ALKYLATION OF 5-SUBSTITUTED 1-H-TETRAZOLES BY MANNICH BASES UNDER THE ACTION OF ULTRASOUND

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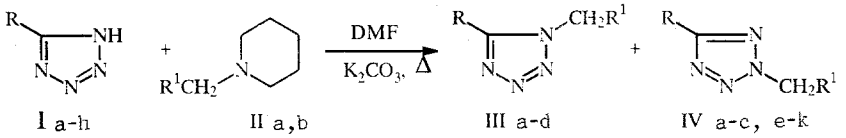
Alkylation of 5-substituted 1-H-tetrazoles by Mannich bases — N-(3,5-dimethyl-4-hydroxybenzyl)piperidine and N-(2-hydroxy-3-methoxy-5-formylbenzyl)piperidine — under the action of ultrasound increases the yield of the desired products, reduces the reaction time, and improves the regioselectivity.

Alkylation of 5-substituted 1-H-tetrazoles by Mannich bases in dimethylformamide at 130°C in the presence of catalytic quantities of potash under a current of inert gas gives a 48 to 77% yield of 1,5- and 2,5-disubstituted tetrazoles and their mixtures which are difficult to separate [1]. Several of the compounds so prepared (N_1- and N_2-isomers and their mixtures) display high biological activity [2]. Hence it became necessary to find a regioselective method for the alkylation of 5-substituted 1-H-tetrazoles by Mannich bases for the purpose of preparing the individual products.

It is known that ultrasound has a specific effect on many reactions, including alkylation under phase-transfer conditions [3, 4]. Little attention has been paid to its use for the alkylation of heterocyclic compounds under homogeneous conditions. In the present communication, we report the results of a study of the effect of ultrasound on the alkylation of tetrazoles (Ia-h) by Mannich bases (IIa, b) (scheme 1).

The reactions were carried out in dimethylformamide at 105-130°C in the presence of catalytic quantities of potash and under the action of ultrasound:

Scheme 1



I a-h II a,b III a-d IV a-c, e-k

I, III, IV a R = 4-pyridyl; b R = 4-nitrophenyl; c R = 4-bromophenyl; d R = 4-chlorophenyl; e, i R = phenyl; f, j R = 4-methoxyphenyl; g, k R = 3,4-dimethoxyphenyl; h R = 3,pyridyl; IIa, IIIa-d, IVe-h R^1 = 3,5-dimethyl-4-hydroxyphenyl; IIb, IVa-c, i-k R^1 = 2-hydroxy-4-methoxy-5-formylphenyl.

In this way we were successful in all cases in obtaining high yields (63-92%) of one of the two possible N_1- or N_2-isomers (III or IV) and in reducing the reaction times by factors of 2 to 15 in comparison with the times cited in [1] (Table 1).

It is well known that the alkylation reaction proceeds through the formation, from the base II, of the corresponding quinonemethides (V) [5-7] with subsequent addition thereto of the 5-substituted-1-H-tetrazoles I (scheme 2).

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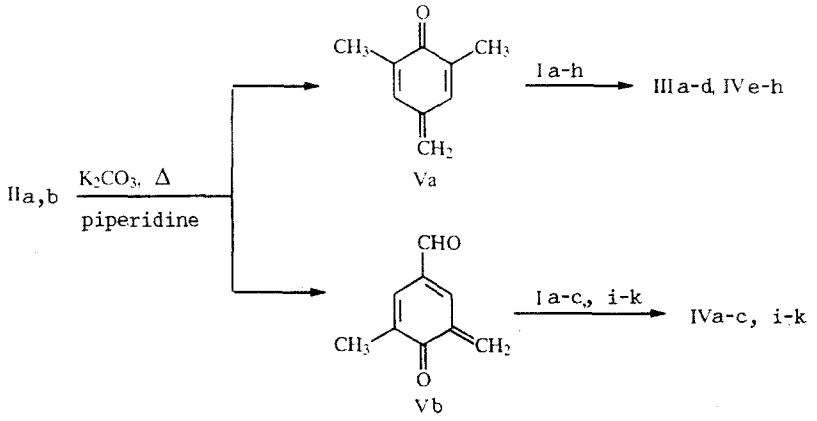
TABLE 1. Results of Alkylation of 5-Substituted 1-H-Tetrazoles by Mannich Bases under Different Conditions

Starting material	Ultrasound K_2CO_3				T 130 °C, K_2CO_3*		
	reaction tmp., °C	reaction time, h	reaction product	yield, %	reaction time, h	reaction product (ratio III:IV)	yield, %
Ia, IIa	130	0,4	IIIa	87	6,5	IIIa	59
Ib, IIa	118	1,5	IIIb	88	22,0	IIIb	69
Ic, IIa	118	1,7	IIIc	77	10.0	IIIc	70
Id, IIa	112	0,3	IIId	90	3,0	IIId	79
Ie, IIa	120	0,4	IVe	87	6,5	IVe	77
	118	2,7	IVe***	73			
If, IIa	118	0,7	IVf	88	22,0	IVf	69
	118	1,5	IVf**	68			
Ig, IIa	121	0,5	IVg	77	6,0	IVg	67
	120	1,6	IVg **	74			
Ih, IIa	105	0,7	IVh	80	6,0	IVh	60
Ia, IIb	120	3,0	IVa	63	33,0	IIIa, IVa (1 : 1,2)	70
Ib, IIb	120	2,0	IVb	70	17,0	IIIb IVb (1 : 1,2)	63
Ic, IIb	120	2,7	IVc	92	26,0	IIIc, IVc (1 : 3,0)	53
Ie, IIb	118	3.0	IVi	64	15,0	1 : 4	61
If, IIb	110	1,7	IVj	74	15,0	IVj (trace IIIj)	48
Ig, IIb	120	3,7	IVk	67	18,0	IIIk, IVk (1 : 2,5)	57

*Quoted from literature [1].

**Alkylation carried out without catalyst.

Scheme 2



The formation of the quinonemethides Va and Vb in the course of the alkylation was observed by the appearance of characteristic bands at 276 [8, 9], and 285, 320 nm, respectively, in the UV spectrum of the reaction mixture. It should be further noted that the electronic spectra of the products of the conversion of the Mannich bases IIa and IIb were identical for both alkylation under the conditions described earlier [1] and for alkylation under the action of ultrasound. Under the action of ultrasound, compounds V are already recorded after 10 min reaction whereas in solutions of Mannich bases which are simply heated to 130°C the characteristic bands of the quinonemethides are observed only after holding at this temperature for 8 h.

Thus, under the action of ultrasound, the quinonemethide formation stage is accelerated and is evidently the limiting stage. At the same time, a reduction in the side reactions which are characteristic for compound V, and an increase in regioselectivity with increased yields, shows that ultrasound also has a direct effect on the stage of alkylation of the tetrazoles I by quinonemethides.

The process of alkylation in an ultrasonic field is markedly slowed by the absence of catalyst (Table 1) although the reaction time in such cases is still several times less than in the method described earlier.

TABLE 2. Characteristics of Compounds IIIa-d, IVa-c, e-k

Compound	Empirical formula	mp, °C	R_f*	Chemical shift, CH_2 group, δ, ppm
IIIa	$C_{15}H_{15}N_5O$	177...178	0,94	5,84
IIIb	$C_{16}H_{15}N_5O_3$	183...184	0,95	5,75
IIIc	$C_{16}H_{15}BrN_4O$	146	0,63	5,72
IIId	$C_{16}H_{15}ClN_4O$	144...145	0,97	5,78
IVa	$C_{15}H_{13}N_5O_3$	208...209	0,49	6,02 (5,96)**
IVb	$C_{16}H_{13}N_5O_5$	208...210	0,78	6,03 (5,96)**
IVc	$C_{16}H_{13}BrNO_3$	194...196	0,78	6,00 (5,90)**
IVe	$C_{16}H_{16}N_4O$	126...127	0,97	5,78
IVf	$C_{17}H_{18}N_4O_2$	124...127	0,95	5,66
IVg	$C_{18}H_{20}N_4O_3$	166...168	0,86	5,68
IVh	$C_{15}H_{15}N_5O$	156	0,71	5,83
IVi	$C_{16}H_{14}N_4O_3$	169...171	0,84	6,00 (5,92)**
IVj	$C_{17}H_{14}N_4O_4$	178...180	0,80	5,96 (5,87)**
IVk	$C_{18}H_{18}N_4O_5$	196...197	0,78	5,95 (5,83)**

*In system: 8:2:2:1 butyl acetate–acetone–acetic acid–water (IVi-k, IIId); 2:1 acetone–hexane (IIIc); 8:2:2:1 ethyl acetate–acetone–acetic acid–water (remaining compounds).

**Chemical shifts for $N-CH_2$ group protons of N_1-isomers (data of [1]).

The structure of compounds III and IV prepared in this way was established on the basis of physicochemical analyses. Thus, in the IR spectra of all the compounds prepared, there were observed absorption bands in the 1100-1000 cm^{-1} region characteristic of the skeletal vibrations of the tetrazole ring [11]. Assignment of the products as N_1- or N_2-isomers was effected on the basis of the data of [12, 13] according to which the PMR signals of the methylene group protons in the N_1 position are shifted 0.1 to 0.3 ppm upfield in comparison with the N_2-isomers. The PMR spectra of compounds IIIa-h and IVe-h were identical to the spectra of the corresponding compounds prepared by the method of [1].

EXPERIMENTAL

Ultrasonic fields were generated at 22 kHz by a UZDN-2T ultrasonic disperser with a power rating of 160-296 W. PMR spectra were run on a Tesla BS 597 A (100 Hz) spectrometer in DMSO-d_6. UV spectra of the reaction solutions in DMF were obtained on a Specord UV-Vis instrument. IR spectra were recorded on a UR-20 as mulls in mineral oil or in perfluorohydrocarbon oil. The progress of the reactions was monitored and the purity of the alkylation products assessed by TLC on Silufol UV-254 plates in 8:2:2:1 butyl acetate–acetone–acetic acid–water, 1:2 acetone–hexane, or 8:2:2:1 ethyl acetate–acetone–acetic acid–water.

The results of elemental analyses for C, H, N were in agreement with those calculated.

5-Substituted 1-H-tetrazoles were prepared by the method of [10].

Compounds IVa, IVc, IVh, and IVf, which have not been reported previously, were prepared by alkylation of tetrazoles Ia, c, h, f by bases IIa and IIb as described in [1].

1(2)-Arylmethyl-5-aryl(heteryl)tetrazoles. A solution of 6.8 mmole 5-substituted 1-H-tetrazole I, 2.9 mmole base II, and 0.005 g potash in 15 ml DMF was prepared at room temperature. Ultrasonic irradiation was then applied by introducing the ultrasound emitter of a UZDN-21 disperser while heating the solution until the initial compound II had disappeared (Table 1). Progress of the reaction was monitored by removing samples for TLC analysis periodically (every 5-15 min). The mixture was cooled, poured into water and the precipitated product filtered off, dried, and recrystallized from aqueous alcohol.

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