Vicarious Nucleophilic Substitution of Hydrogen in 5- and 6-Nitroindole Derivatives[1]

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Introduction of a side chain into position 4 or 7 of 5- and 6-nitroindole derivatives via the Vicarious Nucleophilic Substitution has been developed.

Vicarious Nucleophilic Substitution (VNS) is a general method of the introduction of a α-functionalized carbon side chain into molecules of electrophilic arenes or heteroarenes.[2] This reaction proceeds via addition of a carbanion, bearing a leaving group X and an electron-withdrawing group Y, to an arene, followed by base-induced β-elimination of HX from the formed σ-adduct, leading to the anion of the substitution product. Numerous aromatic nitro compounds and nitro derivatives of such heterocycles as furane,[3] pyrrole,[3] thiophene,[3] imidazole,[4] pyridine,[5] and quinoline[6] enter this reaction. Also some electrophilic heterocycles without a nitro group react according to the VNS scheme.[7]

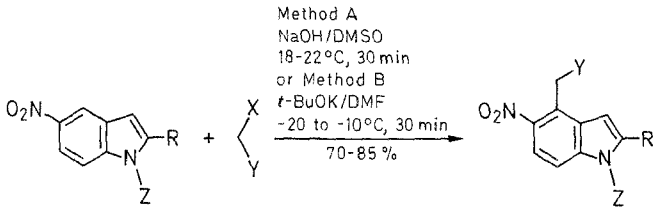
Amongst the heterocyclic compounds the most extensively investigated are indole derivatives both in terms of synthesis of the ring system as well as its transformations.[8] In our previous papers we have presented a few variants of the VNS approach to the synthesis of the indole ring system.[9] One of the problems encountered in the synthesis of many naturally occurring indole derivatives (such as ergot alkaloids, clavicipitic acid, teleocidines, etc.) is the introduction of a side chain into position 4 or 7 of the indole nucleus. In recent years there have been

developed various methods solving this problem, e.g.; palladium-mediated olefination,[10-12], Pictet-Spengler cyclization,[13] Friedel–Crafts alkylation.[14]

In this paper we show that also the VNS reaction can provide an useful tool for the introduction of a functionalized alkyl side chain into the indole derivatives namely when nitroindole derivatives are employed. 5- and 6-nitroindoles in strongly basic medium, in which the VNS reactions are carried out, exist in form of the corresponding anions and are unreactive towards the carbanions, therefore it was necessary to protect the acidic N–H group. For this purpose we have employed various substituents such as methyl, alkoxymethyl, benzyl, or tosyl groups, which differ in respect of ability to be removed after the reaction.

Reactions of 5-nitroindole derivatives **1** with chloromethyl sulfones performed in the presence of powdered sodium hydroxide in dimethyl sulfoxide (Method A) gave high yields of the expected products **3a, c, e** with hydrogen substitution in position 4.

However in the reaction of 2-methyl-5-nitro-1-tosylindole with chloromethyl tolyl sulfone carried out under these conditions the VNS did not occur, but hydrolysis of the starting material to 2-methyl-5-nitroindole took place. On the other hand, when potassium *tert*-butoxide in dimethylformamide (Method B) was used the reaction gave high yield of the expected product **3g**. The reaction of 4-chlorophenoxyacetonitrile with 5-nitroindole derivatives in the presence of potassium *tert*-butoxide in dimethylformamide resulted in the introduction of a cyanomethyl substituent into position 4.

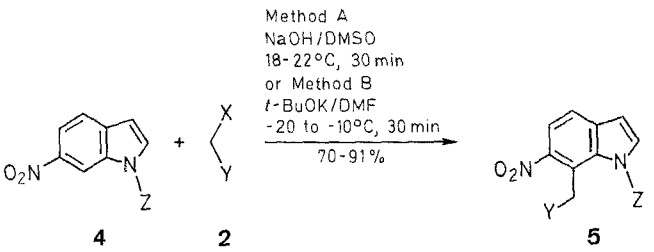


3	R	Z	X	Y
a	H	CH_3OCH_2	Cl	4-$CH_3C_6H_4SO_2$
b	H	$C_6H_5CH_2$	4-ClC_6H_4O	CN
c	H	$C_6H_5CH_2$	Cl	4-$CH_3C_6H_4SO_2$
d	CH_3	CH_3	4-ClC_6H_4O	CN
e	CH_3	$C_6H_5CH_2$	Cl	4-$CH_3C_6H_4SO_2$
f	CH_3	4-$CH_3C_6H_4SO_2$	4-ClC_6H_4O	CN
g	CH_3	4-$CH_3C_6H_4SO_2$	Cl	4-$CH_3C_6H_4SO_2$

Similar results were obtained in the reactions of 6-nitroindole derivatives **4** with **2**, which according to expectations, lead to the substitution products **5** containing sulfonyl- or cyanomethyl substituents exclusively at position 7.

The orientation patterns in these reactions were analogous to those observed earlier for the VNS in other bicyclic nitroarenes, such as 2-nitronaphthalene[15] and 6-nitroquinoline,[7] namely that the substitution has taken place *ortho* to the nitro group. The main factor deciding upon the reaction site was the conservation of the aromatic character of the "second" ring in the intermediate σ-adduct. In the case of 5- and 6-nitroindole derivatives the attack of the carbanion on positions 6 and 5, respectively, has not been observed because it would lead to the dearomatization of the five-membered ring.

The structures of the obtained products were confirmed by means of elemental analysis and ^{1}H-NMR spectra (Table 2). The spectra of products **5a, c–e, g–i** obtained from 6-nitroindole derivatives **4** and α-chloromethyl sulfones exhibit an interesting feature. Due to the hindered rotation signals of the methylene protons of the protecting group and the introduced substituent



5	Z	Y	X
a	CH_3	4-$CH_3C_6H_4SO_2$	Cl
b	CH_3OCH_2	CN	4-ClC_6H_4O
c	CH_3OCH_2	*t*-$BuSO_2$	Cl
d	CH_3OCH_2	4-$CH_3C_6H_4SO_2$	Cl
e	$C_6H_5CH_2$	4-$CH_3C_6H_4SO_2$	Cl
f	4-$CH_3OC_6H_4CH_2$	CN	4-ClC_6H_4O
g	4-$CH_3OC_6H_4CH_2$	*t*-$BuSO_2$	Cl
h	4-$CH_3OC_6H_4CH_2$	4-$CH_3C_6H_4SO_2$	Cl
i	3,4-$(CH_3O)_2C_6H_3CH_2$	4-$CH_3C_6H_4SO_2$	Cl

Table 1. 5- and 6-Nitroindole Derivatives **3** and **5** Prepared

Product	Base/ Solvent	Yield (%)	mp[a] (°C) (solvent)	Molecular Formula[b]
3a	NaOH/DMSO	79	136–137 (EtOH)	$C_{18}H_{18}N_2O_5S$ (374.4)
3b	*t*-BuOK/DMF	76	145–146 (EtOH)	$C_{17}H_{13}N_3O_2$ (291.3)
3c	NaOH/DMSO	82	182–183 (2-propanol)	$C_{23}H_{20}N_2O_4S$ (420.5)
3d	*t*-BuOK/DMF	71	198–199 (EtOH)	$C_{12}H_{11}N_3O_2$ (229.2)
3e	NaOH/DMSO	85	204–205 (2-propanol)	$C_{24}H_{22}N_2O_4S$ (434.5)
3f	*t*-BuOK/DMF	81	191–192 (EtOH)	$C_{18}H_{15}N_3O_4S$ (369.4)
3g	*t*-BuOK/DMF	70	210–211 (EtOH)	$C_{24}H_{22}N_2O_6S_2$ (498.6)
5a	NaOH/DMSO	88	204–205 (EtOH)	$C_{17}H_{16}N_2O_4S$ (344.4)
5b	*t*-BuOK/DMF	78	182–183 (EtOH)	$C_{12}H_{11}N_3O_2$ (245.2)
5c	NaOH/DMSO	86	212–213 (EtOH)	$C_{15}H_{20}N_2O_5S$ (340.4)
5d	*t*-BuOK/DMF	80	172–173 (2-propanol)	$C_{18}H_{18}N_2O_5S$ (374.4)
5e	NaOH/DMSO	87	182–183 (2-propanol)	$C_{23}H_{20}N_2O_4S$ (420.5)
5f	*t*-BuOK/DMF	70	129–130 (EtOH)	$C_{18}H_{15}N_3O_3$ (321.3)
5g	NaOH/DMSO	91	127–129 (EtOH)	$C_{21}H_{24}N_2O_5S$ (416.5)
5h	NaOH/DMSO	86	150–151 (EtOH)	$C_{24}H_{22}N_2O_5S$ (450.5)
5i	*t*-BuOK/DMF	79	164–165 (EtOH)	$C_{25}H_{24}N_2O_6S$ (480.5)

[a] Uncorrected, measured with a Büchi SMP-20 apparatus.
[b] Satisfactory microanalyses obtained: C ±0.40, H ±0.31, N ±0.35.

Table 2. ^{1}H-NMR Spectra of the Obtained Products **3** and **5**

Product	^{1}H-NMR ($CDCl_3$/TMS)[a,b] δ, J(Hz)
3a	2.39 (s, 3H, TolCH$_3$); 3.24 (s, 3H, OCH$_3$); 5.31 (s, 2H, CH$_2$SO$_2$); 5.44 (s, 2H, NCH$_2$O); 6.69 (dd, 1H, J = 3.4, 0.7, H$_{ind}$-3); 7.18–7.23 (m, 2H); 7.33 (d, 1H, J = 3.4, H$_{ind}$-2); 7.50 (dd, 1H, J = 9.0, 0.7, H$_{ind}$-7); 7.52–7.56 (m, 2H); 7.89 (d, 1H, J = 9.0, H$_{ind}$-6)
3b	4.36 (s, 2H, CH$_2$CN); 5.39 (s, 2H, NCH$_2$O); 6.84 (dd, 1H, J = 3.3, 0.8, H$_{ind}$-3); 7.08–7.12 (m, 2H); 7.28–7.37 (m, 4H); 7.38 (d, 1H, J = 3.3, H$_{ind}$-2); 8.03 (d, 1H, J = 9.0, H$_{ind}$-6)
3c	2.40 (s, 3H, TolCH$_3$); 5.35 (s, 4H, NCH$_2$O, CH$_2$SO$_2$); 6.77 (dd, 1H, J = 3.3, 0.8, H$_{ind}$-3); 7.07–7.13 (m, 2H); 7.18–7.23 (m, 2H); 7.28 (d, 1H, J = 3.3, H$_{ind}$-2); 7.29 (dd, 1H, J = 9.0, 0.8, H$_{ind}$-7); 7.31–7.36 (m, 3H); 7.53–7.57 (m, 2H); 7.86 (d, 1H, J = 9.0, H$_{ind}$-6)
3d	2.49 (s, 3H, IndCH$_3$); 3.72 (s, 3H, NCH$_3$); 4.30 (s, 2H, CH$_2$CN); 6.53 (s, 1H, H$_{ind}$-3); 7.28 (d, 1H, J = 9.0, H$_{ind}$-7); 8.01 (d, 1H, J = 9.0, H$_{ind}$-6)
3e	2.38 (d, 3H, J = 0.8, IndCH$_3$); 2.39 (s, 3H, TolCH$_3$); 5.32 (s, 4H, NCH$_2$O, CH$_2$SO$_2$); 6.54 (s, 1H, H$_{ind}$-3); 6.91–6.95 (m, 2H); 7.16–7.24 (m, 2H); 7.26–7.33 (m, 2H); 7.54–7.59 (m, 2H); 7.79 (d, 1H, J = 8.9, H$_{ind}$-6)
3f	2.39 (s, 3H, TolCH$_3$); 2.67 (d, 3H, J = 1.0, IndCH$_3$); 4.21 (s, 2H, CH$_2$CN); 6.59–6.61 (m, 1H, H$_{ind}$-3); 7.27–7.32 (m, 2H); 7.67–7.73 (m, 2H); 8.06 (d, 1H, J = 9.2, H$_{ind}$-6); 8.28 (dd, 1H, J = 9.2, 0.6, H$_{ind}$-7)
3g	2.40 (s, 6H, TolCH$_3$); 2.61 (d, 1H, J = 1.0, IndCH$_3$); 5.15 (s, 2H, CH$_2$SO$_2$); 6.51–6.54 (m, 1H, H$_{ind}$-3); 7.17–7.22 (m, 2H); 7.29–7.33 (m, 2H); 7.49–7.53 (m, 2H); 7.69–7.73 (m, 2H); 7.91 (d, 1H, J = 9.2, H$_{ind}$-6); 8.26 (dd, 1H, J = 9.2, 0.6, H$_{ind}$-7)
5a	2.45 (s, 3H, TolCH$_3$); 4.23 (s, 3H, NCH$_3$); 5.17, 5.95 (2d, 2H, J = 14.3, CH$_2$SO$_2$); 6.56 (d, 1H, J = 3.1, H$_{ind}$-3); 7.23 (d, 1H, J = 3.1, H$_{ind}$-2); 7.25–7.30 (m, 2H); 7.49–7.53 (m, 2H); 7.60, 7.62 (AB, 2H, J = 8.6, H$_{ind}$-4, H$_{ind}$-5)
5b	3.39 (s, 3H, OCH$_3$); 4.58 (s, 2H, CH$_2$CN); 5.75 (s, 2H, NCH$_2$); 6.68 (d, 1H, J = 3.25, H$_{ind}$-3); 7.65 (d, 1H, J = 3.25, H$_{ind}$-2); 7.73 (d, 1H, J = 8.65, H$_{ind}$-4*); 7.85 (d, 1H, J = 8.65, H$_{ind}$-5*)
5c	1.54 (s, 9H, C(CH$_3$)$_3$); 3.28 (s, 3H, OCH$_3$); 5.05 (br s, 1H); 5.34 (br s, 1H); 5.82 (br s, 1H); 6.39 (br s, 1H); 6.58 (d, 1H, J = 2.0, H$_{ind}$-3); 7.32 (d, 1H, J = 2.0, H$_{ind}$-2); 7.66, 7.78 (AB, J = 8.6, H$_{ind}$-4, H$_{ind}$-5)
5d	2.46 (s, 3H, TolCH$_3$); 3.24 (s, 3H, OCH$_3$); 5.17 (d, 1H, J = 8.1); 5.42 (d, 1H, J = 13.3); 5.91 (d, 1H, J = 13.3); 6.53 (d, 1H, J = 8.1); 6.62 (d, 1H, J = 3.2, H$_{ind}$-3); 7.29–7.36 (m, 2H); 7.39 (d, 1H, J = 3.2, H$_{ind}$-2); 7.61–7.81 (m, 2H); 7.67, 7.70 (AB, J = 8.6, H$_{ind}$-4, H$_{ind}$-5)
5e	2.43 (s, 3H, TolCH$_3$); 4.68 (br s, 1H); 5.62 (br s, 2H); 6.20 (br s, 1H); 6.70 (d, 1H, J = 3.2, H$_{ind}$-3); 6.88–6.93 (m, 2H); 7.23–7.33 (m, 5H); 7.41 (d, 1H, J = 3.2, H$_{ind}$-2); 7.50–7.55 (m, 2H); 7.63, 7.68 (AB, J = 8.6, H$_{ind}$-4, H$_{ind}$-5)
5f	3.78 (s, 3H, OCH$_3$); 4.01 (s, 2H, CH$_2$CN); 5.65 (s, 2H, NCH$_2$); 6.71 (d, 1H, J = 3.2, H$_{ind}$-3); 6.80–6.94 (m, 4H); 7.12 (d, 1H, J = 3.2, H$_{ind}$-2); 7.69 (d, 1H, J = 8.7, H$_{ind}$-4*); 7.81 (d, 1H, J = 8.7, H$_{ind}$-5*)
5g	1.43 (s, 9H, C(CH$_3$)$_3$); 3.78 (s, 3H, OCH$_3$); 4.44 (d, 1H, J = 13.3); 5.46 (d, 1H, J = 17.6); 5.57 (d, 1H, J = 13.3); 6.05 (d, 1H, J = 17.6); 6.67 (d, 1H, J = 3.2, H$_{ind}$-3); 6.77–6.88 (m, 4H); 7.34 (d, 1H, J = 3.2, H$_{ind}$-2); 7.70, 7.78 (AB, 2H, J = 8.6, H$_{ind}$-4, H$_{ind}$-5)
5h	2.44 (s, 3H, TolCH$_3$); 3.76 (s, 3H, OCH$_3$); 4.76 (br s, 1H); 5.55 (br s, 1H); 5.66 (br s, 1H); 6.10 (br s, 1H); 6.68 (d, 1H, J = 3.1, H$_{ind}$-3); 6.78–6.88 (m, 4H); 7.23–7.30 (m, 2H); 7.41 (d, 1H, J = 3.2, H$_{ind}$-2); 7.49–7.55 (m, 2H); 7.61, 7.68 (AB, J = 8.5, H$_{ind}$-4, H$_{ind}$-5)
5i	2.44 (s, 3H, TolCH$_3$); 3.75 (s, 3H, OCH$_3$); 3.82 (s, 3H, OCH$_3$); 4.78 (br s, 1H); 5.55 (br s, 1H); 5.66 (br s, 1H); 6.10 (br s, 1H); 6.33–6.39 (m, 1H); 6.55 (d, 1H, J = 2.0); 6.69 (d, 1H, J = 3.2, H$_{ind}$-3); 6.74 (d, 1H, J = 8.3); 7.23–7.32 (m, 2H); 7.41 (d, 1H, J = 3.2, H$_{ind}$-2); 7.52–7.57 (m, 2H); 7.61, 7.68 (AB, 2H, J = 8.6, H$_{ind}$-4, H$_{ind}$-5)

[a] Recorded on a Bruker AM-500 (500 MHz) spectrometer.
[b] The assignment of protons marked with asterisk (*) may be interchanged.

in these compounds form separate doublets or broad singlets. In the spectra of the analogous, less hindered, cyano derivatives **5b, f** protons of the both methylene groups are represented by singlets.

The introduction of α-functionalized alkyl substituents into the nitroindole moiety provides versatile starting materials for the synthesis of complex indole derivatives. The work on this subject is currently in progress.

The following starting materials were obtained as described in the literature: *tert*-butyl chloromethyl sulfone,[15] chloromethyl tolyl sulfone,[16] 4-chlorophenoxyacetonitrile,[17] 2-methyl-5-nitroindole,[18] 6-nitroindole.[19] Alkyl derivatives of nitroindoles were prepared via alkylation of the nitroindoles with the corresponding alkyl chlorides in the presence of solid NaOH in DMSO. 5-Nitro-1-tosylindole was prepared in the reaction of 5-nitroindole with tosyl chloride in the presence of solid NaOH with a catalytic amount of tetrabutylammonium bromide in CH_2Cl_2. Other starting materials were commercial products.

1-Methoxymethyl-5-nitro-4-(4-tolylsulfonylmethyl)indole (3a); Typical Procedure for Method A:

To a stirred suspension of powdered NaOH (2.0 g, 50 mmol) in DMSO (10 mL) a solution of chloromethyl 4-tolyl sulfone (1.02 g, 5 mmol) and 1-methoxymethyl-5-nitroindole (1.06 g, 5 mmol) in DMSO (10 mL) is added dropwise at 18 to 22 °C. The reaction mixture is stirred for 30 min and poured into 5% HCl (200 mL). The solid product is filtered off, washed with H_2O (2 × 100 mL), dissolved in CH_2Cl_2 (50 mL), and dried ($MgSO_4$). The solution is passed through a short silica gel column (2 × 5 cm) and concentrated *in vacuo*. Product **3a** is recrystallized from EtOH; yield: 1.48 g (79%); mp 136–137 °C.

7-Cyanomethyl-1-(4-methoxyphenylmethyl)-6-nitroindole (5f); Typical Procedure for Method B:

A solution of 4-chlorophenoxyacetonitrile (0.92 g, 5.5 mmol) and 1-(4-methoxyphenylmethyl)-6-nitroindole (1.4 g, 5 mmol) in DMF (10 mL) is added dropwise to a solution of *t*-BuOK (1.7 g, 15 mmol) in DMF (20 mL) at −20 to −10 °C. The reaction mixture is stirred at this temperature for 30 min and poured into ice-cold 5% HCl (200 mL). The product is filtered off, washed with H_2O (2 × 100 mL), dissolved in CH_2Cl_2 (100 mL), and dried ($MgSO_4$). The solution is passed through a short silica gel column (2 × 5 cm) and concentrated *in vacuo*. Product **5f** is recrystallized from EtOH; yield: 1.12 g (70%); mp 129–130 °C.

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