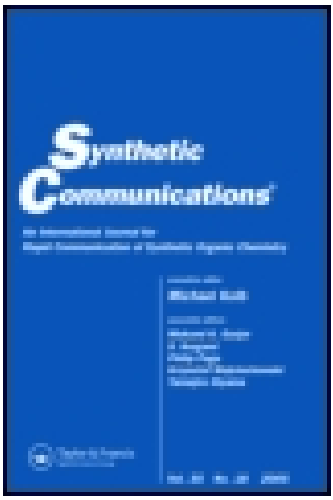

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$S_{RN}1$ Based Methodology for Synthesis of 2-Substituted Nitropyridines

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$S_{RN}1$ BASED METHODOLOGY FOR SYNTHESIS OF 2-SUBSTITUTED NITROPYRIDINES

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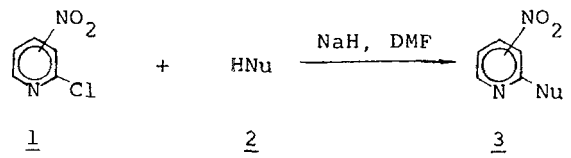
ABSTRACT: 2-Chloronitropyridines react with the anion of benzyl cyanide, benzotriazole, imidazole, pyrrole, and phthalimide to give the corresponding 2-substituted nitropyridines. The $S_{RN}1$ mechanism was confirmed by EPR spectroscopy and depression of reaction rate by the addition of an inhibitor.

Since the radical nucleophilic substitution mechanism ($S_{RN}1$) was first reported in 1966,[1] much work has been carried out in this field.[2] A versatile $S_{RN}1$ based methodology allows straight-forward access to a variety of compounds, and some are heterocyclic compounds with biological interest.[3] In 1976, Rossi et al.[4] reported the $S_{RN}1$ reaction of 2-chloropyridine with cyanomethyl anion, and the substituted pyridine product was obtained in high yield. Other $S_{RN}1$ reactions of pyridine derivatives have been reported recently.[5] Here, we wish to report the synthesis of 2-substituted nitropyridines by $S_{RN}1$ reaction of 2-chloronitropyridines with the anions derived from

benzyl cyanide, benzotriazole, imidazole, pyrrole, and phthalimide, respectively.

2-Chloro-3-nitropyridine (1a) or 2-chloro-5-nitropyridine (1b) reacted with the anion of 2, prepared from 2 with sodium hydride in dimethylformamide, to give the 2-substituted nitropyridines 3.



1 2 3

a 3-NO_2 a C_6H_5-CH-CN a 3-NO_2, C_6H_5-CH-CN

b 5-NO_2 b b 3-NO_2,

c c 5-NO_2, C_6H_5-CH-CN

d d 5-NO_2,

e e 5-NO_2,

f 5-NO_2,

g 5-NO_2,

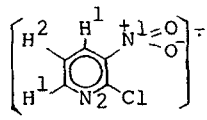
The structures of the products were determined by MS, elemental analyses, and other spectroscopic data. The reaction conditions, yields, and melting points of the products are listed in Table 1. From the results in Table

Table 1. The reaction conditions of 1 with 2, and the yields and melting points of 3

Entry	reactant		reaction time, h	product	yield %	m.p. °C
1	1a	2a	64	3a	9	131-131.5
2	1a	2b	35	3b	67	159-159.5 (153-155)[7c]
3	1b	2a	40	3c	37	viscous liquid
4	1b	2b	5	3d	95	240-241 (242.5-246)[8]
5	1b	2c	5	3e	71	201(dec.)
6	1b	2d	57	3f	67	169-170
7	1b	2e	48	3g	11	238-238.5

1 (Entries 1 - 4), it is obvious that 2-chloro-5-nitropyridine (2b) is more active and gave higher yields of products than the 3-nitro isomer 2a.

In order to explore the $S_{RN}1$ mechanism of this reaction, the course of the reaction was investigated by EPR spectroscopy and the effect of radical reaction inhibitor on the product yield. The reaction mixture was EPR active, and the EPR spectrum of the radical anion 4



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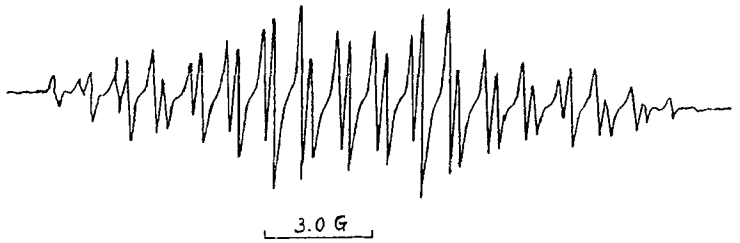
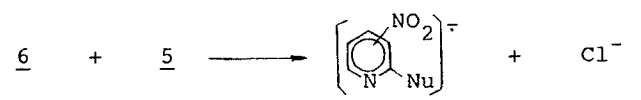


Fig. 1. The EPR spectrum of the radical anion 4 recording during the reaction of anion of 2a with 1a in DMF

of 2-chloro-3-nitropyridine recorded during the reaction of the anion derived from 2a with 1a in dimethylformamide is shown in Fig. 1. The hyperfine coupling constants of the radical anion 4 are: a_N1 = 5.07G, a_N2 = 2.03 G, a_H1 = 1.01 G, and a_H2 = 0.70 G. Addition of anhydrous ferric chloride (50 mol %) into the reaction mixture of 2-chloro-3-nitropyridine (1a) with the anion of benzotriazole (2b) inhibited the reaction compltely.[6] Thus, a radical nucleophilic substitution mechanism, $S_{RN}1$, is proposed for this reaction as follows:

1 5 6 7



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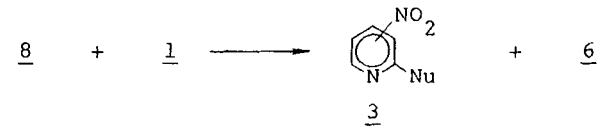

3

(Nitropyridinyl)benzotriazoles (3b, 3d) have been synthesized by the reaction of 2-halo-nitropyridines with benzotriazole at higher temperature,[7] and 3d has also been synthesized by diazotization of 2-o-aminoanilino-5-nitropyridine.[8] The method described above for the synthesis of 2-substituted nitropyridines via $S_{RN}1$ mechanism possess several advantages: mild reaction conditions with relatively high yield and minor by-product for easy purification of the products.

EXPERIMENTAL

Melting points were uncorrected. Mass spectra were obtained on a AEI MS-50 instrument. IR spectra (KBr disk) were recorded on a Perkin-Elmer 782 spectrometer. ^1H NMR spectra were recorded on a Varian EM-360L instrument. EPR spectra were measured on a Bruker ESR 300D spectrometer. Elemental analyses were carried out by the Analytical Laboratory of the Institute.

α-(3-Nitro-2-pyridinyl)benzyl Cyanide (3a):

A mixture of 2a (900 mg, 7.7 mmol) and sodium hydride (280 mg, 11.6 mmol) in dry DMF (20 ml) was allowed to react at room temperature, until the escape of hydrogen gas was stopped. To this solution 1a (1.22g, 8.4 mmol) in dry DMF (10 ml) was added, and the reaction mixture was stirred at

room temperature for 64 h (monitored by TLC). After the addition of water (20 ml), the mixture was extracted with chloroform (3 x 20 ml). After removal of solvent, the crude product was purified by silica gel column chromatography using ethyl acetate- light petroleum (60-90°C) as eluent. 160 mg of 3a was obtained. IR: ν = 2240 (CN), 1580, 1558, 1522 and 1348 cm^{-1} (NO_2). ^1H NMR ($CDCl_3$): δ = 6.32 (s, 1H), 7.26-7.60 (m, 6H), 8.38 (d, J = 8 Hz, 1H), 8.94 (d, J = 4 Hz, 1H). MS: m/z = 239 (M^+, 3.5%), 222 (82), 205 (27), 196 (22), 192 (100), 181 (16), 164 (42), 154 (36), 139 (30), 116 (23). Anal. calc. for $C_{13}H_9N_3O_2$: C, 65.27; H, 3.79; N, 17.57. Found C, 64.84; H, 3.45; N, 17.54.

1-(3-Nitro-2-pyridinyl)-1H-benzotriazole (3b):

According to the procedure for 3a, but the crude product was filtered out upon the addition of water, and recrystallized from ethyl acetate. 1.2 g of 3b was obtained from 1a (1.17 g, 8.1 mmol) and 2b (880 mg, 7.4 mmol). IR: ν = 1588, 1568, 1534 and 1356 cm^{-1} (NO_2). ^1H NMR ($CDCl_3$): δ = 7.40-7.72 (m, 3H), 8.12-8.36 (m, 3H), 8.77-8.84 (m, 1H). MS: m/z = 241 (M^+, 43%), 213 (7), 183 (17), 167 (89), 155 (18), 140 (49), 92 (100). Anal. calc. for $C_{11}H_7N_5O_2$: C, 54.77; H, 2.93; N, 29.04. Found C, 54.84; H, 2.87; N, 28.56.

α-(5-Nitro-2-pyridinyl)benzyl Cyanide (3c):

According to the procedure for 3a, 3c (680 mg) was obtained from 1b (1.22 g, 8.4 mmol) and 2a (900 mg, 7.7 mmol). IR: ν = 2240 (CN), 1593, 1568, 1518 and 1346 cm^{-1} (NO_2). ^1H NMR ($CDCl_3$): δ = 5.43 (s, 1H), 7.33-7.49 (m, 5H),

7.60 (d, J = 8 Hz, 1H), 8.49 (dd, J = 8, 4 Hz, 1H), 9.39 (d, J = 4 Hz,1H). MS: m/z = 239 (M^+, 98%), 238 (100), 212 (10), 192 (90), 166 (30), 140 (16), 116 (46). Anal. calc. for $C_{13}H_9N_3O_2$: C, 65.27; H, 3.79; N, 17.57. Found C, 65.21; H, 3.65; N, 17.60.

1-(5-Nitro-2-pyridinyl)-1H-benzotriazole (3d):

According to the procedure for 3b, 3d (1.70 g, recrystallized from ethanol) was obtained from 1b (1.17 g, 8.1 mmol) and (880 mg, 7.4 mmol). IR: ν = 1590, 1570, 1515 and 1345 cm^{-1} (NO_2). ^1H NMR ($CDCl_3$): δ = 7.44-7.76 (m, 2H), 8.16 (d, J = 8 Hz, 1H), 8.48-8.79 (m, 3H), 9.47 (d, J = 4 Hz, 1H). MS: m/z = 241 (M^+, 40%), 213 (21), 167 (100), 155 (13), 140 (31). Anal. calc. for $C_{11}H_7N_5O_2$: C, 54.77; H, 2.93; N, 29.04. Found C, 54.77: H, 2.96; N, 28.36.

2-(1H-Imidazol-1-yl)-5-nitropyridine (3e):

According to the procedure for 3b, 3e (1.0 g, recrystallized from ethanol) was obtained from 1b (1.17 g, 8.1 mmol) and (500 mg, 7.4 mmol). IR: ν = 1603, 1580, 1510 and 1349 cm^{-1} (NO_2). ^1H NMR ($CDCl_3$): δ = 7.26 (s, 1H), 7.49 (d, J = 8 Hz, 1H), 7.69 (s, 1H), 8.46 (s, 1H), 8.61 (dd, J = 8,4 Hz, 1H). MS: m/z = 190 (M^+, 100%), 163 (21), 117 (46), 105 (17), 90 (25). Anal. calc. for $C_8H_6N_4O_2$: C, 50.53; H, 3.18; N, 29.46. Found C, 50.55; H, 3.22; N, 29.00.

5-Nitro-2-(1H-pyrrol-1-yl)pyridine (3f):

According to the procedure for 3b, 3f (930 mg, recrystallized from light petroleum) was obtained from 1b (1.17 g, 8.1 mmol) and 2d (500 mg, 7.5 mmol). IR: ν = 1598, 1582,

1510 and 1340 cm^{-1} (NO_2). ^1H NMR ($CDCl_3$): δ = 6.42 (t, J = 2 Hz, 2H), 7.38 (d, J = 8 Hz, 1H), 7.56 (t, J = 2 Hz, 2H), 8.51 (dd, J = 8, 4 Hz, 1H), 9.25 (d, J = 4 Hz, 1H). MS: m/z = 189 (M^+, 100%), 142 (18), 116 (66), 89 (28). Anal. calc. for $C_9H_7N_3O_2$: C, 57.14; H, 3.73; N, 22.21. Found C, 57.71; H, 3.71; N, 22.15.

N-(5-Nitro-2-pyridinyl)phthalimide (3g):

According to the procedure for 3b, 3g (210 mg, recrystallized from ethyl acetate) was obtained from 1b (1.17 g, 8.1 mmol) and 2e (1.09 g, 7.4 mmol). IR: ν = 1780 and 1724 (C=O), 1598, 1575, 1514 and 1345 cm^{-1} (NO_2). ^1H NMR ($CDCl_3$): δ = 7.71-8.07 (m, 5H), 8.66 (dd, J = 8, 4 Hz, 1H), 9.49 (d, J = 4 Hz, 1H). MS: m/z = 269 (M^+, 50%), 241 (100), 223 (10), 196 (15), 168 (11), 130 (12). Anal. calc. for $C_{13}H_7N_3O_4$: C, 58.00; H, 2.62; N, 15.61. Found C, 58.08; H, 2.40; N, 15.64.

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