NEW DERIVATIVES OF N-VINYLTRIAZOLES: 1,3-DIARYL-3-(1H-1,2,4-TRIAZOL-1-YL)-2-PROPEN-1-ONES

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We have synthesized previously unknown N-vinyltriazoles: 1, 3-diaryl-3-(1H-1, 2, 4-triazol-1-yl)-2-propen-1-ones. We discuss a hypothesis for a probable reaction mechanism.

Among modern systemic fungicides inhibiting biosynthesis of ergosterol, an important place is occupied by N-vinyltriazoles: 1,3-diaryl-2-(1H-1,2,4-triazol-1-yl)-2-propen-1-ones (I), formed under Knoevenagel reaction conditions from aryl(1H-1,2,4-triazol-1-ylmethyl) ketones and aromatic aldehydes [1]. However, their regioisomers 1,3-diaryl-3-(1H-1,2,4-triazol-1-yl)-2-propen-1-ones (II), which are of interest for studying the structure-activity relation, have been unknown. In this report, we describe a method for obtaining such compounds.

The method involves condensation of the bromination products of the chalcones (IIIa-g) (the chalcone dibromides (IVa-g)) with 1,2,4-triazole in DMSO. We have established that raising the condensation temperature from room temperature up to 130°C and using an excess of 1,2,4-triazole has a positive effect on the yield of this reaction. The products are formed in high yields when the reaction is carried out for ~ 4 h at 110-130°C for a IV:triazole mole ratio equal to 1:10. In addition to DMSO, suitable solvents include THF and dioxane, but using them leads to an increase in the reaction time. Thus in the case of the chalcone dibromide IVb, condensation in boiling dioxane goes to completion within 8 h, while in a DMSO medium the reaction takes 3.5 h.



II--V a $R = R^{1} = H$; b R = 4-Cl, $R^{1} = H$; c R = 4-Cl, $R^{1} = Cl$; d $R^{2} = 2,4$ -Cl₂, $R^{1} = NO_{2}$; e R = H, R¹ = OMe; f R = 4-Cl, $R^{1} = OMe$; g R = 4-Cl, $R^{1} = NO_{2}$

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Com-	Empirical	Found, % Calculated, %			mp, °C	Yield,
pound	formula	с	н	И	•	70
lla	C17H13N3O	74.44	<u>4.54</u> 4.76	<u>15.38</u> 15.26	140142	50
Иb	C17H12CIN3O	<u>66.20</u> 65.92	<u>4.05</u> 3.91	<u>13.75</u> 13,57	176178	72
11 C	C17H11Cl2N3O	<u>59,10</u> 59,32	<u>3.41</u> 3,22	<u>12.05</u> 12,21	205206	96
II d	C17H10Cl2N4O3	<u>52.17</u> 52,46	<u>2.73</u> 2,59	<u>14.68</u> 14,40	155160	85
11e	C ₁₈ H ₁₅ N ₃ O ₂	<u>70.56</u> 70,80	<u>5.08</u> 4,95	<u>13.97</u> 13,76	149151	45
нf	C18H14CIN3O2	<u>63,91</u> 63,63	<u>4.32</u> 4,15	<u>12.11</u> 12,37	124126	48
нg	C17H11ClN4O3	<u>57.48</u> 57,55	<u>3,35</u> 3,13	<u>15.54</u> 15,79	168171	70
IV a	C15H12Br2O	<u>49,22</u> 48,94	<u>3.04</u> 3,29	—	158159	78
IVb	· C15H11Br2ClO	<u>44.51</u> 44,76	<u>2.97</u> 2.76	-	186187	70
1V C	C15H10Br2Cl2O	<u>41.01</u> 41,23	<u>2,16</u> 2,31	-	159160	92
IV d	C15H9Br2Cl2NO3	<u>37,11</u> 37,38	<u>2,01</u> 1,88	-	145147	65
IVe	C ₁₆ H ₁₄ Br ₂ O ₂	<u>48,44</u> 48,27	<u>3.75</u> 3.54	-	140142	58
1V f	C16H13Br2ClO	<u>46.39</u> 46,13	<u>3.40</u> 3,15	-	173175	75
iv g	C ₁₅ H ₁₀ Br ₂ ClNO ₃	<u>40,04</u> 40,26	<u>2.39</u> 2,25	-	161163	68
Va	C ₁₅ H ₁₁ BrO	<u>62.61</u> 62,74	<u>4.03</u> 3,86	-	—	80
Vb	C ₁₅ H ₁₀ BrClO	<u>56.30</u> 56,02	<u>3,31</u> 3,13	-	_	70
vc	C15H9BrCl2O	<u>50,79</u> 50,60	$\frac{2.41}{2.55}$	-	-	65
Ve	$C_{10}H_{13}BrO_2$	$\frac{51.34}{51,13}$	<u>4.40</u> 4,13	-	9293	70
Vf	C ₁₀ H ₁₂ BrClO	$\frac{56,96}{57,26}$	3,41 3,61	-	110112	60

TABLE 1. Characteristics of Synthesized Compounds II, IV, V

The products of the condensation described above are identified as 1,3-diaryl-3-(1H-1,2,4-triazol-1-yl)-2-propen-1-ones IIa-g on the basis of ¹³C NMR spectroscopy. We should note that analysis of the ¹H NMR spectra does not allow us to unambiguously assign structures I or II to the synthesized compounds, since the chemical shifts of the signals from protons in their aryl substituents, the triazole ring, and the vinyl group in the 7.20-7.80 ppm region are very close to the chemical shifts for analogous protons in compounds I [2]. Previously in [3], devoted to the study of the ¹³C NMR spectrum of compounds with structure I and II, we established that the most informative signals for resolving regioisomerism questions are from the $C_{(2)}$ nucleus (structure II) (located in the 114-125 ppm region) and the $C_{(3)}$ nucleus (located in the 141-144 ppm region). In the same paper, we showed that for any regioisomer, the signals from the ¹³C $_{(2)}$ and ¹³C₍₆₎ nuclei of the *E* isomers are upfield from the analogous signals for the *Z* isomers. In the ¹³C NMR spectra we obtained for compounds IIb,d,g, we see a double set of signals from the carbon atoms, suggesting that the compounds are formed as a mixture of *E* and *Z* isomers. Considering the data presented above and the confirmation of the structure of the *E* isomers IIb, d by x-ray diffraction in [4], based on analysis and also measurement of the intensities of the signals in the ¹³C NMR spectra of the vinyltriazoles IIa-f we have determined that compound IId is an ~1:1 mixture of stereoisomers; compounds IIb and IIg are mixtures of 80-85% *E* isomer and 15-20% *Z* isomer; and compounds IIa,c,e,f are *E* isomers ($\geq 95\%$).

Thus, condensation of the chalcone dibromides IVa-g with 1,2,4-triazole leads to regioselective formation of the Nvinyltriazoles IIa-g in the form of E isomers or a mixture of E and Z isomers. Such exclusive formation of the indicated isomers suggests that, in contrast to known reactions of chalcone dibromides [5], the orientation of the condensation under study does not depend on the nature of the R¹ radical. This fact allowed us to hypothesize that synthesis of compounds II is preceded by formation of intermediate a-bromochalcones (5), Michaels addition of 1,2,4-triazole to which, followed by dehydrobromination, leads to the target products II. In order to test our hypothesis, we carried out condensation of the a-bromochalcones Va-c,e,f with 1,2,4-triazole under conditions conducive to formation of N-vinyltriazoles II (DMSO, 110-130°C). In this case, in fact we obtained the N-vinyltriazoles IIa-c,e,f in high yields, which supports the validity of our hypothesis.

The composition of all the synthesized compounds is consistent with elemental analysis data (see Table 1). The structure of chalcone dibromides IVa-g is confirmed by the PMR spectra, in which along with multiplets from methyl group protons in the 7.50-8.40 ppm region we see signals from vicinal protons (CHBr-CHBr) forming an AB system in the 5.69-6.58 ppm region. We synthesized a-bromochalcones Va-c,e,f by dehydrobromination of the corresponding chalcone dibromides IV by triethylamine in dry benzene [6]; these are characterized by mass spectra in which the most intense peaks are for $[M]^+$ and the fragmentary ion $[M-Br]^+$.

EXPERIMENTAL

The ¹H NMR spectra were recorded on a Bruker AC-80 spectrometer (80 MHz) for 2-3% solutions in CDCl₃; internal standard, TMS. The ¹³C NMR spectra were recorded for 10-20% solutions in DMSO-D₆ on Bruker AC-80 and Bruker AM-300 spectrometers at a frequency of 20 and 75.5 MHz respectively. The chemical shifts of the ¹³C nuclei were measured (with full proton decoupling) relative to the internal standard DMSO-D₆ (δ 39.5 ppm). In assigning the signals in the ¹³C NMR spectra recorded using standard multiple-pulse JMODXH and INEPTRD. The mass spectra were recorded on the FINNEGAN MAT-112. The course of the reactions and the purity of the substances were monitored using TLC on Silufol UV-254 plates. The N-vinyltriazoles II and α -bromochalcones V were isolated by preparative TLC on 24 × 24 cm plates (thickness of the adherent layer of adsorbent, 2 mm).

The elemental analysis data for the synthesized compounds II, IV, and V, their melting points and yields are presented in Table 1.

The chalcones IIIa-g were obtained according to the technique in [7]. IIIa. $T_{\rm mp}$ 55-57°C; lit. $T_{\rm mp}$ 57°C [7]. IIIb. $T_{\rm mp}$ 102-103°C; lit. $T_{\rm mp}$ 103-104°C [8]. IIIc. $T_{\rm mp}$ 156-157°C; lit. $T_{\rm mp}$ 156-157°C [9]. IIIe. $T_{\rm mp}$ 77-78°C; lit. $T_{\rm mp}$ 78°C [10]. IIIf. $T_{\rm mp}$ 127-128°C; lit. $T_{\rm mp}$ 128°C [6].

2,4-Dichloro- ω -(**4-nitrobenzylidene**)**acetophenone** (**IIId**). Yield 77%. $T_{\rm mp}$ 154-155°C. Found, %: C 56.18, H 2.70, Cl 22.35, N 4.17. $C_{15}H_9Cl_2NO_3$. Calculated, %: C 55.92, H 2.82, Cl 22.01, N 4.35.

4-Chloro-ω-(4-nitrobenzylidene)acetophenone (IIIg). Yield 64%. T_{mp} 163-164°C. Found, %: C 62.35, H 3.67, Cl 12.65, N 4.73. C₁₅H₁₀ClNO₃. Calculated, %: C 62.62, H 3.50, Cl 12.32, N 4.87.

Chalcone Dibromides (IVa-g) (general technique). 0.1 moles bromine were added dropwise at room temperature with stirring to a solution of 0.1 moles chalcone III in 100-120 ml benzene. The reaction mass was then stirred for 2 h at 20-25°C and afterward the solvent was removed. The products IVa-c, e were isolated by recrystallization of the corresponding residues from benzene; the products IVd, f, g, were obtained similarly by recrystallization from chloroform.

2,3-Dibromo-1,3-diphenyl-1-propanone (IVa). PMR spectrum: 5.78 (1H, AB system, HC(Ph)Br, J = 8.3 Hz), 6.49 (1H, AB system, CH(CO)Br, J = 8.3 Hz), 7.48-8.36 ppm (10H, m, H_{Ar}).

2,3-Dibromo-3-phenyl-1-(4-chlorophenyl)-1-propanone (IVb). PMR spectrum: 5.76 (1H, AB system, HC(Ph)Br, J = 8.3 Hz), 6.50 (1H, AB system, CH(CO)Br, J = 8.3 Hz), 7.42-8.38 ppm (9H, m, H_{Ar}).

2,3-Dibromo-1,3-di(4-chlorophenyl)1-propanone (IVc). PMR spectrum: 5.81 (1H, AB system, HC(Ph)Br, J = 8.3 Hz), 6.52 (1H, AB system, CH(CO)Br, J = 8.3 Hz), 7.45-8.37 ppm (8H, m, H_{Ar}).

2,3-Dibromo-3-(4-methoxyphenyl)-1-phenyl-1-propanone (IVe). PMR spectrum: 3.96 (3H, s, OCH₃), 5.79 (1H, AB system, HC(Ph)Br, J = 8.3 Hz), 6.48 (1H, AB system, CH(CO)Br, J = 8.3 Hz), 5.96-7.07 (2H, m, HC₍₁₄₎, HC₍₁₆₎), 7.56-7.78 (5H, m, H_{Ar}), 8.23-8.36 ppm (2H, m, HC₍₁₃₎, HC₍₁₇₎).

1,3-Diaryl-3-(1H-1,2,4-triazol-1-yl)2-propen-1-ones (IIa-g) (general technique). A solution of 0.01 moles chalcone dibromide IV and 0.1 moles 1,2,4-triazole in 50 ml DMSO was held for 3.5-4 h at 110-130 °C, then cooled down to room temperature, decanted into 500 ml water, and extracted with benzene (4 × 100 ml). The benzene extract was washed with water and then dried with Na₂SO₄. The N-vinyltriazoles IIa-g were isolated by chromatography (Silpearl, 3:2 ethylacetate-hexane) from the residues after removal of the benzene.

E,*Z*-3-(1H-1,2,4-Triazol-1-yl)-3-phenyl-1-(4-chlorophenyl)2-propen-1-one (IIb). ¹³C NMR spectrum: *E* isomer (80-85%): 188.7 ($C_{(1)}$), 115.4 ($C_{(2)}$), 145.3 ($C_{(3)}$), 152.9 ($C_{(4)}$), 145.0 ($C_{(5)}$), 131.9 ($C_{(6)}$), 128.5 ($C_{(7)}$, $C_{(14)}$), 128.9 ($C_{(8)}$, $C_{(10)}$),

130.2 (C₍₉₎), 128.9 (C₁₀₎), 136.2 (C₍₁₂₎), 130.3 (C₍₁₃₎), 129.8 (C₍₁₄₎), 138.6 (C₍₁₅₎), 129.8 (C₍₁₆₎), 130.3 (C₍₁₇₎); Z isomer (15-20%): 188.3 (C₍₁₎), 119.9 (C₍₂₎), 143.3 (C₍₃₎), 152.2 (C₍₄₎), 146.5 (C₍₅₎), 135.6 (C₍₆₎), 127.6 (C₍₇₎, C₍₁₁₎), 128.8 (C₍₈₎, C₍₁₀₎), 131.4 (C₍₉₎), 134.3 (C₍₁₂₎), 130.4 (C₍₁₃₎), 128.9 (C₍₁₄₎), 138.5 (C₍₁₅₎), 128.9 (C₍₁₆₎), 130.4 (C₍₁₇₎).

E-3-(1H-1,2,4-Triazol-1-yl)-1,3-di(4-chlorophenyl)2-propen-1-one (IIc). ¹³C NMR spectrum: 187.7 ($C_{(1)}$), 114.9 ($C_{(2)}$), 144.5 ($C_{(3)}$), 152.6 ($C_{(4)}$), 144.8 ($C_{(5)}$), 135.1 ($C_{(6)}$), 128.3 ($C_{(7)}$), 130.1 ($C_{(8)}$), 133.0 ($C_{(9)}$), 130.1 ($C_{(10)}$), 128.3 ($C_{(11)}$), 135.9 ($C_{(12)}$), 131.4 ($C_{(13)}$), 128.6 ($C_{(14)}$), 138.5 ($C_{(15)}$), 128.4 ($C_{(16)}$), 130.0 ($C_{(17)}$).

E- and *Z*-3-(4-Nitrophenyl)-3-(1H-1,2,4-triazol-1-yl)-1-(2,4-dichlorophenyl)-2-propen-1-one (IId). ¹³C NMR spectrum, *E* isomer (50%): 189.7 ($C_{(1)}$), 117.7 ($C_{(2)}$), 144.7 ($C_{(3)}$), 153.2 ($C_{(4)}$), 145.7 ($C_{(5)}$), 136.8 ($C_{(6)}$), 131.5 ($C_{(7)}$, $C_{(11)}$), 123.4 ($C_{(8)}$, $C_{(10)}$), 148.2 ($C_{(9)}$), 136.6 ($C_{(12)}$), 136.9 ($C_{(13)}$), 129.7 (C_{14}), 137.8 ($C_{(15)}$), 127.5 ($C_{(16)}$), 131.6 ($C_{(17)}$); *Z* isomer (50%): 189.0 ($C_{(1)}$), 124.8 ($C_{(2)}$), 141.0 ($C_{(3)}$), 152.6 ($C_{(4)}$), 146.7 ($C_{(5)}$), 139.9 ($C_{(6)}$), 129.1 ($C_{(7)}$, $C_{(11)}$), 123.9 ($C_{(8)}$, $C_{(10)}$), 148.6 ($C_{(9)}$), 132.2 ($C_{(12)}$), 135.3 ($C_{(13)}$), 130.2 ($C_{(14)}$), 136.8 ($C_{(15)}$), 127.3 ($C_{(16)}$), 131.9 ($C_{(17)}$).

E- and Z-3-(4-Methoxyphenyl)-3-(1H-1,2,4-triazol-1-yl)-1-(4-chlorophenyl)-2-propen-1-one (IIf). ¹³C NMR spectrum: 187.6 (C₍₁₎), 117.1 (C₍₂₎), 145.3 (C₍₃₎), 151.7 (C₍₄₎), 146.1 (C₍₅₎), 126.6 (C₍₆₎), 129.3 (C₍₇₎, C₍₁₁₎), 114.2 (C₍₈₎, C₍₁₀₎), 161.7 (C₍₉₎), 135.9 (C₍₁₂₎), 130.0 (C₍₁₃₎), 128.4 (C₍₁₄₎), 138.3 (C₍₁₅₎), 128.4 (C₍₁₆₎), 130.0 (C₍₁₇₎).

E- and *Z*-3-(4-Nitrophenyl)-3-(1H-1,2,4-triazol-1-yl)-1-(4-chlorophenyl)-2-propen-1-one (IIg). ¹³C NMR spectrum, *E* isomer (80-85%): 188.5 (C₍₁₎), 115.9 (C₍₂₎), 144.4 (C₍₃₎), 152.3 (C₍₄₎), 145.6 (C₍₅₎), 136.0 (C₍₆₎), 131.4 (C₍₇₎, C₍₁₁₎), 123.6 (C₍₈₎, C₍₁₀₎), 148.2 (C₍₉₎), 135.3 (C₍₁₂₎), 130.3 (C₍₁₃₎), 129.1 (C₍₁₄₎), 139.0 (C₍₁₅₎), 129.1 (C₍₁₆₎), 130.5 (C₍₁₇₎); *Z* isomer (10-15%): 188.6 (C₍₁₎), 124.2 (C₍₂₎), 140.4 (C₍₃₎), 151.3 (C₍₄₎), 146.9 (C₍₅₎), 140.9 (C₍₆₎), 129.2 (C₍₇₎, C₍₁₁₎), 124.0 (C₍₈₎, C₍₁₀₎), 148.7 (C₍₉₎), 138.9 (C₍₁₂₎), 130.6 (C₍₁₃₎), 129.0 (C₍₁₄₎), 138.0 (C₍₁₅₎), 129.0 (C₍₁₆₎), 130.6 (C₍₁₇₎).

a-Bromochalcones (Va-c,e,f) (general technique). A solution of 0.04 moles triethylamine in 5 ml absolute benzene was added to a solution of 0.01 moles chalcone dibromide IVa-c,e,f in 30 ml absolute benzene and the mixture obtained was stirred for 24 h at room temperature. The precipitate of triethylamine hydrobromide formed was filtered off and the filtrate was evaporated under vacuum; the residue was chromatographed (SiO₂; eluent, benzene), isolating the products Va-c,e,f.

2-Bromo-1,3-diphenyl-2-propen-1-one (Va). Mass spectrum, m/z: 288 [M]⁺, 209 [M-Br]⁺.

2-Bromo-3-phenyl-1-(4-chlorophenyl)-2-propen-1-one (Vb). ¹³C NMR spectrum: 190.5 ($C_{(1)}$), 121.9 ($C_{(2)}$), 142.5 ($C_{(3)}$), 133.3 ($C_{(6)}$), 128.6 ($C_{(7)}$, $C_{(11)}$), 128.9 ($C_{(8)}$, $C_{(10)}$), 130.6 ($C_{(9)}$), 134.8 ($C_{(12)}$), 131.2 ($C_{(13)}$), 130.4 ($C_{(14)}$), 139.1 ($C_{(15)}$), 130.4 ($C_{(16)}$), 131.2 ($C_{(17)}$). Mass spectrum, *m/z*: 320 [M]⁺, 241 [M-Br]⁺.

2-Bromo-1,3-di(4-chlorophenyl)-2-propen-1-one (Vc). Mass spectrum, m/z: 354 [M]⁺, 275 [M-Br]⁺.

2-Bromo-3-(4-methoxyphenyl)-1-phenyl-2-propen-1-one (Ve). Mass spectrum, m/z: 316 [M]⁺, 237 [M-Br]⁺. **2-Bromo-3-(4-methoxyphenyl)-1-(4-chlorophenyl)-2-propen-1-one (Vf).** Mass spectrum m/z: 350 [M]⁺, 27f

 $[M - Br]^+$.

By means of condensation of compounds Va-c,e,f with 1,2,4-triazole under the conditions described for the analogous reaction of the chalcone dibromides IV, we synthesized the vinyltriazoles IIa-c,e,f in 71, 80, 90, 75, and 86% yields respectively. The samples of the indicated compounds II obtained by different methods were identical (T_{mp} , TLC).

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