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NON-CATALYTIC ADDITION OF 1,2,4-TRIAZOLE TO NUCLEOPHILIC AND ELECTROPHILIC ALKENES

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Non-catalytic addition of 1,2,4-triazole to vinyl ethers and esters occurs on heating (65-175°C, 4-20 h) to give Markovnikov adducts (yield 30-100%). Electron-deficient alkenes (acrylonitrile, acrylic acid, 4-phenyl-3-buten-2-one) react with 1,2,4-triazole (78-190°C, 4-20 h) to give anti-Markovnikov adducts in yields of 45-83%.

Keywords: acrylic acid, acrylonitrile, vinyl ethers, Markovnikov and anti-Markovnikov adducts, 1,2,4-triazole, 4-phenyl-3-buten-2-one, addition.

Triazoles and their derivatives are of constant interest to researchers as highly reactive structural units and intermediates [1-3], among which substances with antibacterial, spasmolytic, analgesic, and cardiostimulating activities [4-7], and other practically valuable properties [8, 9] were found so that the search for new suitable routes to functionalized triazoles is a timely problem. One of the promising means for introducing functional substituents into the triazole ring is the addition of triazoles to functionally substituted alkenes.

In this work the rules of the addition of 1,2,4-triazoles to double bonds of various types have been studied using vinyl ethers and esters, acrylic acid, acrylonitrile, and 4-phenyl-3-buten-2-one as examples. Information on similar reactions is, so far as we know, limited to three papers [10-12] in which the addition of symmetrical and vicinal triazoles to vinyl ethers, catalyzed by orthophosphoric acid [10], and to electron-deficient alkenes (acrylic and crotonic acids and their derivatives, benzalacetophenone, etc) in the presence of bases [11, 12] is briefly reported.

We have shown here for the first time that 1,2,4-triazole (**1**) can add to both nucleophilic and electrophilic alkenes in the absence of catalysts, although for quantitative conversion of the starting materials somewhat more vigorous temperature conditions are required in this case.

Thus triazole **1** reacts with alkyl and aryl vinyl ethers **2a-j** and also with vinyl acetate **2k** on heating (65-175°C, 4-20 h) to give 1-[1-alkoxy(aroxy)ethyl]-1H-1,2,4-triazoles **3a-k**, the yields of which depend on the structure of the starting vinyl ethers **2a-k** and on the reaction conditions (Table 1).

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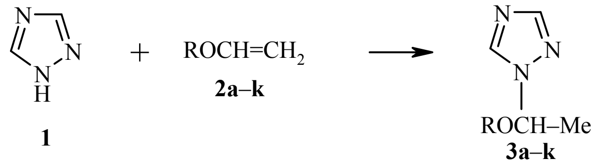

a R = *n*-Pr, **b** R = *n*-Bu, **c** R = *n*-C_7H_{15}, **d** R = Ph, **e** R = 3-MeC_6H_4, **f** R = 4-MeC_6H_4,
g R = 3-MeOC_6H_4, **h** R = 4-MeOC_6H_4, **i** R = 4-BrC_6H_4, **j** R = 3-ClC_6H_4, **k** R = AcO

The structures of the functionally substituted heterocycles **3a-k** synthesized was demonstrated by ^{1}H NMR spectroscopy and confirmed by mass spectrometry and elemental analysis (Table 2). The presence of a doublet for the methyl group (1.5-1.9 ppm) and the quartet for the methyne proton (5.4-6.8 ppm) corresponds to the Markovnikov structure of the adduct, while the presence of two signals for protons of the triazole ring in the region of 7.8-8.2 ppm indicates the non-equivalence of atoms 3-H and 5-H in the ring, and shows that addition of triazole **1** to the vinyl ethers and esters occurred with participation of atom $N_{(1)}$.

Conditions were found (120°C, 5 h) to obtain adducts **3a-c**, on basis of alkyl vinyl ethers, in quantitative yields (Table 1, exp 2,4,5). Addition of triazole **1** to aryl vinyl ethers **2d-j** required more vigorous conditions evidently due to the known [13] reduced nucleophilicity of the double bond in these compounds in comparison with alkyl vinyl ethers. For example, vinyl phenyl ether **2d** reacted with triazole **1** to give adduct **3d** (Table 1, exp. 6). Heating triazole **1** under these conditions with 3- and 4-methylphenyl vinyl ethers gave 1-[1-phenoxyethyl]-1H-1,2,4-triazoles **3e,f** (Table 1, exp 7, 8). 3- and 4-Methoxyphenyl vinyl ethers are still less reactive: the yields of the corresponding adducts **3g,h** under more vigorous temperature conditions were 35 and 30% (Table 1, exp. 9 and 10). On the other hand, the presence of a halogen atom in the aromatic ring increased the reactivity of the vinyloxy group: 1-[1-(4-bromo and 3-chloro)phenoxyethyl]-1H-1,2,4-triazoles (**3i,j**) were obtained in yields of 74 and 71% respectively (Table 1, exp. 11, 12).

TABLE 1. Conditions for the Reactions of 1,2,4-Triazole with Alkenes **2** and **4** and the Yields of the Adducts **3** and **5**

Experiment	Alkene	T, °C	Time, h	Adduct	Yield of adduct, %*
1	**2a**	65	20	**3a**	48
2	**2a**	120	5	**3a**	97
3	**2b**	93	7	**3b**	77
4	**2b**	120	5	**3b**	97
5	**2c**	120	5	**3c**	96
6	**2d**	155	18	**3d**	42
7	**2e**	150	18	**3e**	35
8	**2f**	150	18	**3f**	50
9	**2g**	175	12	**3g**	35
10	**2h**	175	12	**3h**	30
11	**2i**	175	12	**3i**	74
12	**2j**	170	18	**3j**	71
13	**2k**	120	15	**3k**	42
14	**4a**	78	20	**5a**	83
15	**4b**	120	4	**5b**	73
16	**4c**	190	20	**5c**	50

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* Based on the amount of 1,2,4-triazole **1** used.

TABLE 2. Characteristics of Compounds **3a-j** and **5a-c**

Compound	Empirical formula	Found, % Calculated, %			bp, °C (mm Hg)	^{1}H NMR spectrum ($CDCl_3$), δ, ppm			
		C	H	N		OCHN; R'CH_2N*	Me; RCH_2*	3-H, s	5-H, s
3a	$C_7H_{13}N_3O$	53.86 54.18	8.58 8.44	27.20 27.06	40 (2)	5.52, q	1.65, d	7.89	8.21
3b	$C_8H_{15}N_3O$	56.55 56.78	8.76 8.93	24.77 24.82	60 (2) 73 (1) [9]	5.42, q	1.54, d	7.84	8.13
3c	$C_{11}H_{21}N_3O$	62.55 62.53	9.76 10.02	19.77 19.87	105 (2)	5.50, q	1.65, d	7.89	8.21
3d	$C_{10}H_{11}N_3O$	63.67 63.48	6.00 5.85	22.81 22.23	105 (3)	6.25, q	1.83, d	7.89	8.16
3e	$C_{11}H_{13}N_3O$	65.10 65.01	6.49 6.45	20.92 20.66	140 (1)	6.21, q	1.86, d	7.92	8.15
3f	$C_{11}H_{13}N_3O$	65.20 65.01	6.58 6.45	20.20 20.66	146 (2)	6.26, q	1.85, d	7.93	8.19
3g	$C_{11}H_{13}N_3O_2$	60.90 60.26	6.15 5.97	18.95 19.16	175 (2)	6.13, q	1.91, d	7.94	8.12
3h	$C_{11}H_{13}N_3O_2$	60.20 60.26	6.31 5.97	19.50 19.16	140 (2)	6.28, q	1.88, d	7.93	8.18
3i	$C_{10}H_{10}BrN_3O$	44.92 44.80	3.70 3.76	15.18 15.66	175 (2)	6.25, q	1.91, d	7.94	8.19
3j	$C_{10}H_{10}ClN_3O$	54.15 53.71	4.55 4.50	18.53 18.78	154 (1)	6.27, q	1.86, d	7.93	8.21
3k	$C_6H_9N_3O_2$	46.20 46.45	5.44 5.84	26.96 27.07	83 (3)	6.80, q	1.80, d	7.88	8.22
5a	$C_5H_6N_4$	49.60 49.18	5.08 4.95	45.50 45.86	132 (1)	4.38, t	2.91, t	7.91	8.14
5b	$C_5H_7N_3O_2$	42.80 42.56	5.16 4.99	30.02 29.76	178-179	4.38, t	2.81, t	7.93	8.40
5c	$C_{12}H_{13}N_3O$	66.80 66.96	5.95 6.08	19.17 19.51	163 (2)	5.90, m		7.87	8.09

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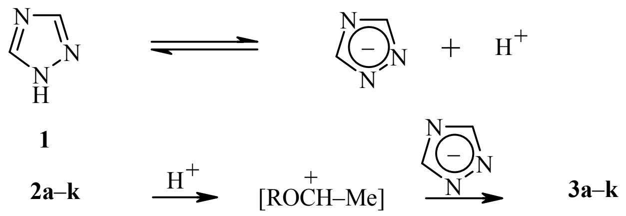
* Proton signals for compounds **5a-c**.

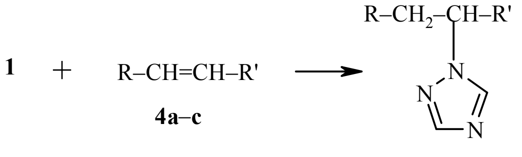
It was shown that vinyl acetate reacted with triazole **1** according to Markovnikov addition scheme to give 1-(1H-1,2,4-triazol-1-yl)ethyl acetate (**3k**). However the reactivity of vinyl acetate is considerably lower than that of alkyl vinyl ethers: under comparable conditions (120°C, 15 h) the yield of compound **3k** was 42% (Table 1, exp. 13, cf. exp. 2).

Electrophilic addition of triazole to vinyl ethers is probably catalyzed by the dissociative formation of a proton from triazole **1** and can be presented as follows:



General acid catalysis by the undissociated triazole molecule is not excluded, since it is a relatively strong acid (pK_a 10) [14].

The electrophilic alkenes **4a-c** reacted with 1,2,4-triazole **1** by nucleophilic addition on heating the reagents to give the anti-Markovnikov adducts **5a-c** (Table 1, exp. 14-16; Table 2).



5a–c

4, 5 a R = CN, R' = H, **b** R = COOH, R' = H, **c** R = Ac, R' = Ph

It should be noted that heating (95-140°C) of 1,2,4-triazole **1** with cyclohexene (a symmetrical alkene with a weakly polarized double bond) or styrene (weakly electrophilic alkene) did not give the expected products. Under these conditions starting triazole and cyclohexene underwent no noticeable change, whereas styrene underwent polymerization. Polystyrene was the sole product formed on heating a mixture of styrene and triazole (90-110°C) in the presence of a catalytic amount of acid (phosphoric or styrylphosphonic acid) or base (10% triton B in methanol).

EXPERIMENTAL

^{1}H NMR spectra of $CDCl_3$ solutions with TMS as internal standard were recorded with a Bruker WP-200 (SY) spectrometer (200 MHz). Mass spectra were obtained with a LKB 2091 GCMS apparatus (ionizing voltage 70 eV, direct inlet). 1,2,4-Triazole **1**, vinyl acetate, acrylonitrile, acrylic acid, and 4-phenyl-3-buten-2-one were commercial products. Alkyl and aryl vinyl ethers were synthesized according to [15] and [13] respectively.

Addition of 1,2,4-Triazole 1 to Alkenes 2 and 4 (General Method). A. (Table 1, experiments 1, 3, 6-14, 16). Mixture of triazole **1** (20 mmol) and alkene **2a-k, 4a,c** (26 mmol) was heated in a sealed ampoule. After cooling, the unreacted triazole **1** was filtered off, the filtrate was fractionated in vacuum, to recover the unreacted alkene, and adducts **3a-k**, **5a** and **5c** were obtained. Mass spectra, *m/z*: 155 [M$^+$] (**3a**); 203 [M$^+$] (**3e,f**); 268 [M$^+$] (**3i**); 223 [M$^+$] (**3j**).

B. (Table 1, experiments 2, 4, 5). Mixture of triazole **1** (20 mmol) and alkyl vinyl ether **2a-c** was heated in a 0.25 l steel rotating autoclave (120°C, 5 h). The homogeneous reaction mixture obtained was distilled in vacuum to recover the excess alkene and to obtain adducts **3a-c**.

1-(1H-1,2,4-Triazol-1-yl)propanoic acid (5b) (Table 1, experiment 15). Mixture of triazole **1** (1.38 g, 20 mmol) and acrylic acid (3.66 g, 26 mmol) was heated (120°C) with stirring for 4 h. The fused mixture produced was dissolved in a small quantity of hot water. A white crystalline precipitate of adduct **5b** deposited on cooling. Mp 178-179°C (mp 175-178 °C [11]).

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