

CYCLIZATION OF ISOTHIOSEMICARBAZONES. II.
PREPARATION AND STRUCTURE OF N-ISOPROPENYL-1,2,4-TRIAZOLES.

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In the course of a study¹⁾ on the preparation of 1-arylideneamino- or alkylideneamino-2-mercapto-4-aryl-1H-imidazole derivatives by the condensation of an aldehyde isothiosemicarbazone with an aromatic α -haloketone, substitution of haloacetone for aromatic ones was complicated by the competitive formation of an isomeric cyclized product. On the basis of the spectral data, the elemental analyses, and the chemical behavior, the isomer has been found to be an N-isopropenyl-1,2,4-triazole. In the area of triazole chemistry there are few examples of N-alkenyltriazoles. This paper describes the preparation and structure of a new series of 3,5-disubstituted N-isopropenyl-1,2,4-triazoles obtained from the cyclization of aldehyde isothiosemicarbazones (Scheme 1).

When two moles of I were heated with one mole of bromo- or chloroacetone in ethanolic solution at different temperatures for a sufficient period of time to complete the reaction (1 to 72 hours), a pair of cyclized products²⁾ formed in the ratios shown in Table 1:

Table 1. Imidazole/Triazole Ratios.³⁾

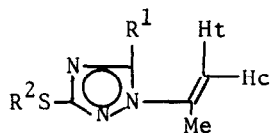
<u>Haloacetone</u>	<u>100</u>	<u>80</u>	<u>60</u>	<u>40(°C)</u>
BrCH ₂ Ac	76/24	65/35	57/43	54/45
ClCH ₂ Ac	27/73	27/73	25/75	22/78

The use of bromoacetone and a higher temperature apparently favored the formation of imidazole but, under these conditions, side reactions occurred which lowered the total yield of heterocycles. The reaction of I with bromoacetone in an equimolar proportion in acetonitrile in the presence of sodium hydrogencarbonate afforded III as a sole cyclized product, and with chloroacetone no reaction occurred. This method was not adapted for preparative purpose because a consider-

able amount of I, from which III could be separated with difficulty, was invariably remained unreacted. On the other hand, the triazole formation was favored in acidic media and, when the reaction was conducted in acetic acid, II was the only heterocycle. Table 2 lists the yields and some properties of II prepared by heating I with chloroacetone in a molar ratio of 1 : 1.2 in glacial acetic acid in the presence of sodium acetate at 60°C for 24 hours. All the yields are based on a homogeneous fraction obtained by means of column chromatography on silica gel using a benzene-ethanol mixture (99 : 1 by volume) as an eluent.

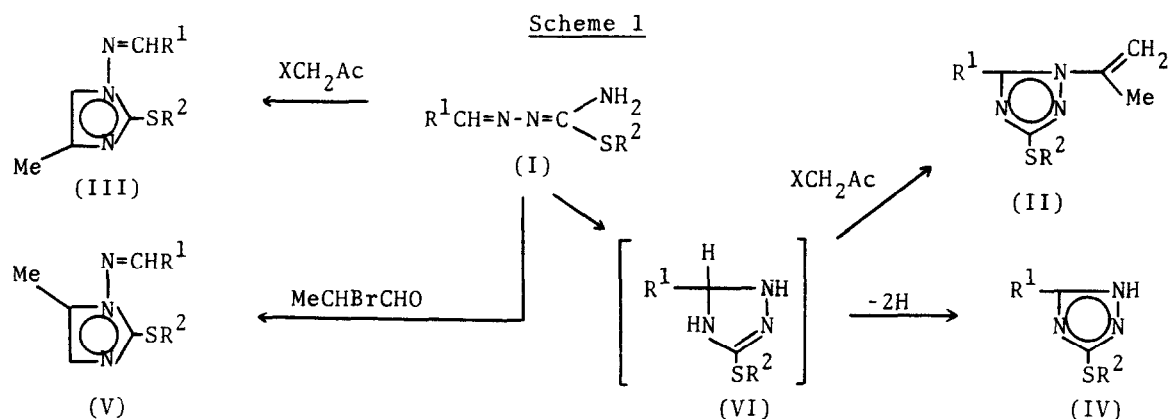
The triazole II_f reacted rapidly with bromine in moist ethyl ether to afford IV_f and bromoacetone, suggesting a 1,2,4-triazole structure having an isopropenyl group attached to one of the nitrogen atoms. All the triazoles II showed a

Table 2.



Compd*	Yield(%)	Mp, °C ^{b)}	ir(CCl ₄)		¹ H nmr(CDCl ₃) ^{a)}			
			νC=C, cm ⁻¹	SCH ₂	SCH ₃	=CCH ₃ ^{c)}	Hc ^{d)}	Ht ^{e)}
IIa	71	73-74	1653	-	2.63	2.19	5.00	5.13
IIb	30 ^{f)}	.g)	1655	-	2.63	2.19	4.68	4.82
IIc	68 ^{f)}	83.5-85	1656	-	2.62	2.19	5.00	5.15
IId	44 ^{h)}	100-101	1659	-	2.63	2.25	5.32	5.42
IIe	71	190-192 ⁱ⁾	1656	-	2.62	2.17	4.68	4.76
II _f	63	83	1655	-	2.61	2.18	5.06	5.16
IIg	70	143 ⁱ⁾	1655	3.82 ^{j)}	-	2.19	5.04	5.15
IIh	65	155.5-156 ⁱ⁾	1658	4.40	-	2.16	4.98	5.09
IIi	70	76	1657	4.39	-	2.15	5.01	5.12
IIj	33 ^{k)}	111-112 ⁱ⁾	1655	-	2.58	2.19	5.01	5.18

a) The figures are δ values in ppm from internal TMS. b) Uncorrected. c) A double doublet (J=0.6 and 1.3 Hz). d) A quartet (J=0.6 Hz). e) A quartet (J=1.3 Hz). f) Heated for 48 hours. g) Crystallization of either the free base or the perchlorate was unsuccessful. h) Heated for 30 hours. i) Perchlorate. j) A double triplet (J=1.0 and 6.5 Hz). k) Prepared by heating in ethanolic solution. * Gave satisfactory elemental analyses.



[X: Br or Cl; a: (R^1 and R^2 given) C_6H_5 , CH_3 ; b: o - ClC_6H_4 , CH_3 ; c: p - ClC_6H_4 , CH_3 ; d: o - HOC_6H_4 , CH_3 ; e: o - $CH_3OC_6H_4$, CH_3 ; f: p - $CH_3OC_6H_4$, CH_3 ; g: p - $CH_3OC_6H_4$, $CH_2=CHCH_2$; h: C_6H_5 , $C_6H_5CH_2$; i: p - $CH_3OC_6H_4$, $C_6H_5CH_2$; j: n - C_3H_7 , CH_3]

strong band near 1655 cm^{-1} ($\nu_{C=C}$) and an ABX_3 splitting pattern arising from the isopropenyl moiety (Table 2). The vinylic proton resonances for IIb and IIe exhibited an upfield shift of 0.32-0.40 ppm relative to those for IIc and II f, respectively. These facts can be rationalized as a result of anisotropic shielding by the phenyl ring twisted and faced toward the vinylic protons due to the steric repulsion between the ortho-substituent and the isopropenyl group. This explanation was confirmed by the spectra of II d which exhibited the most deshielded values for the vinylic protons. Two aromatic rings in II d should be coplanar as evidenced by the internally bonded O-H band (centered at 3040 cm^{-1} at a concentration of 10^{-3} M in carbon tetrachloride), and therefore the vinylic protons of II d are not affected by the ring current of o -hydroxyphenyl group. Furthermore, only a weak anisotropic deshielding effect (0.21 ppm) was observed for the ortho-protons of the phenyl ring in II a compared with that of IV a (0.57 ppm), indicating a smaller degree of coplanarity of the two aromatic rings.⁴⁾

In the uv spectra (methanol), introduction of an isopropenyl group into the triazole ring of IV f [λ_{max} 250 (18,600) and 266 (20,100) nm] and displacement of the methoxyl group from para in II f [λ_{max} 247 (16,800) and 279 (10,400) nm] to ortho in II e [λ_{max} 241 (9,800) and 284 (5,200) nm] on the benzene ring caused progressive decrease in intensity and separation of the two main bands. These observations can also be explained in terms of steric inhibition of coplanarity or resonance between the aromatic rings. Consequently the isopropenyl group of II must

locate at the adjacent positions to R¹ on the triazole ring, i.e., at N-1 or N-4. That no shielding effect was observed for the methyl protons of isopropenyl group might be due to the preferred conformation resulting from n- π electron repulsion between the lone-pair of N-2 and the electron cloud around the ethylenic double bond of isopropenyl group. Thus the isopropenyl group should attach at the 1-position. The 1,3,5-trisubstituted 1H-1,2,4-triazole structure was further confirmed by the unambiguous synthesis⁵⁾ of the reduced compound of IIf, 1-isopropyl-3-methylthio-5-p-methoxyphenyl-1H-1,2,4-triazole [mp 97-98°C; ¹H nmr (CDCl₃, δ ppm from internal TMS): 1.50, d, HC(CH₃)₂, J=6.4 Hz; 2.62, s, SCH₃; 3.85, s, OCH₃; 4.60, m, HC(CH₃)₂, J=6.4 Hz; 6.99, d, p-methoxyphenyl protons, J=9.0 Hz; 7.51, d, p-methoxyphenyl protons, J=9.0 Hz; M⁺= 263], which was obtained by reducing IIf with anhydrous hydrazine in absolute ethanol. No rearrangement was detected during the reduction. The triazole formation may involve an intermediate VI formed by intramolecular addition of the terminal NH₂ to the aldimine double bond by analogy with oxidative cyclization of thiosemicarbazone.⁶⁾ In a few cases, IV has been isolated which may be formed from VI through autoxidation. The assignment of 4-methyl structure to III is based upon the observation of the difference in behavior toward Eu(dpm)₃ by III and the isomer V (Table 3), the latter being prepared by the reaction of I with dl- α -bromopropionaldehyde (Scheme 1). The magnitude of the chemical shifts brought about by addition of the shift reagent were consistent with the assigned structure.

Table 3. Eu-Induced Chemical Shifts of Imidazoles (δ ppm from internal TMS).

Compd	SCH ₃	H-5	Compd	SCH ₃	H-4
IIIa	2.65(-0.02)	7.15(-0.05)	Va	3.57(-1.02)	7.91(-1.13)
IIIb	3.23(-0.48)	7.61(-0.43)	Vb	4.13(-1.55)	8.25(-1.47)
IIIc	3.09(-0.48)	7.42(-0.34)	Vc	3.78(-1.22)	8.05(-1.26)
IIIe	2.85(-0.22)	7.27(-0.12)	Ve	3.35(-0.80)	7.54(-0.78)
IIIf	2.89(-0.28)	7.25(-0.18)	Vf	3.61(-1.09)	7.90(-1.14)

REFERENCES AND NOTES

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- 2) Ij gave only IIj under such conditions.
- 3) The figures are averages of two or three experiments.
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