred solution of formylaminomethyldimethylamine (342 g, 3.35 mol) in anhydr. Et_2O (400 mL) cooled to 5 °C, was slowly added CH_3Br (340 g, 3.58 mol) via dry ice condenser with such a rate to keep temperature below 10 °C. After the addition was complete the mixture was kept at 10 °C for a few hours, then left for a few days at r.t. The solid was filtered, washed with Et_2O and dried; yield: 640 g (97%).

***N*-(Phenylthiomethyl)formamide:**
Formylaminomethyl trimethylammonium bromide (20 g, 0.1 mol) and potassium thiophenoxide (15 g, 0.1 mol) were suspended in DMSO (50 mL) with vigorous shaking. The suspension was heated slowly on an oil bath to reach 110 °C after ca. 4 h. During this time NMe_3 was liberated; intensity of heating should provide smooth, but not vigorous evolution of the gas. The heating bath was removed as soon as the evolution of the gas ceased. After cooling, the mixture was treated with H_2O (200 mL) and toluene (200 mL). The organic layer was washed with H_2O (2 × 100 mL), dried (Na_2SO_4) and the solvent was evaporated; yield: 13.9 g (83%). The product was used in the next step without purification.

Phenylthiomethylisocyanide (1):
To a stirred solution of *N*-(phenylthiomethyl)formamide (10.9 g, 0.065 mol) and NEt_3 (55 g, 0.54 mol) in CH_2Cl_2 (200 mL) was slowly added dropwise $POCl_3$ (10.7 g, 0.07 mol) while the temperature was kept at 20–30 °C. After the addition was complete the mixture was washed with 10% aq Na_2CO_3 (3 × 50 mL), the organic phase was dried (Na_2SO_4), the solvent was evaporated and the product was purified by fast distillation under reduced pressure. Fraction boiling at 65–73 °C/0.3 Torr was collected (Lit.[8] bp 52 °C/0.001 Torr); yield: 4.8 g (50%). Crude product can be also purified by flash chromatography (silica gel, 200–300 mesh, $CHCl_3$ as eluent). From 3.30 g (0.02 mol) of *N*-(phenylthiomethyl)formamide 1.62 g (55%) of the pure final product was obtained.

Reaction of Phenylthioisocyanide Carbanion with Nitroarenes; General Procedure:
To a stirred solution of KOBu-*t* (2.80 g, 25 mmol) in anhydr. DMF (15 mL), cooled to 0 °C, was slowly added a solution of phenylthiomethylisocyanide (1.5 g, 10 mmol) and a nitroarene (10 mmol) in DMF keeping the temperature at ca. 3 °C. After an additional 15 min, the mixture was poured into crushed dry ice (ca. 20 g) followed by slow addition of EtOAc (150 mL). The mixture was washed with cold brine (3 × 50 mL), the organic layer was dried (Na_2SO_4), the solvent was evaporated and the products were isolated and purified by column chromatography using $CHCl_3/CCl_4$ (9:1) solvent system or $CHCl_3$ as eluent.

Table. Products **12–21** Prepared

Product[a]	Yield[b] (%)	mp (°C)[c]	^{1}H NMR (solvent/TMS) δ, J (Hz)
12	7	oil	$CDCl_3$, 100 MHz: 4.85 (s, 2 H, CH_2), 7.20–7.60 (m, 3 H_{arom}), 7.75–8.05 (m, 1 H, H-6)
13[f]	72[d]	95–96	$CDCl_3$, 100 MHz: 5.14 (s, 2 H, CH_2), 7.50 (d, 1 H, H-5, J = 8.5), 7.81 (s, 1 H, H-3), 8.13 (d, 1 H, H-6, J = 8.5)
14a	16[d]	47–51	$CDCl_3$, 200 MHz: 4.85 (s, 2 H, CH_2), 7.56 (t, 1 H, H-5, J = 8.2), 7.78 (dd, 1 H, H-4, J = 8.2, 1.3), 7.97 (dd, 1 H, H-6, J = 8.21, 1.3)
14b	16[d]	71–74	$CDCl_3$, 200 MHz: 5.13 (s, 2 H, CH_2), 7.80 (br s, 2 H, H-4,5), 8.30 (s, 1 H, H-2)
14c	40[d]	92–94	$CDCl_3$, 200 MHz: 5.03 (s, 2 H, CH_2), 7.82 (d, 1 H, H-5, J = 8.5), 8.25 (dd, 1 H, H-6), J = 8.5, 2.2), 8.30 (d, 1 H, H-2, J = 2.2)
15a	33[d]	53–56	$CDCl_3$, 200 MHz: 4.71 (s, 2 H, CH_2), 7.53–7.67 (m, 3 H_{arom})
15b	14[d]	46–49	$CDCl_3$, 200 MHz: 4.74 (s, 2 H, CH_2), 7.42 (dm, 1 H, H-5, J = 8.4), 7.58 (d, 1 H, H-3, J = 1.9), 7.95 (d, 1 H, H-6, J = 8.4)
16[g]	55	60–61	$CDCl_3$, 100 MHz: 5.28 (s, 2 H, CH_2), 8.15, 8.63 (2d, 1 H each, H-5,6, J = 8.2), 9.01 (s, 1 H, H-2)
17a	6[d]	39–40	$CDCl_3$, 200 MHz: 5.16 (s, 2 H, CH_2), 7.79 (t, 1 H, H-5, J = 8.1), 8.05 (dd, 1 H, H-4, J = 7.8, 1.3), 8.35 (dd, 1 H, H-6, J = 8.2, 1.3)
17b	43[d]	58–60	acetone-d_6, 200 MHz: 5.41 (s, 2 H, CH_2), 8.10, 8.32 (2d, 1 H each, H-4,5, J = 8.4),[e] 8.65 (d, 1 H, H-2, J = 1.1)
17c	6[d]	48–50	$CDCl_3$, 200 MHz: 5.02 (s, 2 H, CH_2), 7.97 (d, 1 H, H-5, J = 9.2), 8.56 (dd, 1 H, H-6, J = 9.2, 2.2), 8.57 (d, 1 H, H-2, J = 2.2)
18a[h]	63[d]	109–110	$CDCl_3$, 100 MHz: 4.88 (s, 2 H, CH_2), 7.53–7.97 (m, 5 H_{arom}), 8.04 (d, 1 H, H-4, J = 8.6)
18b	8[d]	132–133	$CDCl_3$, 100 MHz: 5.17 (s, 2 H, CH_2), 8.18 (d, 1 H, H-2, J = 8.1), 7.60–8.00 and 8.42–8.61 (2 m, 5 H_{arom})
19	72[d]	96–97	$CDCl_3$, 100 MHz: 4.13 (s, 3 H, CH_3), 5.20 (s, 2 H, CH_2), 6.85 (d, 1 H, H-3, J = 8.6), 8.35 (d, 1 H, H-4, J = 8.6)
20	58[d]	oil	$CDCl_3$, 100 MHz: 5.05 (s, 2 H, CH_2), 7.21 (d, 1 H, H-4, J = 5.5), 7.50 (d, 1 H, H-5, J = 5.5)
21	50[d]	semisolid	$CDCl_3$, 100 MHz: 4.98 (s, 2 H, CH_2), 7.09–7.63 (m, 5 H_{arom})

[a] Satisfactory microanalyses obtained: C ± 0.28, H ± 0.20, N ± 0.25, Cl ± 0.21, S ± 0.02.
[b] Yield of isolated products.
[c] Uncorrected. Products were recrystallized from EtOH (**13, 15a,b, 16, 17a,c, 19**), hexane/EtOAc (**14a–c**), hexane/CCl_4 (**18a,b**).
[d] Recovered starting materials account for ca. 95% of the material balance.
[e] Signals due to H-4,5 appear as a singlet at δ = 8.08 in $CDCl_3$.
[f] IR (neat): ν = 2175, 1616, 1578, 1528, 1345.
[g] IR (neat): ν = 2160, 1613, 1554, 1530, 1350.
[h] IR (neat): ν = 2158, 1518, 1345.

Hydrolysis of Nitrobenzylic Isocyanides 13, 16 and 18a to Amines 22, 23 and 24:

Isocyanides **13**, **16** and **18a**, respectively (1 mmol), were dissolved in 80% EtOH (10 mL) and a few drops of conc. HCl were added. The mixture was refluxed for 15 min and the solvent was evaporated. The residue was recrystallized from MeOH to give **22**, **23**, and **24**, respectively, as hydrochlorides (C,H,N-analyses: C ± 0.87, H ± 0.12, N ± 0.56).

22 · HCl: mp 264–268 °C (dec, MeOH).

^{1}H NMR (DMSO-d_6, 200 MHz): δ = 8.56 (br s, 3 H, NH_3^+), 8.22 (d, J = 8.8, 1 H, H-6), 7.90 (d, J = 2.2, 1 H, H-3), 7.78 (dd, J = 8.8, 2.2, 1 H, H-5), 4.35 (br s, 2 H, CH_2).

IR (KBr): ν = 2840, 2622, 1610, 1572, 1522, 1340.

23 · HCl: mp 218–220 °C (dec., MeOH).

^{1}H NMR (DMSO-d_6, 100 MHz): δ = 8.60, 8.11 (2 × d, J = 9.0, 2 H, H-5,6), 8.17 (s, 1 H, H-2), 4.46 (s, 2 H, CH_2). (NH_3^+ – not detected).

IR (KBr): ν = 2863, 2600, 1623, 1600, 1541, 1512, 1470, 1358.

24 · HCl: mp 285–287 °C (dec., MeOH).

IR (KBr): ν = 2850, 2605, 1611, 1525, 1500, 1346.

(1) Nystrom, R.F.; Brown, W.G. *J. Am. Chem. Soc.* **1948**, *70*, 3748.
Gould, F.E.; Johnson, G.S.; Ferris, A.F. *J. Org. Chem.* **1960**, *25*, 1658.
Randad, R.S.; Mahran, M.A.; Mehanna, A.S.; Abraham, D.J. *J. Med. Chem.* **1991**, *34*, 752.

(2) Ing, H.R.; Manske, R.H.F. *J. Chem. Soc.* **1926**, 2348.
(3) Zaugg, H.E.; Martin, W.B. *Org. React.* **1965**, *14*, 52.
(4) Maulding, D.R.; Lotts, K.D.; Robinson, S.A. *J. Org. Chem.* **1983**, *48*, 2938.
(5) Russell, G.A.; Pecoraro, J.M. *J. Am. Chem. Soc.* **1979**, *101*, 3331.
(6) Jawdosiuk, M.; Umiński, M.; Kmiotek-Skarżyńska, I.; Mąkosza, M. *Pol. J. Chem.* **1981**, *55*, 1309; *Chem. Abstr. 99*, 38109.
(7) Mąkosza, M.; Winiarski, J. *Acc. Chem. Res.* **1987**, *20*, 282.
Mąkosza, M. *Synthesis* **1991**, 103.
(8) Schöllkopf, U. *Angew. Chem.* **1977**, *89*, 351; *Angew. Chem. Int. Ed. Engl.* **1977**, *16*, 339.
(9) a Terrier, F. *Nucleophilic Aromatic Displacement*, VCH: New York; 1991.
b Umiński, M. *PhD Thesis*, Technical University, Warsaw, 1983.
(10) Jawdosiuk, M.; Umiński, M. *J. Chem. Soc., Chem. Commun.* **1982**, 979.
(11) Schöllkopf, U.; Gerhart, F.; Hoppe, I.; Harmes, R.; Hantke, K.; Scheunemann, K.-H.; Eilers, E.; Blume, E. *Liebigs Ann. Chem.* **1976**, 183.
(12) Mąkosza, M.; Glinka, T.; Kinowski, A. *Tetrahedron* **1984**, *40*, 1863.
Mąkosza, M.; Owczarczyk, Z. *Tetrahedron Lett.* **1987**, *28*, 3021.
Mudryk, B.; Mąkosza, M. *Synthesis* **1988**, 1007.
Ostrowski, S.; Mąkosza, M. *Tetrahedron* **1988**, *44*, 1721.