# ELECTRON TRANSFER REACTIONS IN 5-NITROISOQUINOLINES

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**Abstract:** 1-Chloromethyl-5-nitroisoquinoline, a new reductive alkylating agent, has been prepared and shown for the first time in isoquinoline series to react with 2-nitropropane anion to give C-alkylation by an $S_{RN}1$ mechanism. This has been confirmed by the inhibitory effects of dioxygen, *p*-dinitrobenzene, cupric chloride and TEMPO. This reaction was followed by a base-mediated nitrous acid elimination leading to new isopropylidene derivative.

## Introduction

The inhibitory potency of various isoquinoline thiosemicarbazone derivatives (1) for the enzyme ribonucleotide reductase illustrates interest of the isoquinoline ring for medicinal chemistry.

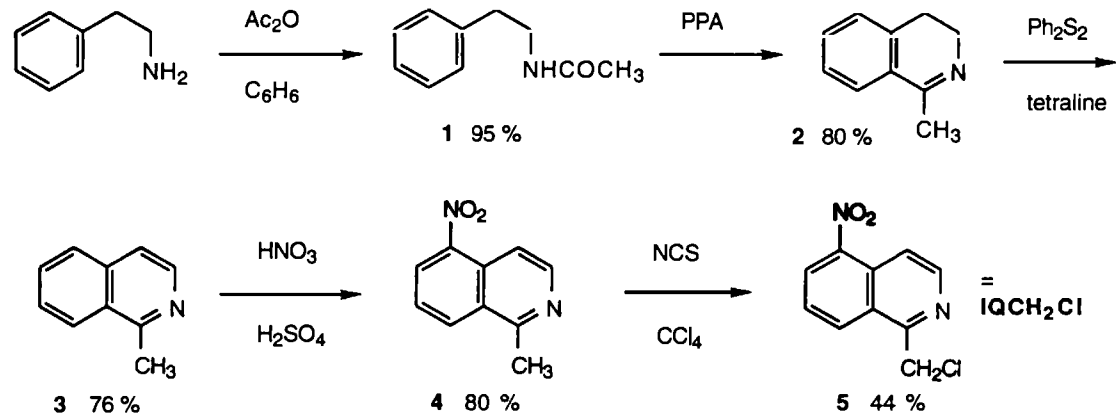
As part of our continuing studies on the $S_{RN}1$ reactions of heterocyclic alkylating agents (2) and in order to prepare new potentially antineoplastic agents involving electron transfer in their mode of action, we have investigated the synthesis of 1-chloromethyl-5-nitroisoquinoline and have studied its reactivity with the 2-nitropropane anion.

## Results

1-Chloromethyl-5-nitroisoquinoline 5 has been prepared in five steps from the inexpensive and commercially available 2-phenylethylamine. The required starting material produced 2-phenylethylacetamide 1 by acetylation. The synthesis of 1-methyl-3,4-dihydroisoquinoline was carried out utilizing the Bischler-Napieralski reaction (3), which was modified by use of polyphosphoric acid (PPA) instead of $POCl_3$ as the dehydrating reagent. The employment of this modification resulted in an increase in the yield of 2 from 30 to 80%. Derivative 2 was then dehydrogenated with diphenyl disulfide as previously reported (4). Nitration of 1-methylisoquinoline with $HNO_3$-$H_2SO_4$ (5) resulted in only one compound, 1-methyl-5-

nitroisoquinoline 4. Free radical chlorination (6) using N-chlorosuccinimide (NCS) of 4 gave 1-chloromethyl-5-nitroisoquinoline 5 in 44% yield.

Scheme1




The chloride 5 reacts with 2-nitropropane anion 6 to give C-alkylation derivatives under conditions conducive to $S_{RN}1$ reactions (nitrogen, light catalysis). The results including mechanistic investigations are reported in the Table I.

$$IQCH_2Cl + M^+ {}^-C(CH_3)_2NO_2 \longrightarrow IQCH_2C(CH_3)_2NO_2 + IQCH{=}C(CH_3)_2 + IQCHO + IQCH_2OH$$

**5** **6** **7** **8** **9** **10**

M = Li, $NBu_4$

## Discussion

The results of table I show that 5 reacts with 6 to give the C-alkylation product 7 which undergoes under these conditions incomplete elimination of nitrous acid to give 1-isopropylidenemethyl-5-nitroisoquinoline 8 (7). When one equivalent of anion is used (entry 1), the yield of derivative 8 is only 5% indicating that the base-promoted nitrous acid elimination involves the 2-nitropropane anion as a base. The nitrous acid elimination is classically observed in nitro heterocyclic system (8) and favoured by using an excess of nitronate anion as shown by the study of the donor/acceptor ratio. Experimentally, the best C-alkylation yield is obtained when 3 to 5 equivalents of 2-nitropropane anion are used (entries 3, 4 and 5) in degassed DMF under Komblum conditions (9). The C-alkylation yield decreases in the phase transfer conditions of Norris using 40% tetrabutylammonium hydroxide in water and dichloromethane (entries 6 and 7) (10) as already described in other series (11). The distribution product also changes because nitrous acid elimination is easier with DMF as solvent leading to the ethylenic compound as observed in the benzoquinone series (12).

Although the $S_{RN}1$ mechanism seems likely in view of the structure of derivatives 7 and 8, classical inhibition experiments (13) such as dark reaction, electron trapping and radical

**Table 1 : Influence of experimental conditions in the reaction of 5 with 6**

| Entry[a] | $M^+$ | Mol. equiv. of 6 | Solvent | Scavenger (Mol. equiv.) | % C-alkylation | Yield[b] 7 | 8 | 9 | 10 | 5 |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Li | 1 | DMF | - | 53 | 48 | 5 | 10 | - | 12 |
| 2 | Li | 2 | DMF | - | 76 | 33 | 43 | 7 | - | - |
| 3 | Li | 3 | DMF | - | 87 | 29 | 58 | - | - | - |
| 4 | Li | 4 | DMF | - | 88 | 26 | 62 | - | - | - |
| 5 | Li | 5 | DMF | - | 90 | 28 | 62 | - | - | - |
| 6 | $NBu_4$ | 3 | $CH_2Ci_2/H_2O$ | - | 74 | 41 | 33 | - | - | - |
| 7 | $NBu_4$ | 4 | $CH_2Ci_2/H_2O$ | - | 79 | 44 | 35 | - | - | - |
| 8 | Li | 3 | DMF | $CuCl_2$ (0.1) | 26 | 4 | 22 | 7 | - | - |
| 9 | Li | 3 | DMF | $CuCl_2$ (1) | 11 | 6 | 5 | 2 | - | - |
| 11 | Li | 3 | DMF | TEMPO (0.1) | 37 | 7 | 30 | 6 | - | - |
| 12 | Li | 3 | DMF | TEMPO (1) | 0 | - | - | trace | - | - |
| 13 | Li | 3 | DMF | *p*-$NO_2C_6H_4NO_2$ (0.1) | 41 | 11 | 30 | - | - | - |
| 14[c] | Li | 3 | DMF | *p*-$NO_2C_6H_4NO_2$ (1) | 17 | 10 | 7 | 17 | 9 | - |
| 15 | Li | 3 | DMF | dark | 81 | 28 | 53 | - | - | - |
| 16 | Li | 3 | DMF | $O_2$ (bubbling) | 2 | 2 | trace | 9 | 19 | 5 |
| 17 | Li | 3 | DMF | dark, $O_2$ (bubbling) | 0 | trace | trace | 7 | 21 | 11 |

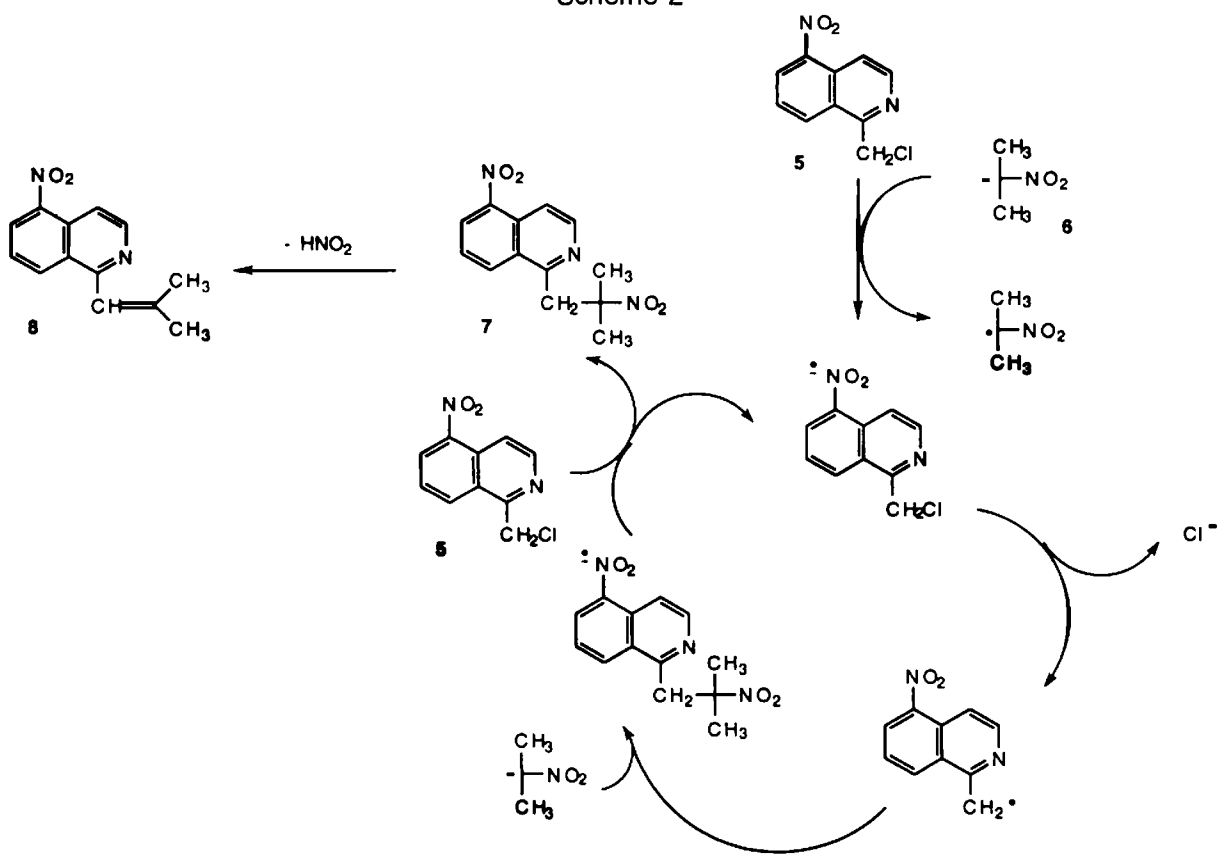
[a]All reactions were irradiated at room temperature during 24 h under nitrogen with fluorescent lamps (2x60W) by using one equivalent of isoquinoline derivative 5 unless otherwise noted. [b]All yields were referred to pure products chromatographically isolated and relative to the electrophile. [c]α,p-dinitrocumene was the major product (61%).

scavenging have been carried out. In these inhibition experiments, the apparition of an increased quantity of resinous products is observed and the formation of derivative 9 is explained by the competitive O-alkylation ($S_N2$) and 10 by the reaction of dioxygen with the intermediate radical 5 (14). When catalytic amounts of cupric chloride, 2,2,6,6-tetramethyl-1,4-piperidinyloxy (TEMPO) or *p*-dinitrobenzene were added, the C-alkyiation yield dropped significantly. The use of higher concentrations of these inhibitors increased this effect and α,*p*-dinitrocumene became the predominant product (61%)( entry 14). The absence of light leads to little inhibition which can be explained by the relatively long time of the reaction (24 h). When dioxygen is bubbled through the reaction mixture, the inhibition is complete and the alcohol derivative 10 is isolated.

When the reaction was performed with 1-chloromethylisoquinoline obtained by chlorination of 3 by NCS and the 2-nitropropane salt under the experimental conditions of entry 3, neither the C-alkylation nor the O-alkylation products are found in the reaction mixture, indicating the necessity of the presence of the electron-withdrawing nitro group for $S_{RN}1$ reaction.

From the results of these classical inhibition experiments, we conclude that an $S_{RN}1$ mechanism is the most probable for the C-alkylation of 1-chloromethyl-5-nitroisoquinoline as shown in scheme 2.

Scheme 2



## Conclusion

All these results show that 1-chloromethyl-5-nitroisoquinoline 5 reacts with 2-nitropropane anion 6 in good yields to give C-alkylation by $S_{RN}1$ mechanism. The extension of this reaction to more complex nitronate anion is in progress. The biological studies of related compounds will be reported elsewhere.

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(7) All derivatives have been isolated as pure products by chromatography on a silica gel column eluting with chloroform and recrystallization from appropriate solvent:

5, yellow solid, mp 120 °C (isopropanol), $^1H$ NMR (200 MHz, $CDCl_3$) δ 5.19 (s, 2H); 7.80 (dd, J = 8.0 and 8.3 Hz, 1H); 8.45 (d, J = 6.2 Hz, 1H); 8.53 (d, J = 8.0 Hz, 1H); 8.63 (d, J = 8.3 Hz, 1H); 8.70 (d, J = 6.2 Hz, 1H).
Anal. Calcd for $C_{10}H_7ClN_2O_2$: C, 53.95; H, 3.17; N, 12.58; Cl, 15.92. Found: C, 54.01; H, 3.19; N, 12.50; Cl, 16.00.

7, pink solid, mp 108 °C (isopropanol), $^1H$ NMR (200 MHz, $CDCl_3$) δ 1.79 (s, 6H); 4.01 (s, 2H);

7.73 (dd, J = 8.3 and 8.5 Hz, 1H); 8.31 (d, J = 6.2 Hz, 1H); 8.44 (d, J = 8.3 Hz, 1H); 8.48 (d, J = 8.5 Hz, 1H); 8.65 (d, J = 6.2 Hz, 1H).
Anal. Calcd for $C_{13}H_{13}N_3O_4$: C, 56.73; H, 4.76; N, 15.27. Found: C, 56.74; H, 4.77; N, 15.29.

8, yellow solid, mp 79 °C (hexane), $^1$H NMR (200 MHz , $CDCl_3$) δ 1.88 (d, J = 1.2 Hz, 3H); 2.09 (d, J = 1.2 Hz, 3H); 6.82 (s, 1H); 7.66 (dd, J = 8.0 and 8.1 Hz, 1H); 8.29 (d, J = 6.2 Hz, 1H); 8.47 (d, J = 8.0 Hz, 1H); 8.52 (d, J = 8.1 Hz, 1H); 8.73 (d, J = 6.2 Hz, 1H).
Anal. Calcd for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30; N, 12.27. Found: C, 68.30; H, 5.31; N, 12.18.

9, yellow solid, mp 175-176 °C (ethanol) Litt ref 5, $^1$H NMR (200 MHz, $CDCl_3$) δ 7.89 (dd, J = 8.5 and 8.6 Hz, 1H); 8.59 (d, J = 8.5 Hz, 1H); 8.74 (d, J = 6.1 Hz, 1H); 9.00 (d, J = 6.1 Hz, 1H); 9.77 (d, J = 8.6 Hz, 1H); 10.41 (s, 1H).
Anal. Calcd for $C_{10}H_6N_2O_3$: C, 59.41; H, 2.99; N, 13.86. Found: C, 59.38; H, 2.92; N, 13.81.

10, yellow solid, mp 138 °C (benzene), $^1$H NMR (200 MHz, $CDCl_3$) δ 4.77 (broad s); 5.23 (s, 2H); 7.70 (dd, J = 8.0 and 8.1 Hz, 1H); 8.22 (d, J = 8.0 Hz, 1H); 8.35 (d, J = 6.2 Hz, 1H); 8.47 (d, J = 8.1 Hz, 1H); 8.63 (d, J = 6.2 Hz, 1H).
Anal. Calcd for $C_{10}H_8N_2O_3$: C, 58.82; H, 3.95; N, 13.72. Found: C, 58.80; H, 4.00; N, 13.69.

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