

PHASE - TRANSFER CATALYSER HYDROGEN-DEUTERIUM EXCHANGE IN THIAZOLES.

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(Received in UK 13 May 1976; accepted for publication 20 May 1976)

**Abstract** : phase transfer catalysis has been used for the first time in a reaction of hydrogen deuterium exchange in heterocyclic chemistry. The method provide a good synthetic path for the synthesis of D - 2 thiazoles by direct exchange. Moreover, even with substituents such as t-butyl, hydrogen exchange on positions adjacent to the alkyl group occurred.

Phase transfer catalysis has been shown to be a very powerful tool in synthetic reactions ( 1, 2 ). Substitutions, condensations, carbenes formations, oxidations ... , have been performed, but isotopic exchange has not been widely studied and only a few papers ( 3,4 ) dealing with this problem under such conditions, and none appears in heterocyclic chemistry.

We wish to present, in this work, firstly a synthetic approach to the synthesis of isotopic thiazoles by hydrogen-deuterium exchange, and secondly the first results concerning a study of the lability in basic medium of the hydrogen atoms of several alkyl thiazoles.

Synthetic approach - Experimental reaction conditions .

We have chosen 5-ethyl thiazole as the starting compound to establish the experimental reaction conditions under phase - transfer catalysis. In fact, effect of temperature, base concentration, type of salt and solvent, have to be determined.

In table 1 we have examined the effect of varying the concentration of the quaternary salts, octadecyltrimethylammonium bromide, one of the most efficient catalysts for the reaction ( table 4 ) . A plot of per cent exchange ( after 1/4 h. ) vs molar concentration of catalyst concentration as been observed for other reactions ( 4,5,6 ). However, from the limited data available and the possibility that those reactions carried out in the presence of  $2.4 \times 10^{-4}$  mole

catalyst may be so fast that a virtual plateau has been reached in less than a quarter of an hour one cannot be sure and it may well be that the dependence on catalyst concentration may be more pronounced. Table 1 also reveals that the effect of increasing the reaction period is minimal at the higher catalyst concentration.

Table 2 shows that temperature has a marked effect on the rate of exchange, an effect more important than expected owing surely to additive equilibrium displacement : exchange  $\text{Br}^- \rightleftharpoons \text{OH}^-$  in the basic phase, extraction by solvent of the ammonium hydroxide catalyst, medium viscosity, etc... Table 2 shows also that no exchange occurs in the absence of added salt and table 3 that the strength of the sodium deuterioxide used influences the rate of exchange.

Some of the findings of Herriott and Picker ( 6 ) are corroborated by the data in table 3 . Thus, larger ions are more effective ( i.e. entries 2 and 3 vs 6 ) , the more symmetrical ions are more effective ( 2 vs 1 or 3 ) and phosphonium ions are slightly more effective than ammonium. The total failure of 2,4-dimethylbenzylpyridinium bromide as a catalyst is not unexpected; il may be due to the reaction of this salt with the inorganic base ( hydrogen abstraction from position  $\alpha$  to the nitrogen atom ).

Table 1 .

Effect of the quantity of the quaternary salt,  $\text{Me}_3\text{N}^+\text{C}_{18}\text{H}_{37}\text{Br}^-$ , on the percentage of deuteration in 5-ethylthiazole after various reaction times <sup>a</sup>.

salt ( mole ) x 10 <sup>-4</sup>	% exchange <sup>b</sup> and reaction times		
	1/4 h.	1 h.	3 h.
0.6	30	39	
1.2	38	90	90
1.2		80 <sup>c</sup>	
2.4	78	89	92
3.6	85	86	

<sup>a</sup>All reactions were carried out in tightly stoppered small cylindrical round-bottomed flasks immersed in a constant temperature bath ( 50° C. ) . Vigorous magnetic stirring was maintained throughout the reaction period. For each reaction, unless otherwise stated, 5-ethylthiazole ( 0.004 mole ) was added to  $\text{C}_6\text{D}_6$  ( 2.5 cm<sup>3</sup> ) + 10 M NaOD ( 2 cm<sup>3</sup> ), followed by the stated amount of catalyst.

<sup>b</sup>The given % exchange occurs at the 2 position. Slight variations of the 4 position signal intensity remain in the limit of integration error range ( accuracy of 10 % ) . N.M.R. signals 8.38 ppm 1H, 2 position - 7.39 ppm 1H, 4 position - 2.73 ppm 2H, methylene protons - 1.24 ppm, 3H, methyl group.

<sup>c</sup> Using 5 cm<sup>3</sup> of  $\text{C}_6\text{D}_6$  in place of 2.5 cm<sup>3</sup>.

Table 2 .

Effect of temperature on the % H/D exchange in 5-ethylthiazole <sup>a</sup>.

reaction time	% exchange and reaction temperature		
	25°	50°	50°
3 h.	14	90	0 <sup>b</sup>

<sup>a</sup> Using  $\text{Me}_3\text{N}^+\text{C}_{18}\text{H}_{37}\text{Br}^-$  ( 0.0012 mole ) . See footnotes <sup>a</sup> and <sup>b</sup> to table 1 .

<sup>b</sup> Without added salt no exchange was observed after 70 h.

Table 3 .

Effect of the strength of sodium deuterioxide on the % H/D exchange in 5-ethylthiazole <sup>a</sup>.

reaction time	% exchange and strength of sodium deuterioxide		
	2.5 M	5 M	10 M
1/4 h.	22	19	38
3 h.	62	90	90

<sup>a</sup> Using  $\text{Me}_3\text{N}^+\text{C}_{18}\text{H}_{37}\text{Br}^-$  ( 0.0012 mole ) . See footnotes <sup>a</sup> and <sup>b</sup> to table 1 .

Table 4 .

Effect of various quaternary salts on the percentage H/D exchange in 5-ethylthiazole <sup>a</sup>.

salts	% exchange and reaction time		
	1/4 h.	1 h.	3 h.
Me <sub>3</sub> N-C <sub>18</sub> H <sub>37</sub> Br	38	90	92
n-Bu <sub>4</sub> NBr	55	90	
n-Bu <sub>3</sub> P-C <sub>16</sub> H <sub>33</sub> Br	44		88 <sup>b</sup>
2,4-Me <sub>2</sub> BzNC <sub>5</sub> H <sub>5</sub> Br	0	0	0 <sup>c</sup>
Et <sub>3</sub> N-BzCl			79
Me <sub>4</sub> NCl	0		16 <sup>c</sup>

<sup>a</sup> See footnotes <sup>a</sup> and <sup>b</sup> to table 1 .<sup>b</sup> 10 to 15% exchange is detected in the 4-position.<sup>c</sup>After 19 h.Deuteration in the alkylthiazole series .

The results are presented in table 5 . We can see the important effect of the alkyl group on the lability of the 2 or 5 hydrogens. Nevertheless it is now possible to prepare 2-D thiazoles and even 5-D thiazoles by this method. It is noteworthy that in general 2-D thiazoles have been obtained by longer reaction paths, such as reduction of the halogeno-derivatives by deuterio-acetic acid in the presence of Zn powder ( 7 ) or by hydrolysis with D<sub>2</sub>O of the lithium derivatives ( 8,9 ) , but in all cases mixtures were obtained. The direct exchange in NaOD-D<sub>2</sub>O is possible only for thiazole ( because of poor solubility in the alkyl series ), but ( 7 ) the results have shown that about 15 hours are necessary for full exchange at the 2 position, and, more moreover, by-products arising from the degradation of the thiazole ring may be obtained.

Table 5 .

H/D exchange in various alkyl thiazoles <sup>a</sup>.

thiazoles	% exchange on positions :	
	2	5
thiazole <sup>b</sup>	93	90
benzothiazole <sup>c</sup>	96	
2-n-propylthiazole		80
2-methylthiazole	90	
2-t-butylthiazole <sup>d</sup>		20
4-methylthiazole	93	26
4-t-butylthiazole	83	8.5
5-ethylthiazole	92	

<sup>a</sup>The reaction time was 3 h. All reactions were made following the experimental stated in footnote <sup>a</sup> table 1. The catalyst used was tetrabutylammoniumbromide ( 4 mole % ).

- b After 30 minutes 96 % exchange at the 2 position .  
c After 30 minutes 83 % exchange at the 2 position  
d After more than 15 hours, 80% exchange at the 5 position.

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One of us ( W.J.S.) wishes to thank the National Sciences Council ( Ireland ) and the Centre National de la Recherche Scientifique ( France ) for the award of an Exchange Fellowship, during the tenure of which this work was carried out .