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ISOXAZOLES—XV

CONVERSION OF N-(5-METHYL-3-ISOXAZOLYL)-N'-ARYLFORMAMIDINES INTO 1-ARYL-3-ACETONYL-1,2,4,-TRIAZOLES

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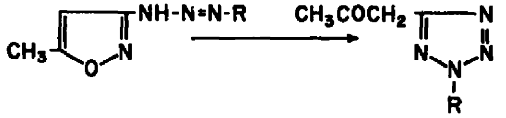
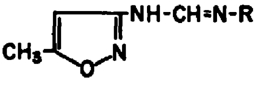
Abstract—A new base-induced conversion of N-(5-methyl-3-isoxazolyl)-N-arylformamidines (IIIa–e) into 1-aryl-3-acetonyl-1,2,4-triazoles (IVa–e) has been explored. The relevant 1-aryl-3-triazolecarboxylic acids (Va–e) and some of their derivatives have been prepared.

IN THE foregoing paper of this series,[1] we have shown that 3-diazoaminoisoxazoles (I) undergo a new type of base-induced isomerization to 2-substituted 5-acetonyltetrazoles (II).

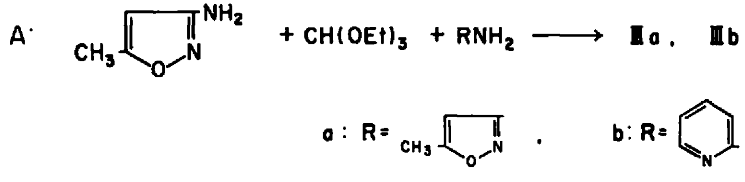


I II



III

In an effort to disclose further reactions of this type, our attention was directed to N-(5-methyl-3-isoxazolyl)-N'-arylformamidine (III), which involves a system having a —NH—CH=N— group in place of the —NH—N=N— group in I. The syntheses of the compounds III were accomplished by the following two routes (A and B) suitable to each product.



$$\text{B:}\quad \text{IIIa} + RNH_2 \xrightarrow{\Delta} \text{IIIc, IIId, IIIe,}$$

c: $R = C_6H_5$, d: $R = p\text{-MeO-}C_6H_4$, e: $R = m\text{-Cl-}C_6H_4$

The formamidines (IIIa–e) were readily converted to the corresponding isomers (IVa–e) in high yields by a short period of heating with ethanolic sodium ethoxide. The use of aqueous sodium hydroxide in place of sodium ethoxide decreased the

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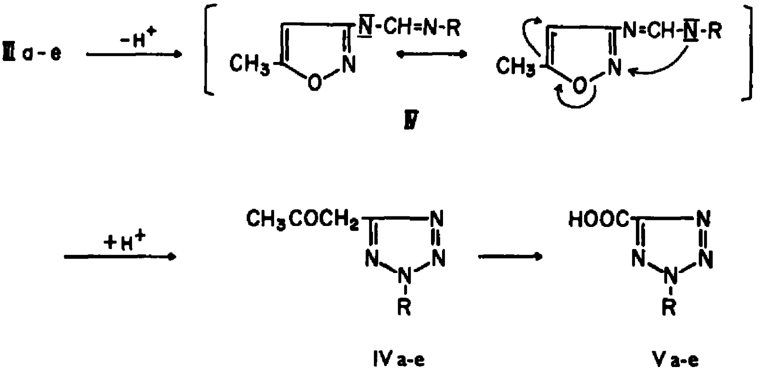
[1] H. Kano and E. Yamazaki, *Tetrahedron* p. 461 (this issue).

yields of IVa–e owing to hydrolysis of the formamidines. Heating of IIIa–e at the melting point for 30 minutes also gave IVa–e. By the analogy between the reaction of this series and that of the compound I, the structures of these products can be deduced as 1-aryl-3-acetonyl-1,2,4-triazoles. The IR spectra of IVa-e exhibited the characteristic carbonyl bands in region 1715–1730 cm^{-1}, and actually the presence of a ketone group in IVa was confirmed by the formation of the oxime of IVa.



Oxidation of IVa–e with potassium permanganate yielded the corresponding carboxylic acids (Va–e). Vc and its methyl ester were identical with the samples prepared by the method of Bladin.[2] Moreover, further oxidation of Va with potassium permanganate gave the known 1,2,4-triazole-3-carboxylic acid (VI), which was identified by comparison with an authentic sample prepared by the method of Jones and Anisworth.[3] From these results the triazole structure assigned to IVa–e was confirmed.

The base-induced conversion of this series can be accounted for by the same mechanism as proposed in the series of the compound I, involving initial formation of the hybrid anion (IV). While the heat-induced conversion which occurred only in this series seems to follow another mechanism; initial rupture of the N—O bond of the isoxazole ring followed by recyclization into the triazoles.

EXPERIMENTAL

M.ps were determined on a Kofler-Block "Monoscope IV" and are uncorrected, UV absorption spectra were recorded on a Hitachi Recording UV Spectrophotometer EPS-2, and IR spectra were taken on a Ko-ken IR Spectrophotometer, Model DS-301.

N,N′-*bis(5-methyl-3-isoxazolyl)formamidine* (IIIa)

A mixture of 12 g 5-methyl-3-aminoisoxazole and 9 g $HC(OC_2H_5)_3$ was heated on a water bath for 1 hr. After cooling, the precipitate was filtered and washed with water. Recrystallization from aqueous ethanol gave white prisms, yield 8·9 g, m.p. 177–179·5°, λ_{max}^{EtOH} 267 mμ (log 4·26), $\nu_{max}^{CHCl_3}$ 3350 cm^{-1} (—NH—), 1650 cm^{-1} (—CH=N—). (Found: C, 52·63; H, 5·17; N, 27·21; $C_9H_{10}O_2N_4$ requires: C, 52·42; H, 4·89; N, 27·17%).

N-(2-*pyridyl*)-N′-(5-*methyl*-3-*isoxazolyl*)-*formamidine* (IIIb)

A mixture of 10 g 5-methyl-3-aminoisoxazole, 10 g 2-aminopyridine and 15 g $HC(OC_2H_5)_3$ was heated in an oil bath at 110–120° for 5 hr. After cooling, 50 ml water was added to the reaction mixture, which precipitated a solid (6 g) on standing for several hr. Recrystallization from dil.

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[2] J. A. Bladin, *Chem. Ber.* 23, 3789 (1890).
[3] R. G. Jones and C. Anisworth, *J. Amer. Chem. Soc.* 77, 1539 (1955).

ethanol gave prisms, m.p. 145°, λ_{max}^{EtOH} 216·5 mμ (log ε 4·28), 303 mμ (log ε 4·28), $\nu_{max}^{CHCl_3}$ 3247 cm^{-1} (—NH—), 1646 cm^{-1} (—CH=N—). (Found: C, 59·02; H, 4·96; N, 27·51; $C_{10}H_{10}ON_4$ requires: C, 59·39; H, 4·98; N, 27·71%).

N-*phenyl*-N′-(*5-methyl-3-isoxazolyl*)-*formamidine* (IIIc)

A mixture of 21 g IIIa and 21 g aniline was heated at 100–110° for 10 min. After cooling, the reaction mixture was treated with 60 ml 5% ethanol to yield 18·5 g crude IIIc. Recrystallization from ethanol gave colorless plates, m.p. 154–155·5°, λ_{max}^{EtOH} 278 mμ (log ε 4·29), $\nu_{max}^{CHCl_3}$ 3238 cm^{-1} (—NH—), 1645·5 cm^{-1} (—CH=N—). (Found: C, 66·20; H, 5·54; N, 20·84; $C_{11}H_{11}ON_3$ requires: C, 65·67; H, 5·51; N, 20·88%).

N-p-*methoxyphenyl*-N′-(*5-methyl-3-isoxazolyl*)-*formamidine* (IIId)

A mixture of 3·1 g IIIa and 1·3 g *p*-anisidine was heated until a transparent solution was obtained (at 100–110°). After cooling, the reaction mixture was treated with 50% ethanol and the resulting precipitate (2·1 g) was recrystallized from acetone to give colorless plates, m.p. 130–131°, λ_{max}^{EtOH} 287 (log ε 4·35). (Found: C, 61·94; H, 5·86; N, 17·87; $C_{12}H_{13}O_2N_3$ requires: C, 62·32; H, 5·86; N, 17·87%).

N-m-*chlorophenyl*-N′-(*5-methyl-3-isoxazolyl*)-*formamidine* (IIIe)

A mixture of 2·1 g IIIa and 4·3 g *m*-chloroaniline in 10 ml ethanol was refluxed for 1 hr. After cooling, the resulting precipitate was recrystallized from dil. ethanol to give colorless crystals (1·3 g), m.p. 138–139°. (Found: C, 56·11; H, 4·34; N, 14·60; Cl, 15·07; $C_{11}H_{10}ON_3Cl$ requires: C, 56·05; H, 4·28; N, 17·82; Cl, 14·60%).

Conversion of N-*aryl*-N′-(*5-methyl-3-isoxazolyl*)-*formamidines* (IIIa–e) *into 1-substituted 3-acetonyl*-1,2,4-*triazoles* (IVa–e)

As a typical procedure, the conversion of IIIa was carried out as follows.

(A) A solution of 21 g of IIIa in 100 ml of alcohol containing 6·8 g sodium ethoxide was heated on a water bath for about 20 min. An exothermic reaction occurred and the sodium salt of IVa precipitated. The reaction mixture diluted with 100 ml water was acidified with 10% acetic acid. The acidified reaction mixture was extracted with $CHCl_3$ and the chloroform extract was dried over Na_2SO_4. Removal of the solvent left 3-acetonyl-1,2,4 triazole IVa in good yield.

The triazoles (IVa–e) obtained by this procedure are listed in Table 1.

(B) A solution of 9·7 g IIIa in 20 ml 10% NaOHaq. was heated on a water bath for 5 min. After cooling, the solution was acidified with acetic acid to give 3 g IVa (31%). The mother liquor, after being basified with NaOHaq., was extracted with $CHCl_3$. The chloroform extract was dried, and evaporated to leave 2·4 g 5-methyl-3-aminoisoxazole.

(C) After heating 1 g IIIa over its m.p. for 30 min, the resulting solid was treated with dil. ethanol to give 0·6 g IVa, which was proved to be identical with the sample prepared by the method A.

Oxime of IVa

To a solution of 0·25 g IVa in 5 ml ethanol, 0·1 g $NH_2OH{\cdot}HCl$ and 1·4 ml 10% Na_2CO_3 were added. The mixture was heated on a water bath for 5 min. Most of the solvent was evaporated to yield a solid (0·25 g). Recrystallization from water gave colorless crystals, m.p. 150–153°. (Found: C, 49·34; H, 5·29; N, 30·98; $C_9H_{11}O_2N_5$ requires: C, 48·86; H, 5·01; N, 31·66%).

1-*Substituted*-1,2,4-*triazole-3-carboxylic acids* (Va–e)

To a solution of 0·01 mole (IVa, b, c, d, or e) in 40 ml 50% aqueous acetone, 0·02 mole $KMnO_4$ was added portionwise at 50–55° with stirring. Heating and stirring were continued until the color of permanganate had disappeared, and the resulting hot mixture was filtered. After evaporation of most of the acetone, the solution was acidified with 10% HCl to yield the carboxylic acid (Va, b, c, d, or e). The product Vc and its methyl ester (m.p. 116–117·5°) were identical with the samples prepared by the method of Bladin.[8]

TABLE 1. 3-ACETONYLTRIAZOLES

Comp.	1-Substituent	Molecular formula	Recrystallization solvent and shape of crystals	Yield (%)	M.P.	Analysis					
						Found %			Required		
						C	H	N	C	H	N
IVa	5-Methyl-3-isoxazolyl	$C_9H_{10}O_2N_4$	ethanol: white plates	83	138–140°	52·79	4·96	27·26	52·42	4·89	27·17
IVb	2-Pyridyl	$C_{10}H_{10}ON_4$	water: colorless plates	88	118–120°	59·13	5·08	27·29	59·39	4·98	27·71
IVc	Phenyl	$C_{11}H_{11}ON_3$	pet. benzine: colorless plates	76	80–81°	65·39	5·67	20·71	65·67	5·51	20·88
IVd	*p*-Methoxyphenyl	$C_{12}H_{13}O_2N_3$	pet. benzine: colorless plates	90	86·5°	62·05	5·85	18·21	62·32	5·67	18·17
IVe	*m*-Chlorophenyl	$C_{11}H_{10}ON_3Cl$	ligroin: colorless plates	100	73°	55·60	4·58	18·39	56·05	4·28	17·82

TABLE 2. 5-TRIAZOLECARBOXYLIC ACIDS

Comp.	1-Substituent	Molecular formula	Recrystallization solvent and shape of crystals	Yield (%)	M.P.	Analysis					
						Found %			Required %		
						C	H	N	C	H	N
Va	5-Methyl-3-isoxazolyl	$C_7H_6O_3N_4$	ethanol-water: pale yellow pillars	70	201·5–202° (dec.)	43·64	3·27	28·58	43·30	3·12	28·86
Vb	2-Pyridyl	$C_8H_6O_2N_4$	ethanol-water: pale yellow pillars	72	207° (dec.)	50·54	3·33	28·89	50·53	3·18	29·47
Vc	Phenyl	$C_9H_7O_2N_3$	water: colorless plates	54	181–182° (dec.)	56·85	3·76	21·85	57·14	3·73	22·21
Vd	*p*-Methoxy-phenyl	$C_{10}H_9O_3N_3$	ethanol-water: colorless plates	78	184–185° (dec.)	54·97	4·30	19·10	54·79	4·14	19·17
Ve	*m*-Chloro-phenyl	$C_9H_6O_2N_3Cl$	water: colorless plates	60	181–182° (dec.)	56·85	3·76	21·85	57·14	3·73	22·21

1,2,4-*Triazole*-3-*carboxylic acid* (VI)

To a solution of 1 g Va in 100 ml water, 2·6 g $KMnO_4$ was added at 60–70° with stirring. Heating and stirring were continued until the color of permanganate had disappeared (about 5·5 hr). The resulting reaction mixture was filtered, concentrated and acidified with HCl to precipitate VI (0·3 g). Recrystallization from water gave colorless crystals, m.p. 135° (dec.). (Found: C, 31·84; H, 3·77; N, 36·90; Calc. for $C_3H_3ON_3$: C, 31·86; H, 3·67; N, 37·16%). This product was identical with a sample prepared by the method of Jones *et al.* by comparison of their IR spectra.

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