

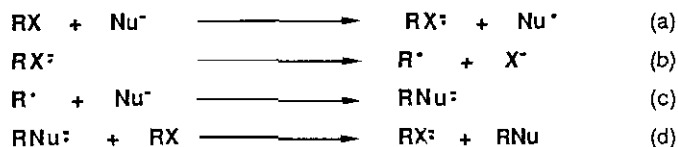
## REACTIVITY OF HETEROCYCLIC AMBIDENT S $\cdots$ N ANIONS IN S<sub>RN</sub>1 SUBSTITUTION REACTIONS

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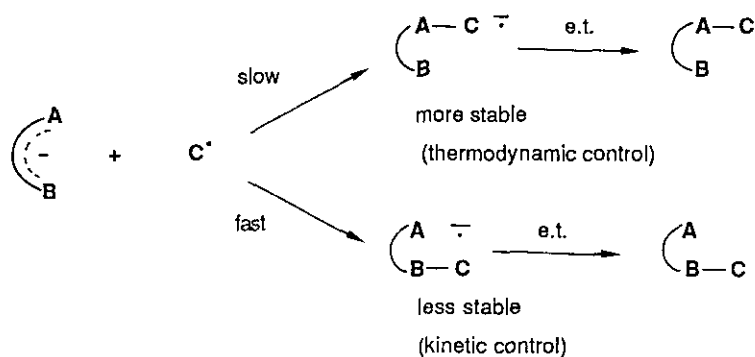
**Abstract.** - Ambident anions of 2-mercaptoazoles react, under photo-stimulation conditions, with  $\alpha$ ,p-dinitrocumene according to an S<sub>RN</sub>1 mechanism (short chain) leading to S-alkylated compounds in agreement with a kinetically controlled reaction. Regioselectivity is governed by 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 the  $\alpha$ ,p-dinitrocumyl radical with the ambident heterocyclic radicals.

The mechanism termed S<sub>RN</sub>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.<sup>1</sup> The interesting possibilities of these kinds of reactions were largely studied<sup>2</sup> with particular reference to heterocyclic reactivity<sup>3a</sup> and heterocyclic synthesis<sup>3b</sup>. The S<sub>RN</sub>1 mechanism, which has been applied in organic chemistry, has its counterparts in inorganic<sup>4a</sup> and organometallic<sup>4b,c</sup> reactions. Radicals and radical anions are involved as intermediates (Scheme 1).



*Scheme 1: S<sub>RN</sub>1 mechanism for a nucleophilic substitution*

When the systems studied contain an ambident anion as the nucleophile, the substitution yields only one product. Kornblum<sup>5</sup> 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 $\cdot$ .

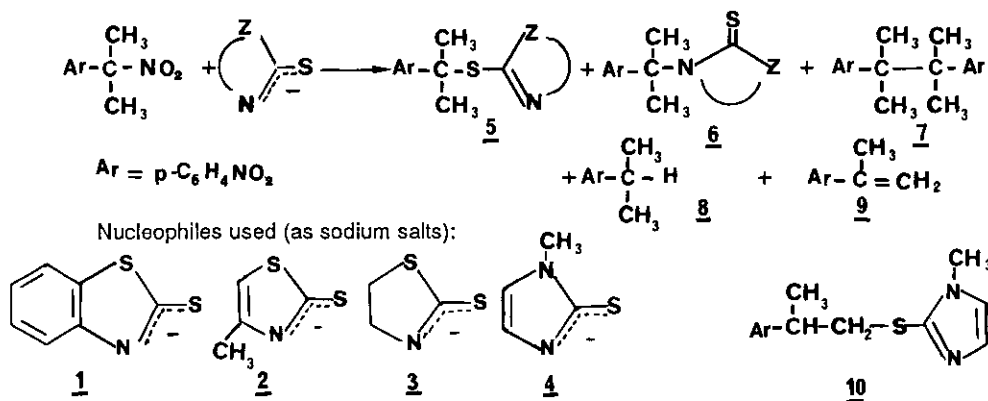


*Scheme 2: Addition of an anion to a radical: two possible reaction pathways.*

On the other hand, Tolbert<sup>6</sup>, Russell<sup>7</sup> and Norris<sup>8</sup> have suggested kinetic control for this reaction. Tolbert<sup>6</sup>, 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<sup>9</sup>. Bowman<sup>10</sup> 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<sup>15</sup> equilibration experiments that N-substituted compounds are more thermodynamically stable than the corresponding S-substituted compounds (noting,<sup>11</sup> 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  $\alpha$ ,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  $\alpha$ ,p-dinitrocumene, which is known to give S<sub>RN</sub>1-type substitutions<sup>1b</sup> (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,<sup>11</sup> or with alkyl halides under phase transfer catalysis conditions<sup>12</sup>. The reactivity scale for S<sub>RN</sub>1 (Table 2) is identical with that for S<sub>N</sub>2 reactions, and in accordance with structural effects. This scale is in agreement with both the basicity of the heterocycles<sup>13</sup> (however, note that the pK<sub>a</sub> is relative to N-protonation) and to their nucleophilicity (evaluated by the reaction of the corresponding N-alkylthiones vs iodomethane)<sup>14</sup>.



*Scheme 3: Reaction of 2-mercaptoazole anions with  $\alpha$ ,*p*-dinitrocumene.*

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

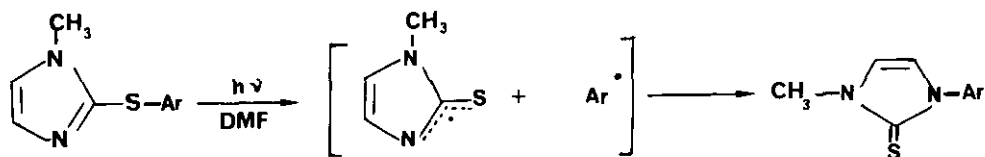
*Table 1: Reaction of nucleophiles 1 to 4 with  $\alpha$ ,*p*-dinitrocumene in % based on transformed electrophiles (by <sup>1</sup>H NMR): DMF as solvent, h $\nu$ , 6 hours (see experimental part). a) Yield of compound 10. b) Reaction of the nucleophiles studied with diazomethane<sup>11</sup> or alkyl halides under phase transfer conditions<sup>12</sup>.*

nucleophile	<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>
transformed electrophile (ratio %)	50	77	91	88
K <sub>A</sub> (conjugated acid, l.mol. <sup>-1</sup> ) <sup>13</sup>	2000	1100	200	300

*Table 2: Reactivity of nucleophiles 1 to 4 with respect to  $\alpha$ ,*p*-dinitrocumene (DMF, h $\nu$ , 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), Scheme 1) 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<sup>10</sup>, 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<sub>RN</sub>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<sup>15</sup>, not previously verified<sup>16</sup>, 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<sub>RN</sub>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-bromosuccinimide) and sodium nitrite in DMF at 25°C for 48 hours, following Kornblum's method<sup>17</sup>. 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<sub>2</sub> over molecular sieves.

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

### 3. General procedure

$\alpha$ , $\beta$ -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<sub>2</sub> 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 <sup>1</sup>H NMR. The separation of the reaction products in each case is described below. <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were performed in CDCl<sub>3</sub> 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<sub>16</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub>S<sub>2</sub> : C:58.16; H:4.27; N:8.48; S:19.41. found : C:58.20; H:4.32; N:8.51; S:19.38. <sup>1</sup>H NMR: 1.96 (s,6H);7.00-8.40 (m, 8H). <sup>13</sup>C NMR: 30.2 (CH<sub>3</sub>); 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<sub>13</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub>S<sub>2</sub> : 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. <sup>1</sup>H NMR : 1.90 (s,6H); 2.40 (s,3H); 6.87 (s,1H); 7.62 (d,2H); 8.13 (d,2H). <sup>13</sup>C NMR : 17.1 (CH<sub>3</sub>); 29.8 (CH<sub>3</sub>); 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<sub>3</sub>). Compound 5 is obtained as a non crystallizable oil. <sup>1</sup>H NMR: 1.92 (s,6H); 3.13 (t, 2H); 3.98 (t,2H); 7.70 (d,2H); 8.10 (d,2H) . <sup>13</sup>C NMR : 29.9 (CH<sub>3</sub>) ; 34.5 (CH<sub>2</sub>) ; 53.1 (C) ; 64.8 (CH<sub>2</sub>) ; 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<sub>3</sub>) . 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<sub>13</sub>H<sub>15</sub>N<sub>3</sub>O<sub>2</sub>S : 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. <sup>1</sup>H 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). <sup>13</sup>C NMR: 29.0 (CH<sub>3</sub>); 35.0 (CH<sub>3</sub>) ; 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 . <sup>1</sup>H 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).  $^{13}\text{C}$  NMR: 18.3 (CH<sub>3</sub>); 29.3 (CH<sub>3</sub>); 38.5 (CH); 54.7 (CH<sub>2</sub>); 123.7 (CH); 123.9 (CH); 126.3 (CH); 128.4 (CH). Quaternary carbons were not identified. -The second fraction contains the  $\underline{S}$ -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.  $^1\text{H}$  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).  $^{13}\text{C}$  NMR: 29.3 (CH<sub>3</sub>); 30.2 (CH<sub>3</sub>); 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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