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Consecutive $S_{RN}1$ and $E_{RC}1$ Reactions in 5-Nitroisoquinolines

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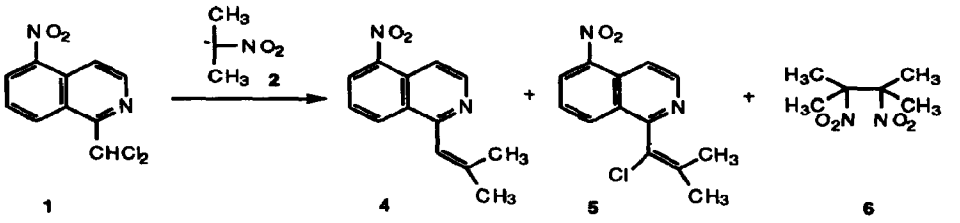
Abstract: *The reaction of 1-(dichloromethyl)-5-nitroisoquinoline with 2-nitropropane anion which gives 1-isopropylidenemethyl-5-nitroisoquinoline as major product is shown to proceed by the consecutive $S_{RN}1$ and $E_{RC}1$ mechanisms. These mechanisms are confirmed by the inhibitory effects of dioxygen, p-dinitrobenzene, cupric chloride and TEMPO.*

Since the discovery in 1966 that carbon alkylation of ambident anions by *p*-nitrobenzyl chloride is an electron-transfer chain process[1a,b] later termed $S_{RN}1$ reaction,[1c] the extensions of that reaction at sp^3 carbons attached to heterocyclic systems have been studied extensively.[2] However, if the reaction of geminal dihalides with nitronate anions in $S_{RN}1$ reaction is well documented in *p*-nitrobenzylic systems,[3] and has been shown to be followed of an $E_{RC}1$ reaction ($E_{RC}1$ standing for *elimination, radical chain, unimolecular*), no such studies have been carried out so far in heterocyclic series to determine the influence of the presence of two chlorine atoms on the same carbon in these reactions proceeding by electron transfer pathways.

As part of our continuing studies on the $S_{RN}1$ reactions of reductive heterocyclic alkylating agents,[4] the pharmacological interest of isoquinoline ring[5] led us to describe the first $S_{RN}1$ reactions in 5-nitroisoquinolines.[6] In connection with mechanistic studies including structure-reactivity-activity relationship deduction, we have explored the reactivity of 1-(dichloromethyl)-5-nitroisoquinoline **1** with nitronate anions.

The starting material **1** has been prepared in five steps from the inexpensive and commercially available 2-phenylethylamine by acetylation, Bischler-Napieralski reaction,[7] dehydrogenation,[8] nitration[9] and free radical chlorination[10] using an excess (4 eq) of N-chlorosuccinimide. The dichloride **1** reacts with 2-nitropropane anion **2** to give three products[11] as indicated in the Scheme 1. The results of the study of this reaction under different experimental conditions are reported in the Table.

Scheme 1



Table

Influence of experimental conditions in the reaction of **1** and **2**[a].

Entry	Mol. equiv. of **2**	Solvent	Scavenger (mol. equiv.)	Yield (%)[b]		
				4[c]	**5**	**1**
1	1	DMF	-	-	-	78
2	2	DMF	-	10	traces	48
3	3	DMF	-	23	traces	9
4	4	DMF	-	36	5	8
5	5	DMF	-	70	traces	-
6	6	DMF	-	72	traces	
7	5	DMF	$CuCl_2$ (1)	45	traces	-
8	5	DMF	dark	40	8	7
9	5	DMF	O_2 (bubbling)	8	-	20
10	5	DMF	dark, O_2 (bubbling)	5	-	27
11	5	DMF	TEMPO[d] (0.1)	8	-	11
12	5	DMF	TEMPO[d] (1)	-	-	-
13	5	DMF	p-$NO_2C_6H_4NO_2$[e] (1)	26	2	-
14	4	CH_2Cl_2/H_2O	-	32	16	8
15	5	CH_2Cl_2/H_2O	-	38	30	9

[a]All reactions were performed unless otherwise noted during 24h by using one equivalent of **1** under nitrogen and irradiation with two 60W fluorescent lamps. [b]All yields were referred to pure products chromatographically isolated and relative to the electrophile. [c]The ratio of the molar yield of the ethylenic derivative **4** to that of the dimer of 2-nitropropane **6** was found to be 1.03 ± 0.05. [d]2,2,6,6-tetramethyl-1-piperidinyloxy. [e]α,*p*-dinitrocumene was the major product.

The above results show that the monosubstituted chloro product **3** (Scheme 2) is not isolated under the reaction conditions and the formation of **4** can be rationalized in terms of an initial $S_{RN}1$ reaction to give **3**, which, by further reaction with 2-nitropropane anion, undergoes a radical chain elimination reaction ($E_{RC}1$) giving the ethylenic derivative **4** and 2,3-dimethyl-2,3-dinitropropane **6**, the radical anion $6^{\bullet-}$ being the chain carrier.[3] Contrarily to the case of *p*-nitrobenzylidene dichloride,[3] where the monosubstituted chloro compound is obtained in 40-50% yield, when the ratio of nitronate anion to dichloride is 2/1, the monosubstituted chloro derivative **3** has not been found even with a low excess of anion **2** (entries 2-4), where the starting dichloride **1** is in part recovered, showing that the reactivities are different in *p*-nitrobenzyl and nitroheterocyclic series.

If formed, the chloride **3** can react by competing $E_{RC}1$ and E_2 elimination reactions. If no E_2 resulting product **5** was formed, we might explain the only formation of **4** by a fast dissociation of the radical anion $3^{\bullet-}$ leading after reaction with 2-nitropropane anion to **4**. A such explanation was proposed by Bunnett in the $S_{RN}1$ reaction of dihalobenzenes with benzenethiolate ion[12] and by Norris in the case of the *p*-nitrobenzylidene dibromide with 2-nitropropane anion[3e] to rationalize the absence of monosubstituted halide derivatives.

Since **5** resulting of an E_2 reaction is observed in low yield in DMF and in higher yield under phase transfer conditions, where the anion **2** is a stronger base, the chloride **3** is necessarily formed in this reaction. These results indicate, that the loss of chloride atom from the radical anion $3^{\bullet-}$ is a relatively low step allowing building up of the intermediate **3**, presumably the greater stability of the nitroheterocyclic radical anion allows sufficient

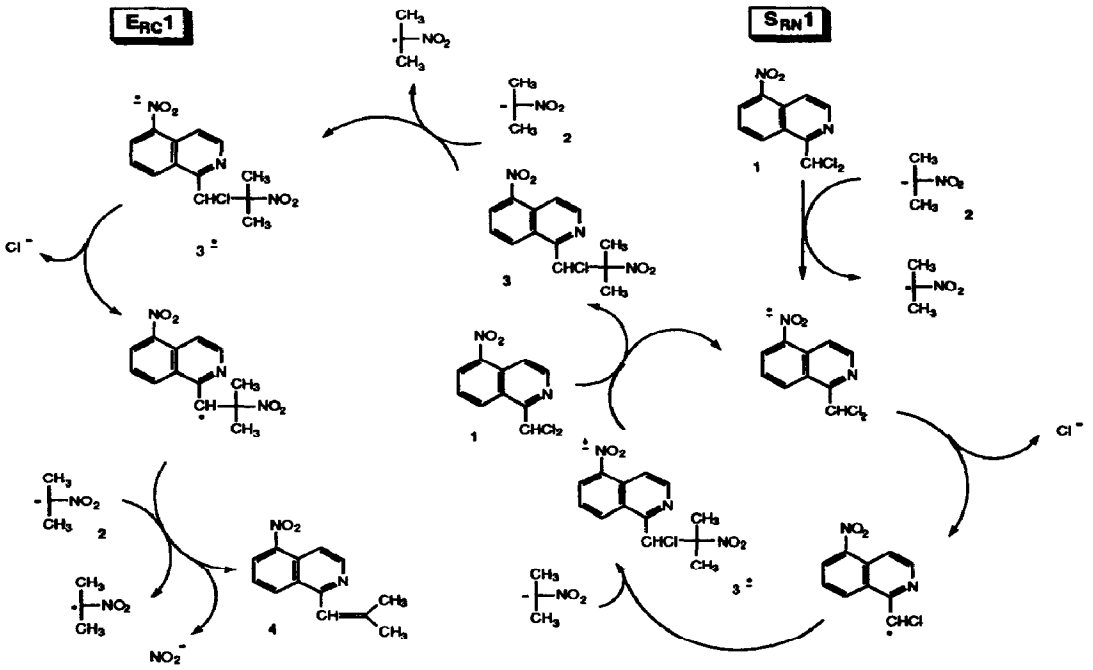
time for successful competition between electron transfer and loss of chloride atom, and that the chloride **3** reacts with 2-nitropropane anion **2** by $E_{RC}1$ and E_2 faster than **1** by $S_{RN}1$ seeing that **3** is not observed even when **1** is recovered.

Furthermore, the E_2 reaction leading to **5** is more efficient under phase transfer conditions[3d] than in DMF (entries 5 and 15) where the same ratio of substrate to anion are used and the yields of products are similar and therefore these experimental conditions could be useful for the preparation of the ethylenic chloride **5**.

The inhibition experiments[13] used classically to demonstrate the operation of an $S_{RN}1$ mechanism may be also valuable for the $E_{RC}1$ one.[3] When bubbling dioxygen (entry 9) or by addition of a stoichiometric quantity of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) (entry 12), the inhibition of the reactions is very strong. The addition of cupric chloride or *p*-dinitrobenzene and the use of dark inhibit significantly the formation of **4**.

All these experimental data provide good evidence for assigning the consecutive $S_{RN}1$ and $E_{RC}1$ mechanisms to the reaction of 1-(dichloromethyl)-5-nitroisoquinoline **1** and 2-nitropropane anion **2**. These mechanisms are illustrated by the following electron transfer pathways (Scheme 2).

Scheme 2



In conclusion, these results show that a geminal dichloride attached to a nitroheterocycle such as 1-(dichloromethyl)-5-nitroisoquinoline **1** reacts with the 2-nitropropane anion **2** to give with good yield 1-isopropylidenemethyl-5-nitroisoquinoline **4** by the consecutive $S_{RN}1$ and $E_{RC}1$ reactions. It is the first example of these two consecutive reactions involving a reductive heterocyclic alkylating agent and an other way for the preparation of 5-nitroisoquinolines bearing a trisubstituted double bond at 2-position. The extension of these reactions to other heterocyclic systems is in progress.

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11 All derivatives have been isolated as pure products and fully characterized: **1**, yellow solid, mp 99 °C (isopropanol), ^{1}H NMR ($CDCl_3$) δ 7.26 (s, 1H); 7.83 (dd, J =8.0 and 8.5 Hz, 1H); 8.50 (d, J = 6.2 Hz, 1H); 8.53 (d, J = 8.0 Hz, 1H); 8.65 (d, J = 6.2 Hz, 1H); 9.12 (d, J = 8.5 Hz, 1H). **4**, yellow solid, mp 79°C (hexane), ^{1}H NMR ($CDCl_3$) 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). **5**, yellow solid, mp 80°C (isopropanol), ^{1}H NMR ($CDCl_3$) δ 1.57 (s, 3H); 2.15 (s, 3H); 7.72 (dd, J = 8.0 and 8.1 Hz, 1H); 8.43 (d, J = 6.2 Hz, 1H); 8.44 (d, J = 8.0 Hz, 1H); 8.52 (d, J = 8.1Hz, 1H); 8.76 (d, J = 6.2 Hz, 1H).

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