

**LIGHT-CATALYZED BROMINATION OF 3,4-DIMETHYL-1,2,5-THIADIAZOLE WITH N-BROMOSUCCINIMIDE**

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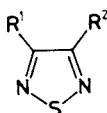
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<sup>1</sup>H NMR study of light-catalyzed bromination of 3,4-dimethyl-1,2,5-thiadiazole with N-bromosuccinimide has been carried out in order to reach conclusions on synthetic possibilities and relative reactivities of several products formed.

The 1,2,5-thiadiazole nucleus is found in several biologically interesting compounds and has been the subject of many studies<sup>1,2</sup> on its chemistry. Its stability towards electrophilic substitution has been shown<sup>3,4</sup> even though a few examples of nuclear halogenation appeared in the literature<sup>5,6</sup>. Recently, Tashiro et al.<sup>7</sup> studied the thermal reaction of alkyl and aryl derivatives of 1,2,5-thiadiazole with N-bromosuccinimide (NBS).

In order to gain further understanding on the structure, reactivity and synthetic possibilities of these compounds, we have undertaken a kinetic and product research work on the light-catalyzed bromination of 3,4-dimethyl-1,2,5-thiadiazole (*I*). Experimental guidelines, results and conclusions that can be drawn from them are given below.



*I*, R<sup>1</sup> = R<sup>2</sup> = CH<sub>3</sub>

**EXPERIMENTAL**

N-Bromosuccinimide (NBS) was recrystallized to constant m.p. from glacial acetic acid prior to use. Benzoyl peroxide was purified by dissolution in CHCl<sub>3</sub> and reprecipitation with MeOH, until a constant m.p. (d) was obtained. High quality CCl<sub>4</sub> was fractionally distilled prior to use.

Compound *I* was prepared and purified according to a published procedure<sup>8</sup>.

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The reaction was started by adding a mixture of purified NBS (13.6 mmol) and benzoyl peroxide (0.2 mmol) to a solution of *I* (1.75 mmol) in  $\text{CCl}_4$  (2 ml). The reaction tube immersed in a constant temperature bath ( $20 \pm 0.2^\circ\text{C}$ ) was illuminated with a visible lamp (100 W, 220V); magnetic stirring was employed with the heterogeneous mixture thus obtained. At different times the illumination was stopped, a sample (approx. 0.5 ml) was taken off, filtered to separate the solid residues (NBS and succinimide) and its  $^1\text{H}$  NMR spectra recorded immediately in a Varian EM 360-L apparatus using  $\text{Me}_4\text{Si}$  as the internal standard. Reaction was reassumed by putting back the solution and the filtered solids in the reaction tube and turning on the lamp again. Extreme care had to be taken throughout this process not only to avoid moisture absorption, but specially due to highly lachrymatory characteristics of the bromomethyl derivatives formed.

## RESULTS AND DISCUSSION

NBS behaves as an allylic halogenating agent in different conditions<sup>9</sup>. According to the  $^1\text{H}$  NMR spectra obtained at different reaction times, five bromo derivatives of the starting substrate are formed (compounds *II*–*VI*, see scheme below). Table I gives their  $\delta$  values and relative integrations.

The positions of the signals confirms that 1,2,5-thiadiazole behaves like an aromatic ring, producing a low-field shift in substituents bound to it ( $\text{CH}_3$  signal in *I* appears very closely to the  $\text{CH}_3$  signal in toluene: 2.3 ppm). The same shift to higher  $\delta$  values is observed in a signal when a bromine atom is introduced in the other substituent ( $\text{CH}_3$  in *I*  $\rightarrow$  *II*  $\rightarrow$  *III*,  $\text{BrCH}_2$  in *II*  $\rightarrow$  *IV*  $\rightarrow$  *V*, etc.).

The proportion in which the five products are present in the reaction mixture varies with time, as it is shown in Fig. 1.

At short reaction times (3.5–4 h) it is possible to obtain the monobromo derivative *II* in quite a good yield (>60%) together with remaining reactant and minor quantities of higher halogenated compounds. As reaction proceeds, the amount of *II*

TABLE I

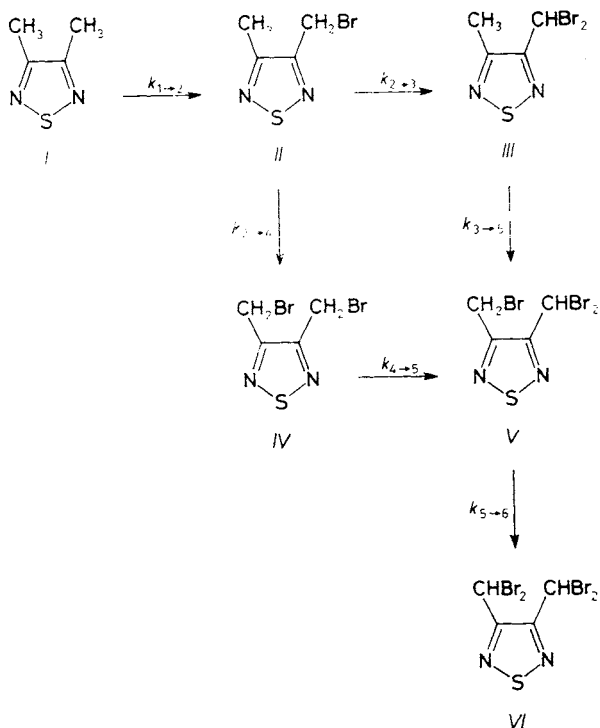
Values of  $\delta$  and relative integrations for species *I* and its five bromo derivatives

Compound	R <sup>1</sup>	R <sup>2</sup>	$\delta(\text{TMS})$ , ppm	Integration ratio
<i>I</i>	$\text{CH}_3$	$\text{CH}_3$	2.50 <sup>a</sup>	—
<i>II</i>	$\text{CH}_3$	$\text{BrCH}_2$	2.61 4.65	3 : 2
<i>III</i>	$\text{CH}_3$	$\text{Br}_2\text{CH}$	2.82 7.03	3 : 1
<i>IV</i>	$\text{BrCH}_2$	$\text{BrCH}_2$	4.78	—
<i>V</i>	$\text{BrCH}_2$	$\text{Br}_2\text{CH}$	4.84 7.04	2 : 1
<i>VI</i>	$\text{Br}_2\text{CH}$	$\text{Br}_2\text{CH}$	7.14	—

<sup>a</sup> Ref.<sup>10</sup>: 2.48.

decreases with the simultaneous increment in the quantities of both dibrominated products *III* and *IV* that reach their maximum yields at c. 9–10 hours. From 20 hours on, the main components of the system are the tri- and tetrabromo derivatives *V* and *VI* and the conversion *V* → *VI* goes on to reach a ratio 1 : 7 after about 40 hours of reaction. Experience has shown that it is not wise to follow the process beyond this point, as decomposition and darkening of the system become important.

The experimental results can be accommodated in the following scheme that links the resulting products (see Scheme 1).



SCHEME 1

A further knowledge of the corresponding rate constants,  $k$ , is obtained by considering the kinetic expressions:

$$-\frac{d[I]}{dt} = k_{1 \rightarrow 2}[I] \quad (1)$$

$$\frac{d[II]}{dt} = k_{1 \rightarrow 2}[I] - (k_{2 \rightarrow 3} + k_{2 \rightarrow 4})[II] \quad (2)$$

$$\frac{d[III]}{dt} = k_{2 \rightarrow 3}[II] - k_{3 \rightarrow 5}[III] \quad (3)$$

$$\frac{d[IV]}{dt} = k_{2 \rightarrow 4}[II] - k_{4 \rightarrow 5}[IV] \quad (4)$$

$$\frac{d[V]}{dt} = k_{3 \rightarrow 5}[III] + k_{4 \rightarrow 5}[IV] - k_{5 \rightarrow 6}[V] \quad (5)$$

$$\frac{d[VI]}{dt} = k_{5 \rightarrow 6}[V]. \quad (6)$$

For the disappearance of 3,4-dimethyl-1,2,5-thiadiazole a first-order kinetic law holds, and from the integrated form of Eq. (1) the value of  $k_{1 \rightarrow 2}$  can be evaluated, resulting to be  $0.93 \text{ h}^{-1}$ . However, for short reaction times ( $< 1.5 \text{ h}$ ) a departure from linearity is observed, with a certain kind of "induction period" where *I* decomposes quite slowly. A possible explanation for this effect could be the presence of traces of atmospheric oxygen acting as free-radical scavenger, once this contaminating agent disappears the reaction takes its "normal" value.

By dividing the whole run in different periods it is possible to evaluate several rate ratios. For instance, from 2 to 6 hours the only conversions that are happening are those represented by Eqs (1)–(3). Then, by dividing and rearranging the kinetic expressions, a relation  $[III] = (k_{2 \rightarrow 3}/k_{2 \rightarrow 4})[IV]$  is obtained, and from a plot of

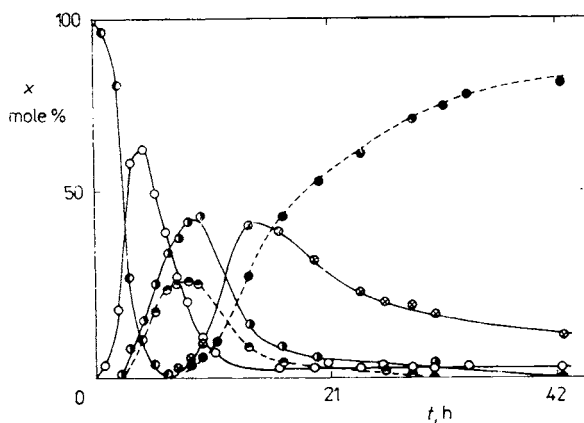


FIG. 1

Time dependence of reaction mixture composition for the light-catalyzed reaction of *I* with NBS ( $\text{CCl}_4$ ,  $20^\circ\text{C}$ ); *I*  $\circ$ , *II*  $\circ$ , *III*  $\bullet$ , *IV*  $\circ$ , *V*  $\circ$ , *VI*  $\bullet$

[III] vs [IV] the ratio  $k_{2 \rightarrow 3}/k_{2 \rightarrow 4} = 1.5$  results. In a similar way, analysis of the period 6–20 h gives values for  $k_{3 \rightarrow 5}/k_{2 \rightarrow 4} = 3.1$  and  $k_{4 \rightarrow 5}/k_{2 \rightarrow 4} = 3.2$  (what means that  $k_{4 \rightarrow 5}/k_{3 \rightarrow 5} = 1.1$ ). From 26 hours on the situation allows to calculate  $k_{3 \rightarrow 5}/k_{5 \rightarrow 6} = 6.0$ . In this period, the conversion of V to VI follows a first-order kinetic law, with a  $k_{5 \rightarrow 6}$  value of  $0.04 \text{ h}^{-1}$  (from the integrated form of Eq. (5)). From this and  $k_{1 \rightarrow 2}$  together with the rate ratios given, the following values of the rate constants at  $20^\circ\text{C}$  (in  $10^{-2} \text{ h}^{-1}$ ) result:

$k_{1 \rightarrow 2}$	$k_{2 \rightarrow 3}$	$k_{2 \rightarrow 4}$	$k_{3 \rightarrow 5}$	$k_{4 \rightarrow 5}$	$k_{5 \rightarrow 6}$
93.0	11.7	7.8	24.1	25.3	4.0

Among the conclusions that can be drawn from the above figures it appears the enhanced reactivity (towards substitution by Br) of an H atom bound to a carbon that already holds a bromine (shown by  $k_{2 \rightarrow 3} > k_{2 \rightarrow 4}$ ). This assert could lead to predict a  $k_{1 \rightarrow 2}$  value minor than  $k_{2 \rightarrow 3}$  which is against our results; being this a clear indication of the influence that steric effects have on the rates. This is also the reason of the relative low value that  $k_{5 \rightarrow 6}$  presents.

Further research on the influence of different variables (kind of light, temperature, catalysts) on the reaction here considered is being conducted in our laboratory and will be reported in due time.

From the synthetic point of view, the above considerations give tools to choose irradiation times that allow for the best possible yields of a given derivative.

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