AN ELECTRON TRANSFER REACTION IN THE IMIDAZO[2,1-*b*]THIAZOLE SERIES§

Patrice Vanelle *, Nacer Madadi , and José Maldonado

Laboratoire de Chimie Organique, Université d'Aix-Marseille 2, Faculté de Pharmacie,

27 Bd J. Moulin, 13385 Marseille Cedex 04, France

Luc Giraud, Jean-François Sabuco, and Michel P. Crozet *

"Radicaux Libres et Synthèse", CNRS URA N° 1412, Université d'Aix-Marseille 3,

Faculté des Sciences et Techniques de Saint-Jérôme, BP 562, 13397 Marseille Cedex 13, France

Abstract ---- The C-alkylation reaction of 5-nitro-6-chloromethylimidazo[2,1-*b*]thiazole by the 2-nitropropane anion is shown to proceed by the $S_{RN}1$ mechanism. This mechanism is confirmed by the inhibitory effects of dioxygen, *p*-dinitrobenzene, cupric chloride and TEMPO.

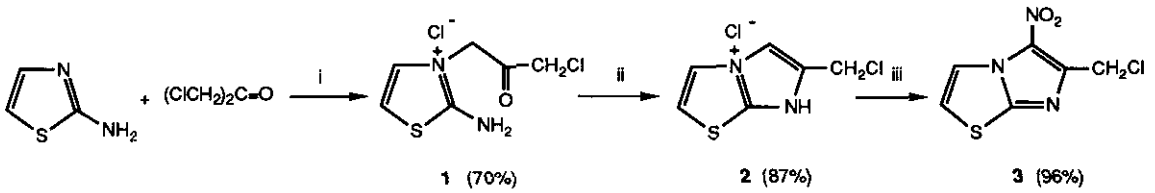
Due to our interest in medicinal chemistry and our ongoing research into the area of $S_{RN}1$ reactions in nitroheterocycles,[1] we investigated the potential of the imidazo[2,1-*b*]thiazole ring as a supporting group for a number of selected pharmacophores. Indeed, this heterocycle is present in partially reduced form in levamisole.[2,3] This very interesting drug, a well-known anthelmintic[2] against intestinal nematode worms, affects also the immune response[3] and restores depressed T-cell functions. Recently, new imidazo[2,1-*b*]thiazoles have been shown to stimulate the proliferation of thymic lymphocytes and were found more active than levamisole.[4]

As a part of this study , we have prepared 5-nitro-6-chloromethylimidazo[2,1-*b*]thiazole (**3**) and studied its reactivity with the 2-nitropropane anion in order to determine the influence of the fused thiazole ring and to design new potentially active derivatives.

Reaction of 2-aminothiazole with dichloroacetone gave derivative (**1**), which was cyclised to imidazolium salt (**2**)[5] by refluxing in acetonitrile. Nitration of **2** with H_2SO_4-HNO_3[6] followed by basification led to (**3**).[7]

§This paper is respectfully dedicated to Professor Jacques Metzger, a pioneer of thiazole chemistry, on the occasion of his appointment as Professeur Emérite.

Scheme 1



i : acetone, 20°C, 24 h; ii : CH_3CN, reflux, 2 h; iii : 1) H_2SO_4-HNO_3; 2) $NaHCO_3$

The imidazothiazole derivative (**3**) was treated with 2-nitropropane salt (**4**) under conditions conducive to $S_{RN}1$ reactions (nitrogen, light catalysis) to yield the ethylenic compound (**6**)[8] as shown in Scheme 2. Table I reports the yield of (**6**) under a variety of experimental conditions. Variables included the molar equivalents of **4**, the solvent, and the presence or absence of an inhibitor.

Scheme 2

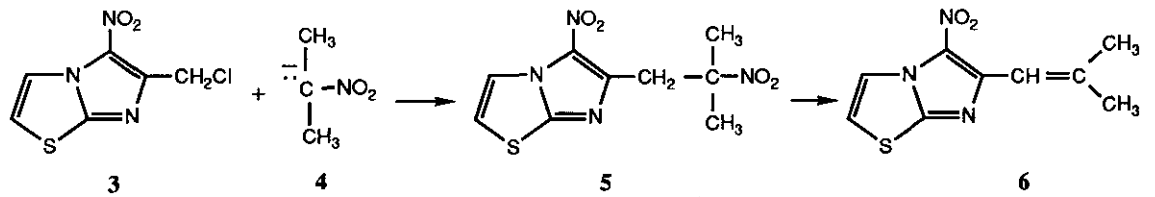


Table I

Influence of experimental conditions in the reaction of **3** with **4**

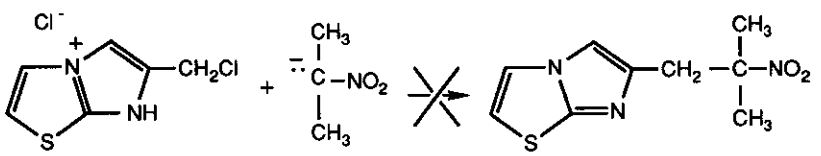
Entry[a]	Mol. equiv. of **4**	Solvent	Scavenger (Mol. equiv.)	**6** Yield[b]
1	1	CH_2Cl_2/H_2O	-	33
2	2	CH_2Cl_2/H_2O	-	77
3	3	CH_2Cl_2/H_2O	-	99
4	3	CH_2Cl_2/H_2O	dark, O_2 (bubbling)	66
5	3	CH_2Cl_2/H_2O	*p*-$NO_2C_6H_4NO_2$ (0.1)	26
6	3	CH_2Cl_2/H_2O	*p*-$NO_2C_6H_4NO_2$ (1)	10
7	3	CH_2Cl_2/H_2O	TEMPO (0.1)	16
8	2	DMF	-	97
9	2	DMF	$CuCl_2$ (6×10^{-4})	22
10	2	DMF	$CuCl_2$ (1.2×10^{-2})	14

[a]All reactions were irradiated at room temperature during 24 h under nitrogen with fluorescent lamps (2 x 60W). One equivalent of imidazothiazole (**3**) was used. [b]% yield relative to the electrophile.

The C-alkylation product (**5**) is not isolated in any of the reactions. Because of the acidity of the protons of the methylene group, nitrous acid elimination is very rapid in basic medium. This leads in an excellent yield to the ethylenic compound, 5-nitro-6-isopropylidenemethylimidazo[2,1-*b*]thiazole (**6**), as observed in 5-nitroimidazole system[9] and 3-nitroimidazo[1,2-*a*]pyridine series.[10] The competitive O-alkylation, which would give the aldehyde derivative, is not observed. The best C-alkylation yield is obtained when DMF is used as solvent under the conditions described by Kornblum[11] (entry 8). Using a phase transfer technique[12] with 40% tetrabutylammonium hydroxide in water and dichloromethane, 3 equivalents of nitronate anion are necessary for a similar yield (entry 3). When one equivalent of anion is used, the yield of derivative (**6**) is only 33%, showing that the base-promoted nitrous acid elimination involves the 2-nitropropane anion as a base (entry 1).

To demonstrate the operation of an $S_{RN}1$ mechanism, we have used classical inhibition experiments[13] such as reaction in the dark, electron trapping and radical scavengers. When bubbling dioxygen in the dark, the formation of **6** decreases (entry 4). Strong green colours, which faded on completion, were observed in all the reactions. This could be caused by charge-transfer complexes between the nitroimidazothiazole chloride and the anion prior to light-catalysed single electron transfer.[14] The addition of cupric chloride, *p*-dinitrobenzene or 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) in catalytic quantities strongly inhibited the chain reaction (entries 5, 7, 9 and 10). The use of stoichiometric quantities of these inhibitors increased this effect (entry 6) and α,*p*-dinitrocumene became the predominant product (58% yield). The importance of nitro group is demonstrated by the reaction of (**2**) with the 2-nitropropane salt (**4**) under the experimental conditions of entries 2 and 8, where neither the C-alkylation nor the O-alkylation derivatives have been extracted from the reaction mixture, indicating that the imidazo[1,2-*b*]thiazole moiety alone is not an electron-withdrawing strong enough for an $S_{RN}1$ reaction in the case of a primary chloride (Scheme 3).

Scheme 3

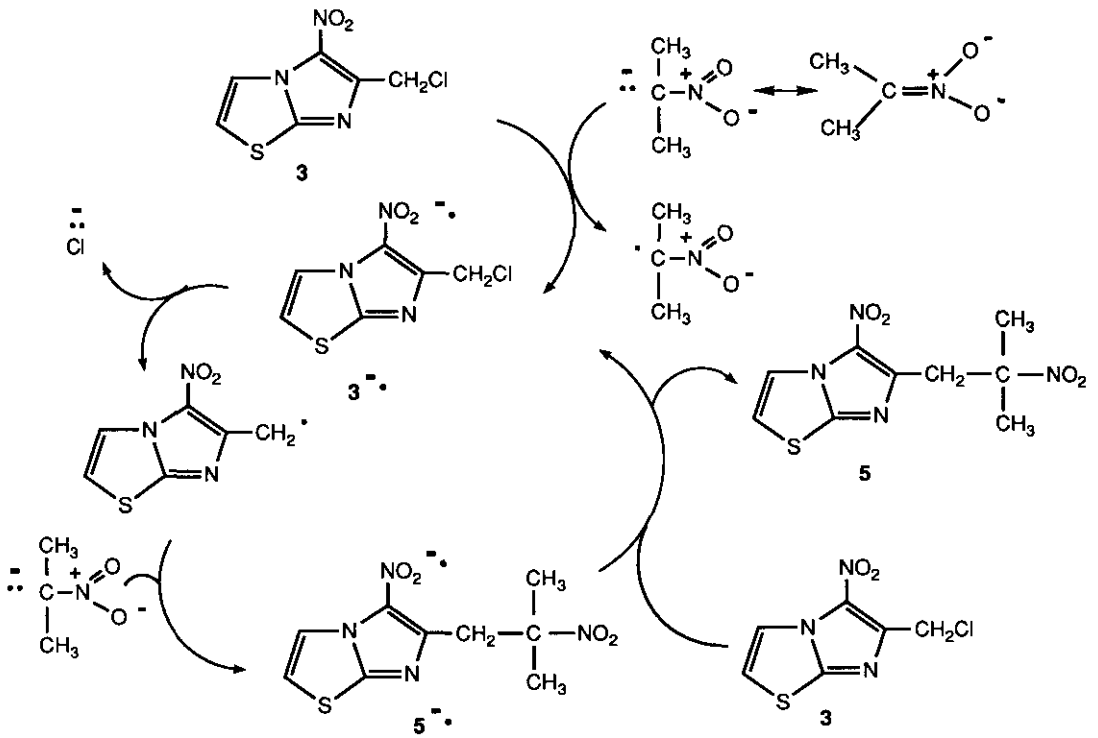


2 **4**

All these experimental data provide good evidence for assigning the $S_{RN}1$ mechanism to the reaction of 5-nitro-6-chloromethylimidazo[2,1-*b*]thiazole (**3**) and 2-nitropropane anion (**4**). This mechanism is illustrated by the

following classical chain Scheme (Scheme 4).

Scheme 4



In conclusion, this study shows that $S_{RN}1$ reaction of 2-nitropropane anion succeeds with 5-nitro-6-chloromethylimidazo[2,1-*b*]thiazole and opens a new way for the exploration of the chemical and biological properties of new 5-nitroimidazo[2,1-*b*]thiazoles with trisubstituted double bonds at 6-position. As derivative (**6**) shows interesting pharmacological properties,[15] extension to more complex aliphatic, cyclic and heterocyclic nitronate anions readily available, which may constitute a powerful synthetic tool, are under investigation.

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5. (**2**), White solid, mp 197° C (ethanol); ^{1}H nmr (DMSO-d_6) δ 4.94 (s, 2H); 7.01 (br. s, 1H); 7.56 (d, J = 4 Hz, 1H); 8.13 (s, 1H); 8.14 (d, J = 4 Hz, 1H).

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7. **3** , Yellow solid, mp 137 °C (methanol); ^{1}H nmr ($CDCl_3$) δ 5.03 (s, 2H); 7.24 (d, J = 4.5 Hz, 1H); 8.30 (d, J = 4.5 Hz, 1H).

8. **6** , Yellow solid, mp 120° C (methanol), ^{1}H nmr ($CDCl_3$) δ 2.07 (s, 3H); 2.30 (s, 3H); 6.98 (t, J = 1.2 Hz, 1H); 7.10 (d, J = 4.5 Hz, 1H); 8.28 (d, J = 4.5 Hz, 1H).

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15. These unpublished results and a portion of this work were presented at the XXVIIth Rencontres Internationales de Chimie Thérapeutique, 2-5 July, 1991, Caen, France.

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