Pergamon

Tetrahedron 54 (1998) 8797–8810

TETRAHEDRON

Oxidative Nucleophilic Substitution of Hydrogen in Nitroarenes with Phenylacetonitrile Derivatives

Mieczysław Mąkosza* and Krzysztof Staliński

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

Received 13 March 1998; revised 14 May 1998; accepted 21 May 1998

Abstract: Tertiary carbanions generated from α-substituted phenylacetonitriles in liquid ammonia add to nitrobenzenes in the *para* position to form the corresponding σ^H-adducts which are transformed, depending on the starting nitriles and the reaction conditions, to products of oxidative nucleophilic substitution of hydrogen, ONSH or vicarious nucleophilic substitution, VNS.

Keywords: carbanions; nitroarenes; σ^H adducts; oxidation

INTRODUCTION

It is well recognised and documented that addition of nucleophilic agents to electrophilic arenes proceeds faster in positions bearing hydrogen, resulting in the formation of the σ^H-adducts, rather than their addition in positions bearing leaving groups including halogens[1,2,3]. These σ^H-adducts can be further transformed into products of nucleophilic substitution of hydrogen *via* numerous mechanisms and pathways. The most general of these pathways appears to be Vicarious Nucleophilic Substitution (VNS) which occurs when nucleophiles containing leaving groups X at the nucleophilic centre interact with electrophilic arenes. The intermediate σ^H-adducts produced in such a reaction undergo base induced β-elimination of HX giving products of VNS[4,5].

0040-4020/98/$19.00
PII: S0040-4020(98)00472-4

Amongst many other methods available for the conversion of σ^H-adducts, the most obvious one seems to be removal of the hydride anion *via* oxidation, which should result in oxidative nucleophilic substitution of hydrogen (ONSH)[6]. In looking for a specific oxidant which would oxidise σ^H-adducts faster than nucleophiles such as carbanions we have assumed that the negative charge in anionic σ^H-adducts is more delocalized than in nucleophilic agents and should favour oxidation of the σ^H-adducts by anionic oxidants. It has been known that $KMnO_4$ in liquid ammonia can be used as an efficient oxidant for oxidation of σ^H-adducts of ammonia or sodium amide to electrophilic heteroarenes[6,7]. Since both $KMnO_4$ and sodium or potassium derivatives of carbanions form rather loose ion-pairs in liquid ammonia it was reason-able to expect that, in liquid ammonia, stronger electrostatic repulsion between carbanions and MnO_4^- anions than between σ^H-adducts and MnO_4^- should favour oxidation of the latter.

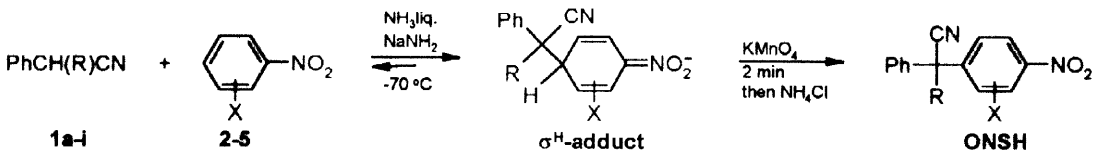
In our preliminary communication we have reported that the carbanion of 2-phenylpropionitrile adds in liquid ammonia to nitrobenzene in the *p*-position to give the corresponding σ^H-adduct which is relatively stable and undergoes rapid oxidation with $KMnO_4$ to 2-(4-nitrophenyl)-2-phenylpropionitrile[8]. We have also shown that our hypothesis is partially correct, namely oxidation of the σ^H-adduct of the carbanion to nitrobenzene with $KMnO_4$ indeed proceeds faster than oxidation of the carbanion, however the major factor responsible for the effectiveness of ONSH and high yields of the product is full conversion of the carbanion into the σ^H-adduct. Further studies have shown that other nitroarenes with free *para* positions to the nitro group enter the oxidative process and the relationships established for the reaction of the carbanion of 2-phenylpropionitrile with nitrobenzene and the oxidant seem to be of general character[9].

RESULTS AND DISCUSSION

In our previous paper the ONSH reaction of a variety of substituted nitrobenzenes with 2-phenylpropionitrile carbanion was described[9]. Here extension of this process to other phenylacetonitrile derivatives PhCHRCN, R=Et, n-C_5H_{11}, Bn, MeO, PhO, $N(Me)_2$, Ph, CH(Me)Ph, $CHPh_2$ **1a-i** and their reaction with some substituted nitrobenzenes **2-5** is presented. Since we have observed that oxidation of σ^H-adducts is very sensitive to steric hindrances it was of interest to learn how substituents R affect this process. Hence the carbanions of **1d** and **1e** can enter the VNS reaction, possible competition between ONSH and VNS when R=MeO or PhO could provide some interesting information. In previous studies[9] we have found that ONSH in nitroarenes proceeds efficiently in liquid ammonia therefore we used the same reaction conditions:

temp. ~-70 °C; reaction time 2 min; molar ratio of **1a-i, 2-5** and $KMnO_4$ 1 : 1 : 1. Results of these experiments are given in Table 1.

Table 1



	R		X	Conv. of: $I^- + ArNO_2$ into σ^H adducts [a] (%)	Yields of ONSH Products [b] (%)	$r = \frac{\text{ONSH (\%)}}{\sigma^H \text{ adduct (\%)}}$
1a	Et	**2**	H	---[c]	**2a** 76	---
		3	3-Cl	---	**3a** 60	---
1b	$n\text{-}C_5H_{11}$	**2**	H	---	**2b** 64	---
1c	Bn	**2**	H	98	**2c** 77	0.79
1d	MeO	**2**	H	98	**2d** 82	0.84
		4	3-F	98	**4d** 83	0.85
		3	3-Cl	98	**3d** 74	0.76
		5	3-I	99	**5d** 51	0.52
1e	PhO	**2**	H	97	**2e** 67	0.69
1f	$N(Me)_2$	**2**	H	95	**2f** 65	0.68
1g	Ph	**2**	H	---	no reaction	---
		4	3-F	---	no reaction	---
1h	CH(Me)Ph	**2**	H	---	**2h** 18[d]	---
1i	$CHPh_2$	**2**	H	---	**2i** 5	---

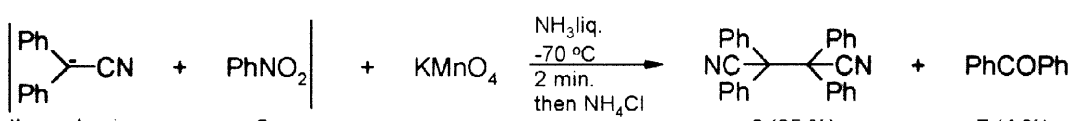
a) Estimated according to the percentages of the recovered nitriles from the reaction: [carbanion + nitrobenzene] + MeI.

b) Yields of the isolated products.

c) Concentration of the σ^H-adduct was not estimated because the corresponding carbanion did not undergo complete alkylation with MeI over 2 min.

d) Mixture of diastereoisomers.

Yields of the ONSH products are good to high for all the investigated carbanions except the carbanions of **1g-i**. The carbanion of 2,2-diphenylacetonitrile (**1g**) when treated under standard conditions with nitrobenzene or *m*-fluoronitrobenzene (*m*-FNB) and $KMnO_4$ formed only products of its oxidation: the dimer (**6**) and benzophenone (**7**) (eq. 1)[10].



the carbanion of **1g** — **2** — **6** (95 %) — **7** (4 %) (1)

Also the carbanions of **1h** and **1i** having bulky substituents showed a low tendency to form ONSH products **2h** and **2i**. When treated with nitrobenzene and then with $KMnO_4$ the carbanion

of **1h** underwent partially the ONSH reaction giving **2h**, 18 % and oxidation to 1,2-diphenyl-propan-1-one **8**, 36 %. The starting nitrile **1h** was also partially recovered (30 %). Treatment of the carbanion of **1i** with $PhNO_2$ and then $KMnO_4$ resulted in formation of a complicated mixture of products of its oxidation whereas the ONSH product **2h** was formed to a small extent (5 %). From the mixture we were able to isolate only 1,1-diphenylacetophenone, **9** (21 %). Variation of the temperature and the reaction time did not improve yields of the ONSH products.

On the basis of the results presented in our preceeding papers on this subject[9] we could conclude that oxidation of the carbanion of 2-phenylpropionitrile proceeds faster than its addition to nitrobenzene ring. In such a situation high conversion of the carbanions to the σ^H-adducts is necessary for high yields of the ONSH products. To clarify this question for the carbanions of **1a-i** we used the reaction with MeI as a reliable measure of the addition equilibrium: *carbanion + nitroarene→σ^H-adduct*, because as it was shown for 2-phenylpropionitrile carbanion, MeI reacts rapidly with the carbanion but not with σ^H-adducts. Thus, formation of the methylated nitriles in the reaction of the system carbanion-nitroarene with MeI is an indirect measure of the concentration of the σ^H-adducts (eq. 2).

$$\begin{array}{lll} \underset{\text{the carbanions of 1c-f}}{\mathrm{PhC(R)CN}} + \mathrm{MeI} & \xrightarrow[\text{2 min. then } NH_4Cl]{NH_3\text{liq. -70 °C}} & \mathrm{PhCMe(R)CN}\ \textbf{10c-f}\ (98\text{-}100\ \%) \\ \underset{\text{the carbanions of 1c-f}}{[\mathrm{PhC(R)CN}} + \underset{\textbf{2}}{\mathrm{PhNO_2}}] + \mathrm{MeI} & \xrightarrow[\text{2 min. then } NH_4Cl]{NH_3\text{liq. -70 °C}} & \mathrm{PhCH(R)CN}\ \underset{(95\text{-}99\ \%)}{\textbf{Recovered nitriles}} + \mathrm{PhCMe(R)CN}\ \textbf{10c-f}\ (1\text{-}5\ \%) \end{array} \qquad (2)$$

First we have shown that the carbanions of **1c-f** were rapidly methylated with MeI in quantitative yields giving the expected products **10c-f**. But when MeI was added to an equimolar mixture of the particular carbanion of **1c-f** and nitrobenzene **2** methylation of the carbanions occurred to a negligible extent, below 5 %. These results indicate that there is practically full conversion of the carbanions of **1c-f** and nitrobenzene into the σ^H-adducts. When the system was quenched with NH_4Cl the starting nitriles **1c-f** were recovered unchanged. On the other hand the reaction of the carbanions of **1g-i** with MeI under the standard conditions: -70 °C, 2 min was slower. Moreover, the results of methylation of the carbanions of **1g-i** after 2 min in the presence or absence of $PhNO_2$ were practically the same, for: **1g**: 48 and 49 %; **1h** 44 and 45 %; **1i** 89 % and 91 %. Thus the carbanions themselves were only partially methylated during 2 min, the first numbers show that presence of nitrobenzene does not affect the extent of methylation. This indicates negligible formation of the corresponding σ^H-adduct. It seems that this is the main reason why these carbanions do not enter the ONSH reaction. In the case of the carbanion of **1g**

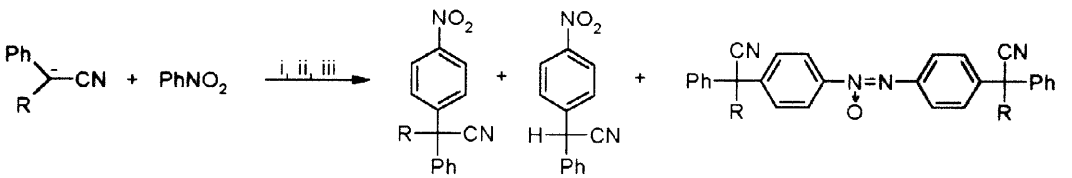
low concentration of the σ^H-adduct is a result of its low nucleophilicity. However, the carbanions of **1h** and **1i**, despite bulky substituents, should retain nucleophilic properties like the carbanion of 2-phenylpropionitrile which gives excellent yields of the ONSH products[9]. In these cases low concentrations of the σ^H-adducts seems to be connected with the steric hindrances on the addition step. To check this possibility we performed a competitive experiment in liquid ammonia at -70 °C using an equimolar mixture of the carbanions of **1h** and **1i**. Treatment of this mixture with *p*-fluoronitrobenzene (*p*-FNB) resulted in the formation of 2-(4-nitrophenyl)-2,3-diphenylbutyro-nitrile (**2h**, 35 %) whereas 2-(4-nitrophenyl)-2,3,3-triphenylpropionitrile (**2i**) was not formed. Under the same conditions the reaction with the carbanion of 2-phenylpropionitrile resulted in the quantitative formation of 2-(4-nitrophenyl)-2-phenylpropionitrile. This result supports our explanation that low concentrations of the σ^H-adduct of the carbanions of **1h,i** to $PhNO_2$ are due to steric hindrances on the addition step.

For all the carbanions of **1c-f** equilibrium of the addition to nitroarenes is shifted to the right, however in spite of the practically identical concentrations of the σ^H-adducts the yields of the ONSH products are not always high. It can be particularly seen in the case of the reaction of **1d** with nitrobenzenes **2-5**. This partial lack of correlation between formation of the σ^H-adducts and yields of the ONSH products could be connected with the influence of the substituents in the aromatic ring on the oxidation step. We have used earlier the coefficient (***r***), ***r*** =yield of ONSH product divided by the degree of formation of the σ^H-adduct as determined *via* the reaction with MeI. It allows comparison of the concentration of the σ^H-adducts and the yields of the corresponding ONSH product hence, the effects of the substituents on the oxidation step. For readily oxidised σ^H-adducts the coefficient should be close to one, a value much below one indicates difficulties in the oxidation step. Unfortunately, this measure cannot be applied to the carbanions of **1a** and **1b** because at -70 °C they were not completely methylated even after 30 min therefore the MeI test cannot be used as a quantitative measure of the concentration of the corresponding σ^H-adducts. However the results of methylation of the carbanion of **1a** (-70 °C) and of **1b** (-48 °C) with $PhNO_2$ (2 min. **10a** 9 %, **10b** 2 %; 30 min. **10a** 25 %, **10b** 27 %) and without $PhNO_2$ (2 min. **10a** 36 %, **10b** 5 %; 30 min. **10a** 63 %, **10b** 56 %) suggest that majority of them are reversibly attached to the arene ring in the form of σ^H-adducts. For the carbanion of **1b** the MeI test was performed at -48 °C because at -70 °C the sodium salt of this carbanion was not soluble in liquid ammonia.

It is well known that σ^H-adducts to nitroarenes of carbanions bearing the leaving group X at the carbanionic center can undergo base induced β-elimination of HX giving products of the VNS reaction. One could therefore expect that in the reaction of the carbanions of **1d** and **1e** with nitrobenzene VNS can also occur and compete with ONSH. We have already shown that MeO and PhO substituents can behave as leaving groups in the VNS reactions[11]. However

since the elimination of MeO and PhO are not fast processes, and at -70 °C proceeds to a negligible extent, the VNS cannot compete with $KMnO_4$ induced ONSH. It is known that ONSH can proceed, although much slower and less efficiently, without external oxidants[12]. Such "spontaneous" oxidation without external oxidants is much slower thus competition of VNS with this type of oxidative process can be studied. When a mixture of the carbanion of **1d** or **1e** with nitrobenzene was kept for 1 h "spontaneous" ONSH proceeded to a moderate extent. On the other hand VNS requires the presence of an additional base. Effects of temperature and base on these reactions can be observed from data collected in table 2.

Table 2



1d R = MeO **1e** R = PhO | **2** | **2d** R = MeO **2e** R = PhO | **11** | **12**

R	Ratio of **1d** (**1e**) : **2**	Conditions	**2d** or **2e** (%)	**11** (%)	**12** (%)
MeO	1 : 1	i	32	traces	5
	2 : 1	i	43	8	5
	2 : 1	ii	45	49	1
	1 : 1	iii	55	9	traces
PhO	1 : 1	i	1	traces	traces
	2 : 1	i	3	1	traces
	2 : 1	ii	5	27	traces
	1 : 1	iii	traces	88	traces

i: NH_3liq., -70 °C, 1h;

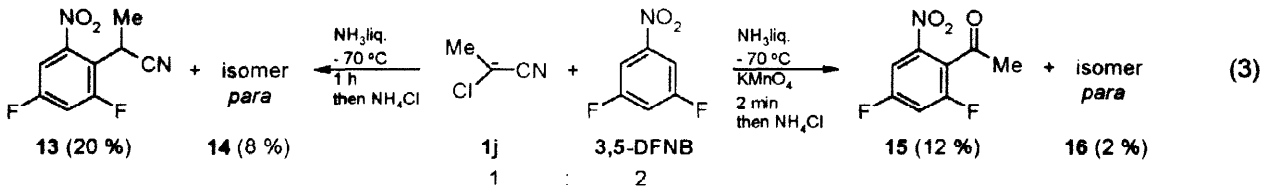
ii: NH_3liq.,~-30 °C, 1h;

iii: NH_3liq., -70 °C, 2 min, *t*-BuOK (2 eq.), -70 °C ↗ ~-30 °C, 10-15 min, ~-33 °C, 15 min.

The conditions **i** and **ii** assured only the presence of a small excess of sodium amide (~10 %) and practically the only base in the system was the carbanion. In the case of **1d** VNS was the minor process in liquid ammonia below -70 °C but at higher temperature the VNS competed with the oxidative process. The presence of **12** (5 %) suggests that the nitroarene acted itself as an oxidant. PhO is a better leaving group than MeO but surprisingly, the σ^H-adduct of the carbanion of **1e** to nitrobenzene did not undergo conversion to the VNS product **11**. The only explanation is that this carbanion is too large to promote base induced β-elimination from the corresponding σ^H-adduct at -70 °C. The conditions **iii** assured a twofold excess of the strong base (*t*-BuOK) and at a higher temperature. These conditions, in the case of **1e** made VNS the only process (**11**, 88 %) but in the case of **1d** ONSH (**2d**, 55 %) still overwhelmed VNS (**11**, 9 %). From these results

we can conclude that the distribution of VNS and ONSH products depends strongly on the leaving group ability in the used carbanions.

In contrast to the carbanions of **1d** and **1e**, the carbanion of 2-chloropropionitrile (**1j**), in which Cl is a very efficient leaving group, failed to react with nitrobenzene or even with very electrophilic 3,5-difluoronitrobenzene (3,5-DFNB) *via* an oxidative pathway in the absence of $KMnO_4$, whereas the VNS products **13**, **14** were formed to a moderate extent (scheme 3). It was apparently due to its rapid self-condensation and lack of additional base to promote β-elimination of HCl from the corresponding σ^H-adduct. This explanation was supported by the results of reactions of the carbanion of **1j** with benzyl bromide and benzaldehyde. Namely, when an equimolar amount of $PhCH_2Br$ or PhCHO was added to the solution of this carbanion in liquid ammonia at -75 °C two minutes after its generation, neither 2-benzyl-2-chloropropionitrile nor 2-cyano-2-methyl-3-phenyloxirane were formed. Application of $KMnO_4$ as an external oxidant was also unsuccessful and resulted in the formation of derivatives of acetophenone (**15**, **16**) formed probably *via* oxidation of the VNS products (scheme 3).



(3)

From these results it is clear that VNS with the carbanion of 2-chloropropionitrile is so fast a process that comparison of its rate with "spontaneous" ONSH is not possible in this way.

EXPERIMENTAL

Melting points are uncorrected. Infrared spectra were recorded on a Perkin Elmer 1640 spectrophotometer. Elemental analyses were performed by the Microanalysis Laboratory of IChO PAN. High resolution EI mass spectra were obtained on a AMD 604 mass spectrometer. ^1H NMR spectra were recorded on a Varian Gemini (200 MHz) spectrometer with either the solvent reference or TMS as internal standards. GC analyses were carried out on a Shimadzu GC-14A instrument using a fused silica capillary column (0.25 mm x 25 m, SE-52-DF-0.25 permabond). Thin layer chromatography (TLC) was carried out on aluminium sheets precoated with silica gel 60 F (Merck 5554). The plates were inspected by UV light. Column chromatography was carried out using silica gel 60 F (Merck, 230-400 mesh). Chemicals were commercial from either Aldrich or Fluka and used as received with the exception of 2-methoxy-phenylacetonitrile[13], 2-phenoxy-phenylacetonitrile[13], 2-*N*,*N*-dimethylamino-phenylacetonit-

rile[14], 2,2-diphenylaceto-nitrile[15], 2,3-diphenylpropionitrile[16], 2-phenylheptanenitrile[17], 2,3-diphenylbutyronitrile [16], 2,3,3-triphenylpropionitrile[16] and 2-phenylbutyronitrile[17], which were synthesized using the described methods. All the reactions were conducted under argon. The yields are of the isolated products without optimisation of the procedures.

1) General procedure for the oxidative nucleophilic substitution of hydrogen in nitroarenes with the carbanions of 1a-i:

The nitrile **1a-i** (1.5 mmol) was added dropwise to a suspension of sodium amide freshly prepared from sodium (38 mg, 1.65 mmol) in liquid ammonia (*ca.* 25 mL) at -70 °C (for **1b** -48 °C). After one minute the nitroarene **2-5** (1.5 mmol) dissolved in DMF (1 mL) was added dropwise at such a rate that the temperature did not exceed -70 °C. The reaction mixture was stirred for 2 min (for **1a** and **1b** - 15 min), after which time solid potassium permanganate (237 mg, 1.5 mmol) was added in one portion. The reaction mixture was stirred for an additional 2 min, quenched with solid ammonium chloride (803 mg, 15 mmoles) and ammonia was evaporated. Extraction with CH_2Cl_2, washing with water and brine, drying with $MgSO_4$ and chromatography yielded the crude product which was recrystallized from EtOH affording the pure nitrocompound.

2-(4-Nitrophenyl)-2-phenylbutyronitrile (2a). Yield 303 mg (76 %); M.p. 96-98 °C (EtOH) (Lit. 95 °C)[12]; ^{1}H NMR (200 MHz, acetone-d_6): δ=1.00-1.10 (3H, t, -$CH_2C\underline{H}_3$), 2.55-3.70 (2H, q, -$C\underline{H}_2CH_3$), 7.33-7.55 (5H, m, Ph), 7.70-7.80 (2H, m, $H_{arom.}$, AA' part of AA'XX' system), 8.25-8.35 (2H, m, $H_{arom.}$, XX' part of AA'XX' system); MS (EI, 70 eV): *m/z*=266 (44, M^+), 237 (100), 220 (6), 207 (6), 191 (85), 178 (10), 164 (16), 152 (6), 89 (7), 77 (11), 51 (7); IR (KBr): ν=2241 (CN), 1517, 1346 (NO_2); Anal. calcd. for $C_{16}H_{14}N_2O_2$: C 72.17, H 5.30, N 10.52; Found: C 72.21, H 5.15, N 10.49.

2-(2-Chloro-4-nitrophenyl)-2-phenylbutyronitrile (3a). Yield 271 mg (60 %); M.p. 73-75 °C (EtOH) (Lit. 75 °C)[12]; ^{1}H NMR (200 MHz, acetone-d_6): δ=0.99-1.10 (3H, t, -$CH_2C\underline{H}_3$), 2.40-3.90 (2H, m, -$C\underline{H}_2CH_3$), 7.26-7.47 (5H, m, Ph), 8.20-8.26 (1H, d, *J*=8.8 Hz, $H_{arom.}$), 8.26-8.29 (1H, d, *J*=2.4 Hz, $H_{arom.}$), 8.35-8.43 (1H, dd, *J*=8.8 Hz *J*=2.4 Hz, $H_{arom.}$); MS (EI, 70 eV): *m/z*=300 (48, M^+), 272 (72), 224 (22), 190 (100), 178 (8), 163 (15), 105 (20), 84 (23), 77 (13), 49 (25); IR (KBr): ν=2235 (CN), 1530, 1355 (NO_2); Anal. calcd. for $C_{16}H_{13}N_2O_2Cl_1$: C 63.90, H 4.36, N 9.31, Cl 11.79; Found: C 63.69, H 4.47, N 9.09, Cl 11.75.

2-(4-Nitrophenyl)-2-phenylheptanenitrile (2b). Yield 296 mg (64 %); Oil; ^{1}H NMR (200 MHz, acetone-d_6): δ=0.80-0.90 [3H, m, -$CH_2(CH_2)_3C\underline{H}_3$], 1.32-1.53 [6H, m, -$CH_2(C\underline{H}_2)_3CH_3$], 2.51-2.64 [2H, m, -$C\underline{H}_2$CPh(CN)Ar], 7.32-7.56 (5H, m, Ph), 7.73-7.82 (2H, m, $H_{arom.}$, AA' part of AA'XX' system), 8.24-8.33 (2H, m, $H_{arom.}$, XX' part of AA'XX' system); MS (EI, 70 eV):

m/z=308 (8, M^+), 238 (100), 221 (5), 207 (3), 190 (11), 165 (6), 71 (4), 43 (18); IR (film): ν=2237 (CN), 1523, 1348 (NO_2); Anal. calcd. for $C_{19}H_{20}N_2O_2$: C 74.00, H 6.54, N 9.08; Found: C 74.02, H 6.28, N 9.07.

2-(4-Nitrophenyl)-2,3-diphenylpropionitrile (2c). Yield 379 mg (77 %); M.p. 94-95 °C (EtOH) (Lit. 95 °C);[12] ^{1}H NMR (200 MHz, acetone-d_6): δ=3.94 (2H, s, H_{benzyl}), 6.96-7.05 (2H, m, Ph), 7.12-7.26 (3H, m, Ph), 7.65-7.76 (2H, m, $H_{arom.}$, AA' part of AA'XX' system), 8.20-8.30 (2H, m, $H_{arom.}$, XX' part of AA'XX' system); MS (EI, 70 eV): *m/z*=328 (4, M^+), 207 (2), 190 (3), 164 (1), 91 (100), 65 (5); IR (film): ν=2238 (CN), 1523, 1348 (NO_2); Anal. calcd. for $C_{21}H_{16}N_2O_2$: C 76.81, H 4.91, N 8.53; Found: C 76.86, H 5.01, N 8.58.

2-Methoxy-2-(4-nitrophenyl)-2-phenylacetonitrile (2d). Yield 330 mg (82 %); M.p. 79-80 °C (EtOH) %) (Lit. 80-81 °C)[18]; ^{1}H NMR (200 MHz, acetone-d_6): δ=3.48 (3H, s, OMe), 7.41-7.61 (5H, m, Ph), 7.80-7.89 (2H, m, $H_{arom.}$, AA' part of AA'XX' system), 8.29-8.38 (2H, m, $H_{arom.}$, XX' part of AA'XX' system); MS (EI, 70 eV): *m/z*=268 (31, M^+), 237 (100), 191 (61), 163 (10), 146 (55), 105 (14), 77 (11); IR (KBr): ν=1517, 1348 (NO_2); Anal. calcd. for $C_{15}H_{12}N_2O_3$: C 67.16, H 4.51, N 10.44; Found: C 67.15, H 4.41, N 10.46.

2-(2-Fluoro-4-nitrophenyl)-2-methoxy-phenylacetonitrile (4d). Yield 356 mg (83 %); M.p. 68-70 °C (EtOH); ^{1}H NMR (200 MHz, acetone-d_6): δ=3.44 (3H, s, OMe), 7.46-7.59 (5H, m, Ph), 8.01-8.10 (1H, m, $H_{arom.}$), 8.13-8.32 (2H, m, $H_{arom.}$); MS (EI, 70 eV): *m/z*=286 (32, M^+), 255 (100), 209 (29), 208 (25), 146 (23), 105 (6), 77 (5); IR (KBr): ν=1524, 1355 (NO_2); Anal. calcd. for $C_{15}H_{11}N_2O_3F_1$: C 62.94, H 3.87, N 9.79; Found: C 62.89, H 3.89, N 9.84.

2-(2-Chloro-4-nitrophenyl)-2-methoxy-phenylacetonitrile (3d). Yield 335 mg (74 %); M.p. 114-116 °C (EtOH); ^{1}H NMR (200 MHz, acetone-d_6): δ=3.39 (3H, s, OMe), 7.44-7.54 (5H, m, Ph), 8.27-8.31 (1H, m, $H_{arom.}$), 8.33-8.46 (2H, m, $H_{arom.}$); MS (EI, 70 eV): *m/z*=302 (41, M^+), 271 (100), 225 (19), 190 (77), 163 (11), 146 (91), 105 (17), 77 (14); IR (KBr): ν=1517, 1344 (NO_2); Anal. calcd. for $C_{15}H_{11}N_2O_3Cl_1$: C 59.52, H 3.66, N 9.25, Cl 11.71; Found: C 59.44, H 3.50, N 9.26, Cl 11.82.

2-(2-Iodo-4-nitrophenyl)-2-methoxy-phenylacetonitrile (5d). Yield 301 mg (51 %); M.p. 123-125 °C (EtOH); ^{1}H NMR (200 MHz, acetone-d_6): δ=3.39 (3H, s, OMe), 7.40-7.55 (5H, m, Ph), 8.23 (1H, d, *J*=8.8 Hz, $H_{arom.}$), 8.48 (1H, dd, *J*=8.8 Hz *J*=2.4 Hz, $H_{arom.}$), 8.76 (1H, d, *J*=2.4 Hz, $H_{arom.}$); MS (EI, 70 eV): *m/z*=394 (100, M^+), 368 (12), 363 (43), 317 (7), 276 (7), 236 (72), 219 (13), 190 (65), 177 (8), 163 (10), 146 (69), 105 (14), 77 (11); IR (KBr): ν=1519, 1344 (NO_2); Anal. calcd. for $C_{15}H_{11}N_2O_3I_1$: C 45.71, H 2.81, N 7.11, I 32.20; Found: C 45.72, H 2.91, N 7.10, I 32.11.

2-(4-Nitrophenyl)-2-phenoxy-phenylacetonitrile (2e). Yield 332 mg (67 %); M.p. 117-118 °C (EtOH) ^{1}H NMR (200 MHz, acetone-d_6): δ=6.80-7.85 (10H, m, Ph), 7.94-8.02 (2H, m, $H_{arom.}$, AA' part of AA'XX' system), 8.32-8.41 (2H, m, $H_{arom.}$, XX' part of AA'XX' system); MS

(EI, 70 eV): *m/z*=330 (1, M^+), 237 (100), 191 (65), 178 (8), 164 (8), 65 (9); IR (KBr): ν=1519, 1346 (NO_2); Anal. calcd. for $C_{20}H_{14}N_2O_3$: C 72.72, H 4.27, N 8.48; Found: C 72.98, H 4.11, N 8.46.

2-*N,N*-Dimethylamino-2-(4-nitrophenyl)-phenylacetonitrile (2f). Yield 274 mg (65 %); Oil; ^{1}H NMR (200 MHz, acetone-d_6): δ=2.33 [6H, d, -N(CH_3)$_2$], 7.26-7.35 (5H, m, Ph), 7.91 (2H, m, $H_{arom.}$, AA' part of AA'XX' system), 8.18 (2H, m, $H_{arom.}$, XX' part of AA'XX' system); Anal. calcd. for $C_{16}H_{15}N_3O_2$: C 68.31, H 5.37, N 14.94; Found: C 68.52, H 5.03, N 14.69.

2,2,3,3-Tetraphenylsuccinonitrile (6). Yield (95 %); M.p. 208-210 °C (EtOH) (Lit. 200-205 °C)[19]; ^{1}H NMR (200 MHz, DMSO-d_6): δ=7.26-7.30 (2H, m, Ph), 7.31-7.44 (3H, m, Ph); LSIMS: *m/z* 385 $(M + H)^+$; IR (KBr): ν=2257 (CN); Anal. calcd. for $C_{28}H_{20}N_2$: C 87.47, H 5.24, N 7.29; Found: C 87.31, H 5.19, N 7.26.

2-(4-Nitrophenyl)-2,3-diphenylbutyronitrile (2h). Yield 92 mg (18 %); Oil (mixture of diastereoisomers); ^{1}H NMR (200 MHz, acetone-d_6): δ=1.52-1.56 [3H, d, *J*=6.8 Hz, -CH(C$\underline{H}_3$)Ph], 1.56-1.60 [3H, d, *J*=6.8 Hz, -CH(C$\underline{H}_3$)Ph], 4.33-4.44 [1H, q, *J*=6.8 Hz, -C$\underline{H}$(CH_3)Ph], 4.36-4.47 [1H, q, *J*=6.8 Hz, -C$\underline{H}$(CH_3)Ph], 7.11-7.61 (18H, m, Ph), 7.53-7.61 (2H, m, $H_{arom.}$, AA' part of AA'XX' system), 7.82-7.90 (2H, m, Ph), 7.98-8.06 (2H, m, $H_{arom.}$, XX' part of AA'XX' system), 8.07-8.16 (2H, m, $H_{arom.}$, AA' part of AA'XX' system), 8.31-8.39 (2H, m, $H_{arom.}$, XX' part of AA'XX' system); MS (EI, 70 eV): *m/z*=342 (0.2, M^+), 279 (0.4), 238 (2), 221 (0.6), 123 (6), 105 (100), 103 (4), 75 (1), 64 (4), 51 (6), 46 (10); IR (film): ν=2239 (CN), 1516, 1346 (NO_2); Anal. calcd. for $C_{22}H_{18}N_2O_2$: C 77.17, H 5.30, N 8.18; Found: C 77.23 , H 5.19, N 8.26.

2-(4-Nitrophenyl)-2,3,3-triphenylpropionitrile (2i). Yield 30 mg (5 %); M.p. 154-156 °C (MeOH); ^{1}H NMR (200 MHz, acetone-d_6): δ=5.64 (1H, s, -C$\underline{H}$$Ph_2$), 7.10-7.39 (13H, m, Ph), 7.50-7.61 (2H, m, Ph), 7.73-7.82 (2H, m, $H_{arom.}$, AA' part of AA'XX' system), 8.10-8.19 (2H, m, $H_{arom.}$, XX' part of AA'XX' system); LSIMS: *m/z* 405 $(M + H)^+$; IR (KBr): ν=2238 (CN), 1523, 1345 (NO_2). Anal. calcd. for $C_{27}H_{20}N_2O_2$: C 80.18, H 4.98, N 6.93; Found: C 80.16 , H 5.00, N 6.95.

1,2-diphenylpropan-1-one (8). Yield 114 mg (36 %); M.p. 48-50 °C (EtOH) (Lit. 48.5-50 °C)[20]; ^{1}H NMR (200 MHz, acetone-d_6): δ=1.47 [3H, d, *J*=6.8 Hz, -CH(C$\underline{H}_3$)Ph], 4.89 [1H, q, *J*=6.8 Hz, -C$\underline{H}$(CH_3)Ph], 7.12-7.56 (8H, m, Ph), 7.98-8.06 (2H, m, Ph); IR (KBr): ν=3030, 1683, 1600, 1589, 1494, 1452, 753, 696.

1,2-diphenylacetophenone (9). Yield 84 mg (21 %); M.p. 133-135 °C (EtOH) (Lit. 134-135 °C)[21]; ^{1}H NMR (200 MHz, acetone-d_6): δ=6.01 (1H, s, C$\underline{H}$$Ph_2$), 7.10-7.55 (13H, m, Ph), 7.90-7.98 (2H, m, Ph). IR (KBr): ν=3060, 1685, 698.

2) Description of the competitive experiment of an equimolar mixture of the carbanions of 1h and of 1i with *p*-FNB.

The nitriles **1h** and **1i** (1.5 mmol of each) in DMF (0.5 mL) were added dropwise to a suspension of sodium amide freshly prepared from sodium (71 mg, 3.1 mmol) in liquid ammonia (*ca.* 25 mL) at -71 °C. After one minute *p*-FNB (212 mg, 1.5 mmol) dissolved in DMF (0.5 mL) was added dropwise. The reaction mixture was stirred for 1h, quenched with solid ammonium chloride (803 mg, 15 mmoles) and ammonia evaporated. Extraction with CH_2Cl_2, washing with water and brine, drying with $MgSO_4$ and chromatography yielded 2-(4-nitrophenyl)-2,3-diphenylbutyronitrile (**2h**, 35 % mixture of diastereoisomers).

3) Description of the experiments according to equation 2.

a) Reaction of the carbanions of 1a-i with MeI: To a solution of the carbanion of **1a-i** (1.5 mmol) at -70 °C (for **1b** -48 °C), prepared as in procedure (1), MeI (213 mg, 1.5 mmol) was added in one portion. After 2 min the mixture was quenched with NH_4Cl, ammonia evaporated and the residue analysed by GC using biphenyl as an internal standard: **10a** (36 % after 2 min, 63 % after 30 min); **10b** (5 % after 2 min, 56 % after 30 min); **10c-f** (98-100 %); **10g** (49 % after 2 min, 73 % after 30 min); **10h** (45 % after 2 min); **10i** (90 % after 2 min).
b) Reaction of MeI with an equimolar mixture of the carbanion of 1a-i and $PhNO_2$: To a solution of the carbanion of **1a-i** (1.5 mmol), prepared as in the procedure (1), and $PhNO_2$ (185 mg, 1.5 mmol) in liquid ammonia at -70 °C (for **1b** -48 °C) MeI (213 mg, 1.5 mmol) was added in one portion. After 2 min the mixture was quenched with NH_4Cl, ammonia evaporated and the residue analysed by GC using biphenyl as an internal standard: **10a** (9 % after 2 min, 11 % after 30 min); **10b** (4 % after 2 min, 7 % after 30 min); **10c-f** (1-5 %); **10g** (48 % after 2 min, 75 % after 30 min); **10h** (44 % after 2 min); **10i** (87 % after 2 min).

4) Description of the experiments according to Table 2.

a) Procedure **i**: The nitrile **1d** or **1e** (1.5 or 3.0 mmol) was added dropwise to a suspension of sodium amide freshly prepared from sodium (71 mg, 3.1 mmol) in liquid ammonia (*ca.* 25 mL) at -70 °C. After one minute $PhNO_2$ (185 mg, 1.5 mmol) dissolved in DMF (1 mL) was added dropwise. The reaction mixture was stirred for 1h, quenched with solid ammonium chloride (803 mg, 15 mmoles) and ammonia evaporated. Extraction with CH_2Cl_2, washing with water and brine, drying with $MgSO_4$ and chromatography yielded the crude product which was recrystallized from EtOH affording the pure nitrocompound.

For stoichiometry of **1d** : **2** = 1 : 1 - **2d** (32 %), **11** (traces), **12** (5 %)
For stoichiometry of **1d** : **2** = 2 : 1 - **2d** (43 %), **11** (8 %), **12** (5 %)
For stoichiometry of **1e** : **2** = 1 : 1 - **2e** (1 %), **11** (traces), **12** (traces)
For stoichiometry of **1e** : **2** = 2 : 1 - **2e** (3 %), **11** (1 %), **12** (traces)

2-(4-Nitrophenyl)-2-phenylacetonitrile (11). M.p. 70-72 °C (EtOH) (Lit. 70-72 °C)[22]; ^{1}H NMR (200 MHz, acetone-d_6): δ=5.85 [1H, s, -CH(Ph)CN], 7.34-7.56 (5H, m, Ph), 7.73-7.83 (2H, m, $H_{arom.}$, AA' part of AA'XX' system), 8.26-8.36 (2H, m, $H_{arom.}$, XX' part of AA'XX' system); MS (EI, 70 eV): *m/z* = 238 (100, M^+), 221 (19), 192 (57), 177 (9), 165 (96), 152 (11), 116 (16), 89 (13), 77 (11); IR (KBr): ν=2250 (CN), 1516, 1342 (NO_2); Anal. calcd. for $C_{14}H_{10}N_2O_2$: C 70.58, H 4.23, N 11.76; Found: C 70.53, H 4.13, N 11.75.

Compound 12. Yield 37 mg (5 %); Oil; ^{1}H NMR (200 MHz, acetone-d_6): δ=3.46 (3H, s, OMe), 3.47 (3H, s, OMe), 7.34-7.61 (10H, m, Ph), 7.68 (2H, m, $H_{arom.}$, AA' part of AA'XX' system), 7.78 (2H, m, $H_{arom.}$, AA' part of AA'XX' system), 8.22 (2H, m, $H_{arom.}$, XX' part of AA'XX' system), 8.39 (2H, m, $H_{arom.}$, XX' part of AA'XX' system); MS (EI, 70 eV): *m/z*=488 (48, M^+), 472 (12), 429 (13), 342 (2), 250 (4), 222 (58), 190 (100), 146 (45), 105 (14); HRMS (EI): calcd for $C_{30}H_{24}N_4O_3$: 488.184841, found 488.185645; IR (film): ν=1598, 1490, 1462, 1410, 1190, 1075.

b) Procedure **ii**: The nitrile **1d** or **1e** (3.0 mmol) was added dropwise to a suspension of sodium amide freshly prepared from sodium (71 mg, 3.1 mmol) in boiling liquid ammonia (*ca.* 25 mL). After one minute $PhNO_2$ (185 mg, 1.5 mmol) dissolved in DMF (1 mL) was added dropwise. The reaction mixture was stirred for 1h, quenched with solid ammonium chloride (803 mg, 15 mmoles) and ammonia evaporated. Extraction with CH_2Cl_2, washing with water and brine, drying with $MgSO_4$ and chromatography yielded the crude product which was recrystallized from EtOH affording the pure nitrocompound. For **1d**: **2d** (45 %), **11** (49 %), **12** (1 %). For **1e**: **2e** (5 %), **11** (27 %), **12** (traces).

c) Procedure **iii**: To a solution of **1d** or **1e** (1.5 mmol) in liquid ammonia, prepared as in the procedure (1), and $PhNO_2$ (185 mg, 1.5 mmol) *t*-BuOK (347 mg, 3.1 mmol) was added in one portion and the mixture was allowed to warm to ~-30 °C (10-15 min). At that temperature the reaction mixture was stirred for 15 min and then quenched with solid ammonium chloride (803 mg, 15 mmol). Evaporation of solvents, extraction with CH_2Cl_2, washing with water and brine, drying with $MgSO_4$ and chromatography yielded the crude product which was recrystallized from EtOH affording the pure products. For **1d**: **2d** (55 %), **11** (9 %), **12** (traces). For **1e**: **2e** (traces), **11** (88 %), **12** (traces).

5) Description of the experiments according to equation 3.

a) Reaction of the carbanion of 2-chloropropionitrile (1j) with 3,5-difluoronitrobenzene: To a solution of 2-chloropropionitrile (134 mg, 1.5 mmol), and 3,5-DFNB (477 mg, 3 mmoles) in liquid ammonia at -70 °C *t*-BuOK (168 mg, 1.5 mmol) was added in one portion. After 1h the mixture was quenched with NH_4Cl, (803 mg, 15 mmol). Evaporation of solvents, extraction with CH_2Cl_2, washing with water and brine, drying with $MgSO_4$ and chromatography yielded the crude product which was recrystallized from EtOH affording the pure nitrocompounds: 3,5-DFNB (47 %), **13** (20 %) and **14** (8 %).

2-(2,4-Difluoro-6-nitrophenyl)propionitrile (13). Yield 64 mg (20 %); Oil; ^{1}H NMR (200 MHz, acetone-d_6): δ=1.72-1.79 (3H, dd, J_{H-H}=7.2 Hz J=0.7 Hz, C<u>H</u>$_3$), 4.66-4.80 [1H, qd, J_{H-H}=7.2 Hz J_{F-H}=1.6 Hz, -C<u>H</u>(CN)CH$_3$], 7.60-7.73 (1H, m, J_{F-H}=8.2 Hz J_{H-H}=2.6 Hz J_{H-H}=0.4 Hz, $H_{arom.}$), 7.75-7.83 (1H, m, J_{F-H}=8.2 Hz J_{H-H}=2.6 Hz J_{F-H}=1.9 Hz, $H_{arom.}$); MS (EI, 70 eV): *m/z*=212 (2, M^+), 197 (7), 195 (9), 185 (100), 181 (6), 170 (63), 165 (34), 151 (25), 141 (23), 140 (56), 139 (48), 138 (51), 127 (71), 119 (53), 113 (27), 99 (20), 93 (8), 88 (10), 75 (14), 74 (7), 63 (14), 57 (7), 43 (43); IR (film): ν=2249 (CN), 1549 (NO_2), 1354 (NO_2); Anal. calcd. for $C_9H_6N_2O_2F_2$: C 50.95, H 2.85, N 13.20; Found: C 51.13, H 2.82, N 12.96.

2-(2,6-Difluoro-4-nitrophenyl)propionitrile (14). Yield 26 mg (8 %); Oil; ^{1}H NMR (200 MHz, acetone-d_6): δ=1.69-1.76 (3H, d, J_{H-H}=7.2 Hz, C<u>H</u>$_3$), 4.58-4.72 [1H, qt, J_{H-H}=7.3 Hz J_{F-H}=1.3 Hz, -C<u>H</u>(CN)CH$_3$], 7.98-8.11 (2H, m, AA' part of AA'XX' system, $H_{arom.}$); MS (EI, 70 eV): *m/z*=212 (100, M^+), 197 (47), 195 (10), 182 (12), 166 (19), 165 (11), 151 (14), 150 (8), 146 (5), 139 (10), 126 (15), 119 (17), 100 (6), 99 (8), 75 (6), 63 (4); IR (film): ν=2250 (CN), 1538 (NO_2), 1353 (NO_2); Anal. calcd. for $C_9H_6N_2O_2F_2$: C 50.95, H 2.85, N 13.20; Found: C 51.24, H 2.72, N 13.11.

b) Reaction of the carbanion of 2-chloropropionitrile (1j) with 3,5-DFNB and $KMnO_4$: To a solution of 2-chloropropionitrile (134 mg, 1.5 mmol), and 3,5-DFNB (477 mg, 3 mmoles) in liquid ammonia at -70 °C *t*-BuOK (168 mg, 1.5 mmol) was added in one portion. The reaction mixture was stirred for 1 min after which time $KMnO_4$ (237 mg, 1.5 mmol) was added in one portion. After further 15 min the mixture was quenched with NH_4Cl, (803 mg, 15 mmol). Evaporation of solvents, extraction with CH_2Cl_2, washing with water and brine, drying with $MgSO_4$ and chroma-tography yielded 3,5-DFNB (220 mg, 46 %) and the mixture of **15** and **16** (43 mg). The mixture was analysed by GC/Ms using biphenyl as internal standard:

2',4'-Difluoro-6'-nitroacetophenone (15). Yield 12 %; ^{1}H NMR (200 MHz, acetone-d_6): δ=2.62 (3H, d, J_{F-H}=2.0 Hz, Me), 7.65-7.75 (1H, m, J_{F-H}=8.4 Hz J_{H-H}=2.4 Hz, $H_{arom.}$), 7.89-7.97 (1H, m, J_{F-H}=8.4 Hz J_{H-H}=2.4 Hz J_{F-H}=1.7 Hz, $H_{arom.}$); GC/MS: *m/z*=201 (2, M^+), 186 (100), 170 (1), 159 (3), 140 (22), 128 (3), 112 (31), 100 (3), 81 (4), 68 (4), 62 (9), 43 (55).

2',6'-Difluoro-4'-nitroacetophenone (16). Yield 2 %; ^{1}H NMR (200 MHz, acetone-d_6): δ=2.65-2.67 (3H, t, J_{F-H}=1.4 Hz, Me), (2H, m, AA' part of AA'XX' system, $H_{arom.}$); GC/MS:

m/z=201 (15, M^+), 186 (100), 170 (2), 156 (18), 140 (52), 128 (13), 112 (22), 100 (3), 93 (3), 81 (5), 68 (4), 62 (8), 43 (47).
IR (film) of the mixture: ν=3104, 2925, 1720, 1547, 1362.

6) Reaction of the carbanion of 2-chloropropionitrile (1j) with $PhCH_2Br$ or PhCHO:

2-Chloropropionitrile (269 mg, 3 mmoles) was added dropwise to a suspension of sodium amide freshly prepared from sodium (69 mg, 3 mmoles) in liquid ammonia (*ca.* 35 mL) at -75 °C. The reaction mixture was stirred for 2 min after which time benzyl bromide (513 mg, 3 mmoles) or benzaldehyde (318 mg, 3 mmoles) was added in one portion. After a further 2 min the mixture was quenched with NH_4Cl, ammonia evaporated and the residue analysed by GC/MS using biphenyl as an internal standard:
For $PhCH_2Br$: $PhCH_2NH_2$ (52 %); $(PhCH_2)NH$ (28 %); $PhCH_2N{=}CHPh$ (8 %); MeCH(Cl)CN (0 %); $MeC(CH_2Ph)ClCN$ (0 %).
For PhCHO: PhCHO (99 %); MeCH(Cl)CN (0 %); PhC(O)CMeCN (traces of two isomers).

Acknowledgements: The authors express gratitude to J. Atherton, PhD for stimulating discussion and to Zeneca Limited, Huddersfield Works, England for financial support.

References and Notes:

1. Mąkosza M. Polish J. Chem. 1992;66:3-23.
2. Mąkosza M. Russ. Chem. Bull. 1996;45:491-503.
3. Terrier F. Nucleophilic Aromatic Displacement, Verlag Chemie, Weiheim, 1991.
4. Mąkosza, M., Goliński J. Tetrahedron Lett. 1978;37:3495-3498.
5. Mąkosza M., Winiarski J. Acc. Chem. Res. 1987;20:282-289.
6. Chupakhin O. N., Charushin V. N., Van der Plas H. C. Nucleophilic Aromatic Substitution of Hydrogen; Academic Press: San Diego, 1994.
7. Van der Plas H. C., Woźniak M. Croatica Chemica Acta 1986;59:33-49.
8. Mąkosza M., Staliński K., Klępka C. Chem. Commun. 1996:837-838.
9. Mąkosza M., Staliński K. Chem. Eur. J. 1997;3:2025-2031.
10. The notation *[A + B] + C* indicates that reagent C was added to a mixture of B + C two minutes after B and C were mixed.
11. Mąkosza M., Winiarski J. J. Org. Chem. 1984;49:1494-1499.
12. Mąkosza M., Jagusztyn-Grochowska M., Ludwikow M., Jawdosiuk M. Tetrahedron 1974;30:3723-3735.
13. Mąkosza M., Goetzen T. Rocz. Chem. 1972;46:1059-1066.
14. Goodson L. H., Christopher H. J. Am. Chem. Soc. 1950;72:358-360.
15. Kirby F. B., Kofron W. G., Hauser Ch. R. J. Org. Chem. 1963;28:2176-2179.
16. Mąkosza M., Serafinowa B. Rocz. Chem. 1965;39:1401-1409.
17. Mąkosza M., Jończyk A.; Masamune S. (Ed.). Wiley. Org. Synth. 1976;55:91-95.
18. Mąkosza M., Goetzen T. Rocz. Chem. 1972;46:1239-1247.
19. Mąkosza M., Jagusztyn-Grochowska M., Jawdosiuk M. Rocz. Chem. 1971;45:851-857.
20. Traynelis V. J., Hergenrother W. L., Livingston J. R. Valicenti J. A. J. Org. Chem. 1962;27:2377-2383.
21. Ciminale F., Lopez L., Mele G. Tetrahedron 1994;50:12685-12696.
22. Davis R. B., Pizzini L. C. J. Org. Chem. 1960;25:1884-1887.