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# STUDIES IN THE ISOXAZOLE SERIES.

## 36.* CONDENSATION OF 4-ARYLAZO-5-METHYLISOXAZOLES WITH AROMATIC ALDEHYDES

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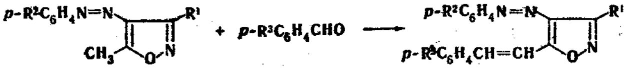
UDC 547.786:542.953

The introduction of electron-accepting substituents into position 4 of isoxazole activates the methyl group on the $C_{(5)}$ atom in aldol condensation–crotonization reactions. As a result, 5-methylisoxazoles containing nitro [2-4], benzoyl, and cyano [5] groups can be condensed with benzaldehyde; moreover in 3,5-dimethylisoxazole derivatives condensation takes place selectively at 5-methyl group [2, 5]. The phenylazo group has not been demonstrated to have this effect in isoxazole, although instances have been described in the aromatic series [6, 7].

Despite the roughly identical chemical shifts of the 5-methyl protons in the PMR spectra of 4-phenylazo- and 4-nitro-3,5-dimethylisoxazoles, deuterium exchange at the 5-$CH_3$ group of the 4-nitro derivative proceeds much more rapidly than in the 4-phenylazo compound [8]. We have found that 4-phenylazo-5-methylisoxazoles also condense with aromatic aldehyde in the presence of a stronger base (KOH instead of piperidine) and that the reaction takes place selectively at the 5-$CH_3$ group.



I II III

I, III a–f $R^3=H$; a $R^1=CH_3$, $R^2=H$; b $R^1=R^2=CH_3$; c $R^1=CH_3$, $R^2=OCH_3$; d $R^1=CH_3$, $R^2=Br$; e $R^1=C_6H_5$, $R^2=H$; f $R^1=CH_3$, $R^2=NO_2$; II, III g–k $R^1=CH_3$; g $R^2=H$, $R^3=NO_2$; h $R^2=NO_2$, $R^3=NO_2$; j $R^2=H$, $R^3=N(CH_3)_2$; k $R^2=NO_2$, $R^3=N(CH_3)_2$

The UV spectra of the synthetic 5-styryl-3-methyl-4-phenylazoisoxazole (IIIa)-(IIId), (IIIf)-(IIIk) resemble that of 5-styryl-3-phenyl-4-phenylazoxazole (IIIe) (Table 1). In the PMR spectra of compounds (III) the

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*For communication 35 see [1].

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TABLE 1. 3-$R^1$-4-Arylazo-5-styrylisoxazoles (III)

| Compounds (III) | mp, °C | UV spectrum, $\lambda_{max}$, nm (log ε) | Found, % | | | Formula | Calculated, % | | | Yield, % |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | C | H | N | | C | H | N | |
| a | 104—105 | 291 (4,40); 368 (4,41) | 74,8 | 5,1 | — | $C_{18}H_{15}N_3O$ | 74,7 | 5,2 | — | 90 |
| b | 127—128 | 296 (4,44); 372 (4,45) | 75,4 | 5,7 | 13,8 | $C_{19}H_{17}N_3O$ | 75,2 | 5,7 | 13,8 | 95 |
| c | 138—139 | 309 (4,41); 382 (4,45) | 71,6 | 5,3 | 13,1 | $C_{19}H_{17}N_3O$ | 71,5 | 5,4 | 13,2 | 72 |
| d | 152—153 | 297 (4,42); 377 (4,43) | 59,0 | 3,7 | — | $C_{18}H_{14}BrN_3O$ | 59,0 | 3,9 | — | 52 |
| e | 140—141 | 299 (4,45); 386 (4,28) | 78,9 | 5,0 | 11,6 | $C_{23}H_{17}N_3O$ | 78,6 | 4,9 | 12,0 | 96 |
| f | 179—180 | 302 (4,42); 400 (4,32) | 64,9 | 4,3 | 16,7 | $C_{18}H_{14}N_4O_3$ | 64,7 | 4,2 | 16,8 | 84* |
| g | 207 (dec.) | 310 (4,32); 380 (4,49) | 64,7 | 4,4 | 16,5 | $C_{18}H_{14}N_4O_3$ | 64,7 | 4,2 | 16,8 | 64 |
| h | 220 (dec.) | 310 (4,37); 389 (4,44) | — | — | 18,5 | $C_{18}H_{13}N_5O_3$ | — | — | 18,5 | 30* |
| j | 140—141 | 321 (4,42); 448 (4,92) | 72,3 | 6,1 | — | $C_{20}H_{20}N_4O$ | 72,3 | 6,1 | — | 48 |
| k | 214 (dec.) | 290 sh<br>360 (4,48); 518 (4,34) | 63,6 | 5,2 | 18,6 | $C_{20}H_{19}N_5O_3$ | 63,7 | 5,1 | 18,6 | 84* |

*In the presence of piperidine.

chemical shift of the methyl group (2.5 ppm) is roughly the same as in 3-methyl-4-nitro-5-styrylisoxazole (2.59 ppm). We found that, as exemplified by compound (Ib), which has a $CH_3$ group in the para position of the 4-phenylazo group, condensation also proceeds selectively at the 5-methyl group of the isoxazole ring. Thus the PMR spectrum of compound (Ib) has three signals at 2.60, 2.42, and 2.30 ppm, due respectively to the $CH_3$ groups in positions 5 and 3 and in the para position of the phenylazo group, whereas the PMR spectrum of compound (IIIb) contains two methyl signals at 2.42 and 2.32 ppm but lacks the signal of the 5-$CH_3$ group.

Introduction of substituents such as $CH_3$, $OCH_3$, and Br into the para position of the 4-phenylazo group causes no marked change in the reactivity of the 4-arylazoisoxazoles in this condensation. Compound (If), which has a p-nitrophenylazo group, reacts in the presence of a weaker base (piperidine) and consequently its methyl group is as reactive as that of 4-nitroisoxazole.

Thus, the 4-arylazo group with either an electron-accepting or electron-donating substituent in the para position selectively activates the 5-methyl group in condensation with aromatic aldehydes. This activating effect is weaker than that of the nitro group in the isoxazole ring but stronger than that of the azo group in azo toluene.

## EXPERIMENTAL

Spectra were recorded on: UV: a Hitachi EPS-3 in chloroform; and PMR: a Jeol C-60 in deuterochloroform with hexamethyldisiloxane (HMDS) as internal standard.

4-Arylazo-3,5-dimethylisoxazoles (Ia)-(Id), (If)* were prepared by the methods of [9]; 3-phenyl-4-phenylazo-5-methylisoxazole (Ie) was prepared from 3-phenyl-4-phenylazoisoxazolin-5-one and methylmagnesium iodide by the method of [10]. The purity of the synthetic compounds was monitored by TLC on Silufol UV-254 in chloroform.

4-Arylazo-5-styrylisoxazoles (IIIa)-(IIIk). A mixture of the 4-arylazoisoxazole (I) (0.01 mole) and of equimolar quantities of the aromatic aldehyde (II) and potassium hydroxide in alcohol (40 ml) was heated to boiling in a water bath and kept at this temperature for 30 min to 3 h. After cooling the precipitate was filtered off, washed with cold alcohol, and recrystallized from ethanol or ethyl acetate. The constants and yields of the synthetic compounds are summarized in Table 1.

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*Compound (If) has mp 157-158°C, which differs from the literature value, mp 108°C.