REACTIVITY OF HETEROCYCLIC AMBIDENT S···N ANIONS IN $S_{RN}1$ SUBSTITUTION REACTIONS

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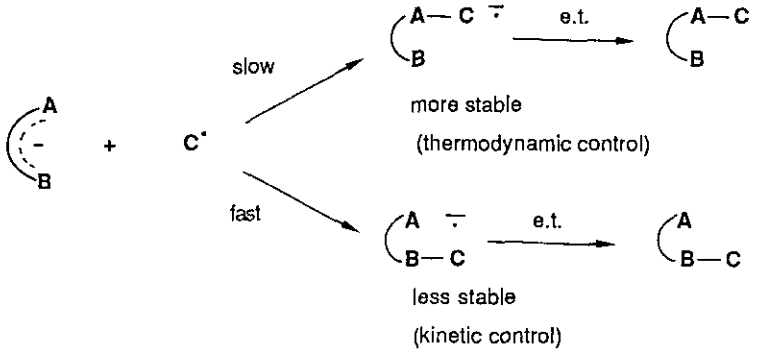
Abstract. - Ambident anions of 2-mercaptoazoles react , under photo- stimulation conditions, with α,p-dinitrocumene according to an $S_{RN}1$ mechanism (short chain) leading to S-alkylated compounds in agreement with a kinetically controlled reaction. Regioselectivity is governed by nucleophilicity and not by the basicity of the heteroatom. The N-alkylation observed in the case of 2-mercaptoimidazole proceeds from a new photochemical rearrangement with homolytic cleavage of the C-S bond followed by the recombination of theα,p-dinitrocumyl radical with the *ambident heterocyclic radicals.*

The mechanism termed $S_{RN}1$ belongs to a general class of nucleophilic chain substitutions initiated either by electron transfer or homolytic bond cleavage. Nucleophilic substitutions at a saturated carbon center have been studied by Kornblum and Russell. [1] The interesting possibilities of these kinds of reactions were largely studied [2] with particular reference to heterocyclic reactivity[3a] and heterocyclic synthesis[3b]. The $S_{RN}1$ mechanism, which has been applied in organic chemistry, has its counterparts in inorganic[4a] and organometallic[4b,c] reactions. Radicals and radical anions are involved as intermediates (Scheme 1).

$$RX + Nu^- \longrightarrow RX^{\cdot -} + Nu^{\cdot} \quad (a)$$
$$RX^{\cdot -} \longrightarrow R^{\cdot} + X^- \quad (b)$$
$$R^{\cdot} + Nu^- \longrightarrow RNu^{\cdot -} \quad (c)$$
$$RNu^{\cdot -} + RX \longrightarrow RX^{\cdot -} + RNu \quad (d)$$

Scheme 1: $S_{RN}1$ mechanism for a nucleophilic substitution

When the systems studied contain an ambident anion as the nucleophile, the substitution yields only one product. Kornblum[5] rationalized this result by proposing that step (c) (i.e.,addition of the nucleophile to the radical) is thermodynamically controlled and leads to the more stable radical anion $RNu^{\cdot -}$.

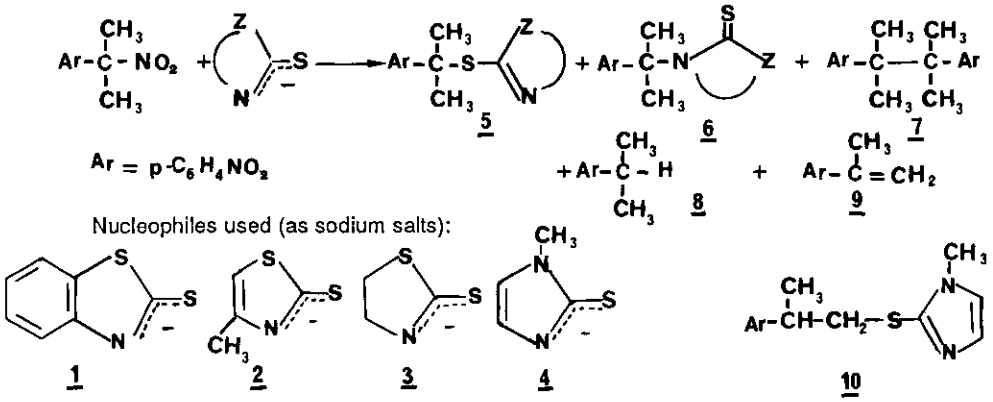


Scheme 2: Addition of an anion to a radical: two possible reaction pathways.

On the other hand ,Tolbert[6], Russell[7]and Norris[8] have suggested kinetic control for this reaction. Tolbert[6], in the case of ambident anions containing two carbon centers , has shown that regioselectivity is certainly governed by the basicity of the site: the more basic site being the most reactive. In ambident heteroaromatic S--N anions, the N-anion is more basic than the S-anion, but the S-anion is more nucleophilic toward carbon than is the N-anion[9]. Bowman[10] showed that in reactions of these kinds of ambident anions with the 2-nitropropyl radical, only S-alkylation products are obtained. Our study of the reactivity of heterocyclic S--N anions toward the p-nitrocumyl radical confirms nucleophilic control of the regioselectivity in this case. This result is further put in perspective by previous studies in our group which showed through catalyzed[15] equilibration experiments that N-substituted compounds are more thermodynamically stable than the corresponding S-substituted compounds (noting,[11] however that steric interactions in N-substituted compounds obtained from **1** and **2** could diminish this thermodynamic stability). The isomeric (N versus S) radical anions formed by the reaction between the α,p-nitrocumyl radical and the heterocyclic ambident nucleophile very probably display the same order of thermodynamic stability (i.e.,the N radical anion is more stable than S radical anion) because the LUMO is mainly localised on the cumyl part of substrates **5** or **6**. Therefore , the results which follow, show that in the systems studied here the products associated with the least stable radical anion are preferentially formed.

We studied the reactivity of 2-mercaptoazole anions (**1** to **4**) with regard to α,p-dinitrocumene , which is known to give $S_{RN}1$-type substitutions[1b](Scheme 3). The reaction is slow at room temperature and becomes faster under irradiation. The influence of UV light and the effect of inhibitors implicate a radical-chain mechanism. The necessity of continuous irradiation seems to show that the reaction proceeds via a short chain.

The data (Table 1) can be compared to the results obtained with the same anion during reactions with diazomethane,[11] or with alkyl halides under phase transfer catalysis conditions[12] . The reactivity scale for $S_{RN}1$ (Table 2) is identical with that for S_N2 reactions, and in accordance with structural effects. This scale is in agreement with both the basicity of the heterocycles[13] (however, note that the pKa is relative to N-protonation) and to their nucleophilicity (evaluated by the reaction of the corresponding N-alkylthiones vs iodomethane)[14].



Scheme 3: Reaction of 2-mercaptoazole anions with α,p-dinitrocumene.

nucleophile	alkylation 5	6	dimerization 7	reduction 8	elimination 9	S-alkylation/N-alkylation in S_N2 reactions[b] (%) ref.11	ref.12
1	36	–	18	20	26	90	100
2	86	–	–	traces	13	80	100
3	92	–	3	5	–	80	100
4	47	10	1	–	23 + 19[a]	70	100

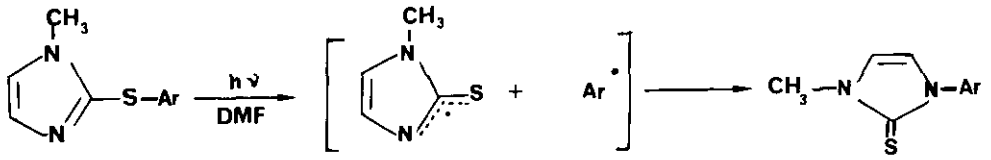
Table 1: Reaction of nucleophiles 1 to 4 with α,p-dinitrocumene in % based on transformed electrophiles (by ^1H NMR): DMF as solvent, hν, 6 hours (see experimental part). a) Yield of compound 10. b) Reaction of the nucleophiles studied with diazomethane [11] or alkyl halides under phase transfer conditions [12].

nucleophile	1	2	3	4
tranformed electrophile (ratio %)	50	77	91	88
K_A(conjugated acid,l.mol.$^{-1}$)[13]	2000	1100	200	300

Table 2: Reactivity of nucleophiles 1 to 4 with respect to α,p-dinitrocumene (DMF, hν, 6 hours, see experimental part).

Concerning the by-products of the reaction : i) dimerization (7) and reduction (8) products are at a maximum for the less reactive nucleophiles, suggesting that the reaction between the nucleophile and the p-nitrocumyl radical is in this case slower than the dimerization and reduction reactions of this radical; ii) the elimination product (9) resulting from the abstraction of a proton of the methyl substituent is at a maximum for the most reactive anion (1-methyl 2-mercaptoimidazole, 4). In this case, the heterocyclic radical arising from the initiation step (reaction (a), Scheme1) can add to the ethylenic compound to give **10**.

The alkylation products result from preferential attack by the S-centered anion. In accordance with previous results[10], the regioselectivity is governed here by nucleophilicity and not by basicity. The N-alkylation product is observable only in the case where 4 is the nucleophile, but we have shown that it is not the result of an $S_{RN}1$ reaction, but rather arises from a secondary reaction. Indeed, in this case, when a DMF solution of the S-alkylated compound is exposed to light, product 5 disappears, and the N-alkylated product is observed. After irradiation for 3 h, the transformation is almost complete. This result is explained through the homolytic cleavage of the C-S bond and subsequent recombination of the p-nitrocumyl and imidazolyl radicals, leading to the most stable product. This reaction scheme has been established by adding a radical trap (galvinoxyle) to the medium. An inhibition of the transformation C-S to C-N is observed in this case, also demonstrating that this radical rearrangement is an out-of-cage process. These results would confirm the previously suggested hypothesis[15], not previously verified [16], concerning the existence of a radical mechanism for some S-R → N-R rearrangements in heterocycles. For the other S-alkylated heterocycles,



we did not observe this kind of behaviour. When the other heterocycles are irradiated in the same fashion, C-S cleavage is observed but C-N bond formation is not. (Or that the C-N bond is formed and rebroken : only reduction and dimerization products have been identified). Therefore, in $S_{RN}1$ reactions involving the α,p-dinitrocumene and 2-mercaptoazole anions, only S-alkylation is observed, demonstrating that the regioselectivity of these reactions is under kinetic control *via* the more nucleophilic center. We are presently performing further experiments to gain deeper insights into the factors which govern radical C-S to C-N rearrangements under irradiation , such as was observed here for the imidazolyl heterocycle.

EXPERIMENTAL

1. Preparation of reagents

•*α,p-dinitrocumene:* Obtained from α-bromo-p-nitrocumene (itself prepared by reaction of p-nitrocumene with N-bromosuccinimid) and sodium nitrite in DMF at 25°C for 48 hours, following Kornblum's method[17]. The α,p-dinitrocumene is recrystallized twice from methanol (mp 63-64°C).

•*Nucleophiles* (1 to 4) : 0,01 mole of 2- mercaptoazole is dissolved in 50 ml of methanol. A stoichiometric quantity of sodium is added. The solvent is evaporated under reduced pressure and the resulting salt is washed with chloroform , then benzene , and dried under vacuum . Commercially available 2-mercaptobenzothiazole (containing some disulfide as an impurity) is purified by dissolution in aqueous ammonia solution followed by filtration, acidification of filtrate and extraction with chloroform.

•*Dimethylformamide*: dried by azeotropic distillation with 10% benzene followed by treatment with alumina and distillation under reduced pressure, and stored under N_2 over molecular sieves.

2. Lamp for light irradiation: 400W, Hg vapor, medium pressure.

3. General procedure

α,p-dinitrocumene (525 mg, 0.0025 moles) is dissolved in 5ml of degassed and dried DMF. 0.0065 moles of the sodium salt of the 2-mercaptoazole is added. The apparatus allowed to stand under an N_2 atmosphere and irradiated for 6h at 20°C. Following this , the DMF is evaporated under reduced pressure; 10 ml of water are added and the mixture is extracted twice with chloroform. The solution is dried over magnesium sulfate and concentrated. The reaction mixture is analyzed by ^1H NMR. The separation of the reaction products in each case is described below. ^1H NMR and ^{13}C NMR spectra were performed in $CDCl_3$ as solvent. The chemical shifts are in ppm vs TMS.

•*Reaction with* 1 . The reaction mixture is purified by silica gel chromatography (eluent benzene followed by chloroform) followed by recrystallization from ethanol-ethyl ether mixture. Compound 5 is obtained : mp 154°C. Anal. Calcd for $C_{16}H_{14}N_2O_2S_2$: C:58.16; H:4.27; N:8.48; S:19.41. found : C58.20; H;4.32; N:8.51; S:19.38. ^1H NMR: 1.96 (s,6H);7.00-8.40 (m, 8H). ^{13}C NMR: 30.2 (CH_3); 54.1 (C); 121.0 (CH); 122.7 (CH); 123.5 (CH); 125.2 (CH); 126.2 (CH); 127.8 (CH); 141.4 (C); 152.8 (C); 175.4 (C).

•*Reaction with* 2 . Recrystallization of the crude product from ethanol gives compound 5 , mp 95°C. Anal. Calcd for $C_{13}H_{14}N_2O_2S_2$: C: 53.04; H: 4.79; N: 9.52; S: 21.78. found: C: 53.06; H: 4.88; N: 9.42; S:21.80. ^1H NMR : 1.90 (s,6H); 2.40 (s,3H); 6.87 (s,1H); 7.62 (d,2H); 8.13 (d,2H). ^{13}C NMR : 17.1 (CH_3); 29.8 (CH_3); 53.5 (C); 123.3 (CH); 127.7 (CH); 146.9 (C); 152.9 (C); 154.4 (C); 157.7 (C).

•*Reaction with* 3 . The reaction mixture is purified by silica gel chromatography (eluent $CHCl_3$). Compound 5 is obtained as a non crystallizable oil. ^1H NMR: 1.92 (s,6H); 3.13 (t, 2H); 3.98 (t,2H); 7.7O (d,2H); 8.10 (d,2H) . ^{13}C NMR : 29.9 (CH_3) ; 34.5 (CH_2) ; 53.1 (C) ; 64.8 (CH_2) ; 123.1 (CH) ; 127.7 (CH) ; 146.5 (C) ; 153.4 (C) ; 162.2 (C).

•*Reaction with* 4 . The reaction mixture is purified by silica gel chromatography (eluent $CHCl_3$) . Two fractions are obtained: -The first fraction contains the N-alkylated product 6 and the addition product 10 . The pure N-alkylation product is obtained by recrystallization of the mixture from ethanol. mp: 223°C. Anal. Calcd for $C_{13}H_{15}N_3O_2S$: C :56.29; H :5.45; N : 15.15; S : 11.56. found : C :56.26; H :5.49 ; N : 15.19; S :11.50. ^1H NMR : 2.06 (s,6H) ; 3.53 (s,3H) ; 6.70 (d,1H) ; 7.00 (d, 1H) ; 7.21 (d,2H) ; 8.07 (d,2H). ^{13}C NMR: 29.0 (CH_3); 35.0 (CH_3) ; 62.5 (C) ; 114.1 (CH) ; 117.6 (CH); 123.7 (CH); 126.3 (CH); 150.9 (C). 152.4 (C).The other constituent of the first fraction has been identified by NMR as compound 10 . ^1H NMR : 1.35

(d,3H); 3.57 (s,3H); 3.60 (2H) ; 4.16 (m,1H) ; 6.25 (d,1H); 6.50 (d, 1H); 7.40 (d,2H) ;8.10 (d,2H) . ^{13}C NMR: 18.3 (CH_3); 29.3 (CH_3) ;38.5 (CH); 54.7 (CH_2) ;123.7 (CH); 123.9 (CH); 126.3 (CH); 128.4 (CH). Quaternary carbons were not identified . -The second fraction contains the S-alkylated product **5** and an unknown product in small quantity (~5%). In this case **5** cannot be obtained as pure compound, but was identified solely by NMR spectroscopy. ^1H NMR : 1.90 (s,6H); 3.20 (s,3H); 6.95 (d,1H); 7.17 (d,1H); 7.45 (d, 2H); 8.10 (d, 2H). ^{13}C NMR: 29.3 (CH_3); 30.2 (CH_3); 53.1 (C); 123.3 (CH); 123.6 (CH); 126.8 (CH); 130.3 (CH); 153.5 (C) ; the other quaternary carbons were non identified.

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Received, 11th November, 1985