Tetrahedron Letters,Vol.28,No.46,pp 5767-5768,1987 0040-4039/87 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

THE USE OF PROTIUM AND DEUTERIUM ANALOGUES IN MECHANISTIC STUDIES OF THIAZOLE SYNTHESES

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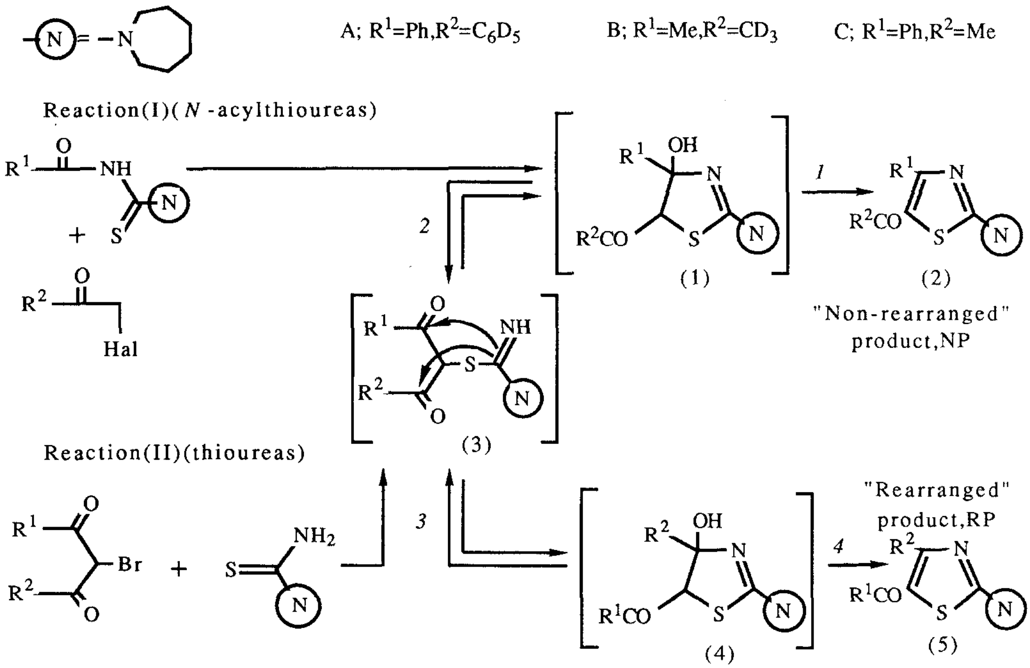
Summary: The mechanisms of two reactions which give isomeric thiazol-5-yl ketones have been elucidated by work with substrates containing pairs of acyl groups and their deuterium-substituted analogues.

In earlier work[1] the two routes to thiazol-5-yl ketones, reactions (I) and (II) in Scheme 1, were shown to give mixtures of isomers (2) and (5), but the factors determining the composition of the mixtures remained obscure. [For brevity the product (2) from reaction (I) in which the 4-substituent (R^1) is derived from the N-acylthiourea is termed the "non-rearranged" product (NP), and the isomer (5) the "rearranged" product (RP).] Although a common intermediate (3) is involved the RP:NP ratios of reaction (I) (as carried out previously using solutions in ethanol containing triethylamine) and reaction (II) (in acetone without base) for the same pair of R^1,R^2 groups are not equal. The simplest explanation, that some of the first intermediate (1) leaks to the NP(2) rather than giving the diketone (3), is discounted by the many instances of the higher ratios being associated with reaction (I). A crucial factor, the relative rates of the isomerisations (steps *2* and *3*) and the dehydrations (steps *1* and *4*), cannot be elucidated by work with conventional pairs of R^1,R^2 groups. However, the required information emerges clearly from a new approach which involves substrates containing pairs of (almost) equally reactive but spectrometrically distinguishable acyl groups (protium and deuterium analogues) denoted by A and B in Scheme 1.

Observation of the expected RP:NP ratios (1:1) in reactions (II)A and (II)B established that possible complications from secondary isotope effects are negligible. For reactions (I)A and (I)B in ethanol containing triethylamine the ratios were again 1:1, but in acetone without base the NPs(4) were the sole products. Thus, in the presence of base the equilibrations are faster than the dehydrations, but in a neutral medium the relative rates are reversed. [Reactions (I) and (II) produce thiazol-5-yl ketones plus 1 mol equiv. of hydrogen halide; in a neutral medium the latter is then available for facilitating the dehydrations, acid-catalysis of which is strongly suggested by related work[2].] These results and those from a typical system (e.g., C in Scheme 1) are accommodated by the expressions for the RP:NP ratios in Scheme 2. The proposed interpretation accounts readily for the marked difference between the outcome of the reactions in a neutral medium: reaction (I) gives only the NP(4) whereas reaction (II) leads to a mixture whose composition is determined by the relative electrophilicities of the acyl groups in the diketone (3) (e.g., MeCO > PhCO). A useful preparative variation of reaction (I), illustrated in Scheme 2, was developed from the mechanistic work.

Scheme 1. Formation of isomeric 2-(*N,N*-disubstituted amino)thiazol-5-yl ketones



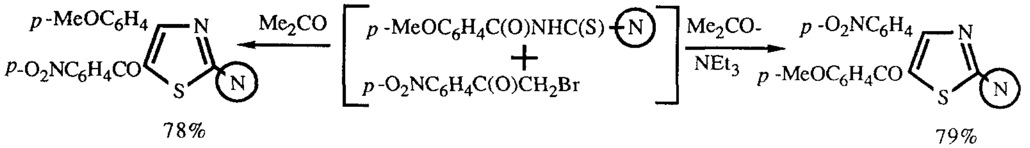
Reaction	Solvent	NEt_3 (mol equiv.)	Ratio RP:NP	Reaction	Solvent	NEt_3 (mol equiv.)	Ratio RP:NP
(I)A	EtOH	2	1:1	(I)C	Me_2CO	0	0[a]
(I)A	Me_2CO	0	0[a]	(I)C	Me_2CO	1.05	10:1
(II)A	Me_2CO	0 and 2	1:1	(I)C	Me_2CO	2	14:1
(I)B	EtOH	2	1:1	(II)C	Me_2CO	0	2.5:1
(I)B	Me_2CO	0	0[a]	(II)C	Me_2CO	1.05	10:1
(II)B	Me_2CO	0 and 2	1:1	(II)C	Me_2CO	2	13;1

[a] No RP(5) detected; the NP(2) was isolated in high yield.

Scheme 2. RP:NP ratios, and preparative variation of reaction(I)

$$\begin{tikzcd}
\text{Reaction(I)} \arrow[r] & (1) \arrow[r, "k_1"] \arrow[d, dashed, shift right] & \text{NP(2)} \\
\text{Reaction(II)} \arrow[r] & (3) \arrow[u, shift right, "k_2"'] \arrow[d, shift left, "k_3"] & \\
& (4) \arrow[u, dashed, shift left] \arrow[r, "k_4"] & \text{RP(5)}
\end{tikzcd}$$

	Reaction	Ratio
In presence of NEt₃ (dehydrations rate-limiting)	(I) and (II)	$k_4\,[4]/\,k_1$ [1]
In neutral medium (isomerisations rate-determining)	(I) (II)	0 $k_3\ /\ k_2$



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2. S.E. Bramley, Viscount Dupplin, D.G.C. Goberdhan, and G.D. Meakins, J.Chem.Soc., Perkin Trans. 1, 1987, 639.

(Received in UK 17 September 1987)