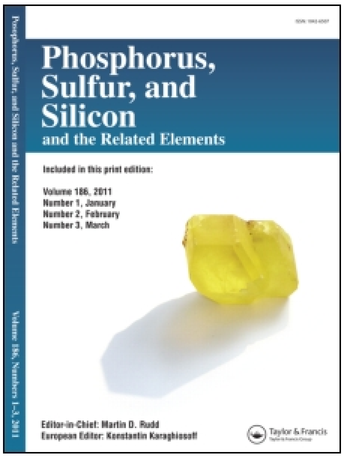

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SUBSTITUTED 1-THIA-3-AZA -1,3-BUTADIENE: DIELS–ALDER REACTION WITH METHYLACRYLATE. DETERMINATION OF ACTIVATION PARAMETERS

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2-Phenyl-4-dimethylamino-1-thia-3-azabutadiene and methylacrylate gave 5,6-dihydro-4H-1,3-thiazine by 4 + 2 cyclocondensation reaction at 55°C. The heterodienes configuration was established by X-Ray spectra. The Diels–Alder character of this reversible reaction was indicated by kinetic and thermodynamic parameters determined by ^{1}H N.M.R.

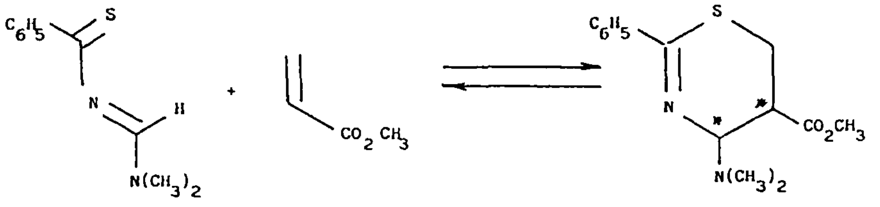
INTRODUCTION

The importance of Diels–Alder reactions and particularly those involving azadienes is well illustrated by the synthetic applications of the resulting cycloaddition products.[1] Results obtained in the laboratory have shown that the original 4 + 2 cycloaddition of 4-amino 1-thia-3-azabutadienes **1** with the usual dienophiles is also general and gives 6H-1,3-thiazines,[2] precursors of cephemes[2–4] and cephalosporines.[5] There is no mention in the literature of a physicochemical study of the reactivity of 1-thia-3-azabutadienes in 4 + 2 cyclocondensations. Polarisation of this heterodiene due to the presence of a sulfur atom in position 1 and of an amino group on C4 under the influence of solvents may be envisaged. In this paper we propose to establish the kinetic and thermodynamic parameters of the 4 + 2 cyclocondensation, to compare them with those known for butadienes and to determine the influence of the solvent in order to optimize the yield of this reaction in the multistep synthesis of cephalosporines derivatives.

RESULTS AND DISCUSSION

Cyclocondensation and cycloreversion

Methylacrylate was used as the dienophile. In fact O–S alkyl or amino substituted-1,3 butadienes are considered as more reactive towards poor dienophile.[6,7] 2-Aza-1,3 butadiene substituted at position 1 by an amino group can presents S cis conformation,[7] which is a favourable factor for 4 + 2 cyclocondensation.[8] The configurational structure of these azabutadienes has been established by ^{13}C NMR studies.[9] Configurational determination of substituted 4-amino 1-thia-3-aza butadienes by ^{13}C N.M.R. presents some difficulties. The T_1 relaxation time of the thiocarbonyl function may be estimated at several ten seconds[10] and an acceptable signal noise ratio spectrum could require a long time. Therefore the configuration of the heterodienic compound **1** was determined by an X-ray spectrum. (Figure 1).



(1)

1 2

Methylacrylate reacts with 4-dimethylamino-2-phenyl-1-thia-3-aza-butadiene **1** in toluene at 55°C and gives exclusively 4-dimethylamino-5-methoxycarbonyl-2-phenyl-5,6-dihydro-4H-1,3-thiazine **2** whose stereochemistry has been described.[11] The total regioselectivity, of this cycloaddition may be compared with that of 1-amino 2-aza-1,3 butadiene.[8]

In order to determine physicochemical parameters of this reaction the stability of the 5,6-dihydro-4H-1, 3 thiazine **2** must be known and the existence or not of any secondary reactions established. In fact use of methylacrylate in large excess

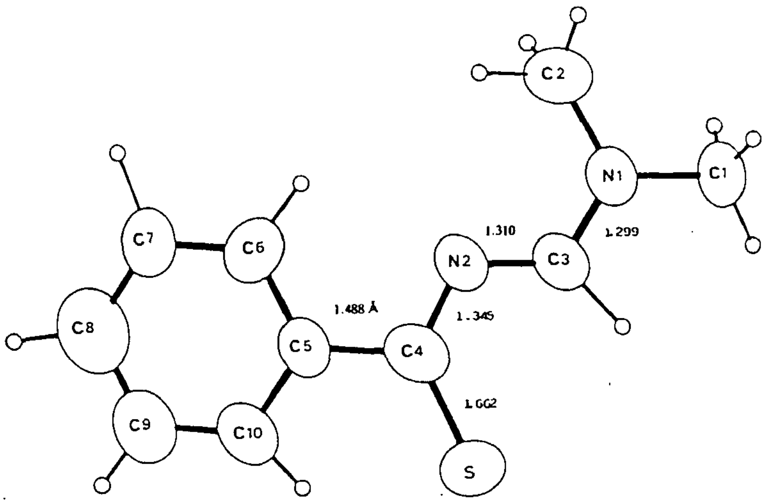


FIGURE 1 O.R.T.E.P. view of 4-dimethylamino-2 phenyl-1-thia-3-aza-1,3-butadiene **1**.

could permit to obtain substituted 6H-1,3-thiazines[2] by elemination of N,N dimethylamino group from the cycloadduct.[2] In our study, thermic evolution in solution of isolated compound **2** was determined by ^{1}H N.M.R. The formation of heterodiene **1** is obtained by equilibrated cycloreversion of compound **2** in C_6D_6 at 333°K. This retro Diels–Alder reaction has been observed by mass spectroscopy under electronic impact.[12]

Determination of the activation parameters for the cyclocondensation

The influence of solvent polarity on the reaction rate for the $4+2$ cyclocondensation of the hererodiene **1** with methylacrylate was examined using successively C_6D_6, $CDBr_3$ and CD_3CN. The reaction Kinetics are very slow below 328°K.

The orders of reaction for the cyclocondensation and cycloreversion were determined using the results obtained in $CDBr_3$ at 328°K with the equations corresponding to the orders of reaction 1/1, 2/1 and 2/2 mentioned in the literature.[13] Correlation coefficients of $r^2_{1/1} = 0.9888$, $r^2_{2/1} = 0.9996$, $r^2_{2/2} = 0.9980$ were obtained. The slight variation in the correlation coefficient r^2 for orders of reaction 2/1 and 2/2 was a problem for their relative signification. In order to remove this ambiguity a 2/1 reaction was simulated using the following equation.

$$x(t) = \frac{a_0^2 x_e\left[\exp\left(k_1 \frac{a_0^2 - x_e^2}{x_e} t\right) - 1\right]}{a_0^2 \exp\left(k_1 \frac{a_0^2 - x_e^2}{x_e} t\right) - x_e^2} \tag{2}$$

$50\,\text{mn} < t < 1000\,\text{mn}$, $a_0 = 0.5\,\text{M}$, $x_e = 0.3\,\text{M}$, $k_1 = 10^{-3}\,\text{M}^{-1}\,\text{mn}^{-1}$.

Some random values, taken in the interval ±0.05 were added to the $x(t)$ values so as to obtain a better simulation of the experimental results. These were then treated by the equations corresponding to orders of reaction 1/1, 2/1 and 2/2. Correlation coefficients of respectively $r^2_{1/1} = 0.870$, $r^2_{2/1} = 0.9479$ and $r^2_{2/2} = 0.9445$ were obtained. Variations of the same size as those found experimentally, especially for $r^2_{2/1}$ and $r^2_{2/2}$ were observed. We can conclude that the slight variation of r^2 obtained experimentally is significant and that only an order of reaction of 2 for the cyclocondensation and an order of reaction of 1 for the cycloreversion may be held. (Figure 2). Having found the order of reaction, the kinetic and thermodynamic parameters were determined in the three solvents mentioned earlier (Table I). The variations in activation entropy are seen to be inferior to the errors of measurement: these variations may therefore be considered as insignificant and the entropy as constant for the three solvents. However, a correlation between ΔS^* and μ/D, with a risk ($t = 18.9$) of about 4%, indicates the existence of a possible slight solvent influence on the reaction.

$$\Delta S^* = -24.2 + 0.6\,\mu D \qquad r^2 = 0.9972$$

The size of the entropy values on the one hand and the small effect of the solvent on the other are factors which normally characterize a Diels–Alder reaction for substituted butadienes.[8] However, the dissymmetry of the diene due to the electron attracting sulphur atom at position 1 and the donating amino group on

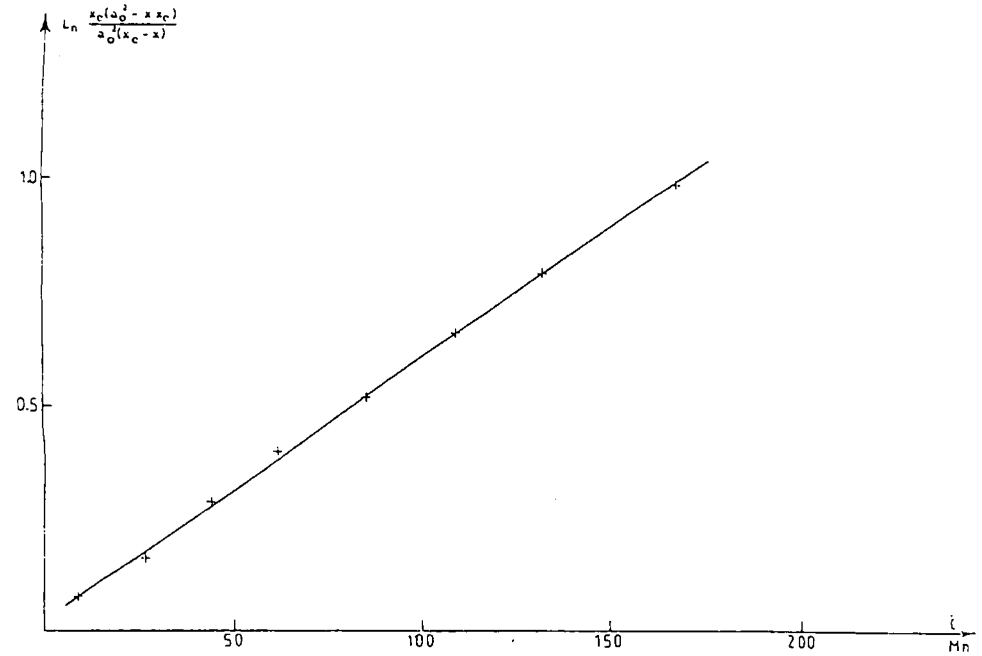


FIGURE 2 Linearity for an order of reaction 2/1 between heterodiene 1 and methylacrylate (a_0 = initial concentration – x = t time concentration – x_e = equilibrium concentration).

position 4 means that the 4 + 2 cyclocondensation with methylacrylate may be considered as an asynchrone reaction.[14,15] This cyclocondensation remains limited by the possible thermical cycloreversion observed above.

TABLE I

Kinetic and thermodynamic parameters for the cyclocondensation between heterodiene 1 and methylacrylate: ε = dielectric constant; μ = dipole moment; r = correlation coefficient; t = Students statistic; R = risk that the linerarity of the points is due to hasard. (*) standard error

Solvent	ε	μN (Debye)	$k_1 \times 10^3$ $M^{-1} sec^{-1}$	T K	ΔH^* Kcal/mol	ΔS^* U.A	r^2	t	R
C_6D_6	2.275	0	0.118 ± 0.003*	328	14.8 ± 1.4	−24.2 ± 4.3	0.981	10.3	<1%
$CDBr_3$	4.39	0.99	0.221 ± 0.006	328.4	14.4 ± 1.2	−23.7 ± 3.6	0.979	12.1	≃0.1%
CD_3CN	37.5	3.44	0.083 ± 0.002	328	15.6 ± 1.1	−22.1 ± 3.4	0.995	13.8	<5%

EXPERIMENTAL

The NMR study was carried out on a BRUKER WM 250 (250 MHz) spectrometer. The accumulation parameters were the following: spectral width, 2500 Hz; magnetization angle, approx. 36°; memory, 8 K; accumulation time, 1.64 s; accumulations, 40. The frequency was locked using the deuterium peak of the solvents used, C_6D_6, $CDBr_3$, CD_3CN, (C.E.A.). The slow kinetics under 328°K and the evaporation of the solvent near the boiling point have imposed to measure the kinetic parameters in different ranges of temperatures along the solvent: 16.2Δ°C for C_6D_6; 15.2Δ°C for CD_3CN; 25.9Δ°C for $CDBr_3$. Spectra was recorded automatically using the KINETICS-ASPECT 2000 programme. Each reaction gave an average fifteen exploitable points. The equilibrium point was determined using measurements recorded over several hours. The probe temperature variation of about 0.5°C was observed during the reactions and the average value was retained as the reaction temperature. The cyclocondensation reaction was followed by integrating the protons on concentrations used were 0.5 M.

Crystal data for Compound **1**. $C_{10}H_{12}N_2S$, Mr = 192.3, monoclinic, space group $P2_1/C$, $a = 6.244(6)$, $b = 21.917(9)$, $C = 7.988(9)$ Å, $\beta = 107.3(3)°$, $V = 1043$ Å^{-3}, $Z = 4$, $D_x = 1.22$ Mg m^{-3}, $\lambda(\text{MoK}\alpha) =$ 0.71073 Å, $\mu = 2.5$ cm^{-1}, F(000) = 408, $T = 296$ K, Final $R = 0.069$ for 1044 observations. Study with a ENRAF–NONIUS CAD 4 automatic diffractometer: cells parameters are determined and refined with a set of high angle reflexions. The sample (0.22 × 0.26 × 0.32 mm) gave 2040 data (2θ max = 50°) within 1044 independent ($R_{\text{Int}} = 0.018$) with $I > 3\sigma(\text{I})$: range H(0–6) K(0–21) L($\bar{7}$–7), scan w/$2\theta = 1$, $t_{\max} = 60$ s, no significative decay of the intensity controls.

The structure is solved with Direct Methods. After refinements in isotropic mode ($R = 0.13$) then anisotropic mode ($R = 0.096$), the hydrogene atoms are located with a Fourier Difference (between 0.47 and 0.20 e Å^{-3}). The best full matrix least-square refinement of the sturcture ($x, y, z, \beta i, j$ for S, N, C and x, y, z for H) gives $R = 0.069$, $R_w = 0.071$, $S_w = 1.18$ and $\Delta e = 0.32$ e Å^{-3}.

The supplementary material belonging to the X-Ray determination is deposited in Cambridge crystallographic data center, U.K.

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