Reaction of Substituted Benzylideneacetylacetones with Hydroxylamine Hydrochloride

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The reaction of α,β-unsaturated β-diketones, such as 3-(*o*-chloro, *m*-nitro, and *o*-nitrobenzylidene)acetylacetones (I, II, and III) with hydroxylamine hydrochloride was carried out. Among them, compound I and II in acetonitrile, methanol, and acetic acid afforded 4-(α-hydroxy, methoxy, acetoxy, and chlorobenzyl)-3,5-dimethylisoxazoles (IV-XI) in fairly good yield. On the other hand, III yielded 3-(3′,5′-dimethylpyrazolo)-5-chloroanthranil (XV) under the almost same conditions by the participation of *o*-nitro group.

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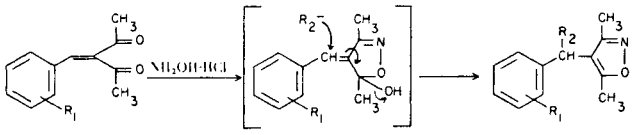
We have reported the reaction of α,β-unsaturated β-diketones, such as substituted benzylideneacetylacetone derivatives (I, II, and III), for the preparation of some heterocyclic compounds (1). Among them, we found that the reaction of *m*-nitrobenzylideneacetylacetone with methyl- or phenyhydrazine in acetonitrile, methanol and glacial acetic acid gives 4-(α-hydroxy-, methoxy- and acetoxy-*m*-nitrobenzyl)-3,5-dimethyl-1-methyl-or phenylpyrazoles *via* the pseudo-bases in good yields, respectively (1d).

The isoxazole ring was synthesized through the long known and extensively elaborated method of condensing β-diketones with hydroxylamine (2). Since no reference was found describing the condensation of α,β-unsaturated β-diketones with hydroxylamine, we examined this reaction, which results will be described.

When *o*-chlorobenzylideneacetylacetone (I) was treated with hydroxylamine hydrochloride in acetonitrile or methanol, 4-(α-hydroxy-*o*-chlorobenzyl)-3,5-dimethylisoxazole (IV) or 4-(α-methoxy-*o*-chlorobenzyl)-3,5-dimethylisoxazole (V) were obtained. On the other hand, a similar reaction was carried out to give a mixture of 4-(α-acetoxy-*o*-chlorobenzyl)-3,5-dimethylisoxazole (VI) and 4-(α-chloro-*o*-chlorobenzyl)-3,5-dimethylisoxazole (VII) in a ratio of 3:1. These were separated by column chromatography. The chloro derivative (VII), which showed a peak in the mass spectrum at m/e 221 (M^+, Cl), was easily converted into V by refluxing in methanol. Similarly, the reaction of *m*-nitrobenzylideneacetylacetone (II) with hydroxylamine hydrochloride in these three solvents afforded the corresponding isoxazole derivatives as summerized in Scheme I. The structure of these compounds was confirmed on the basis of elemental analyses, infrared (ir) and nuclear magnetic resonance (nmr) spectral data. A likely pathway of the formation of these compounds is illustrated in Scheme I.

Scheme I



Starting Material (R_1)	Solvent	Product (R_2)	Yield (%)
I (*o*-Cl)	CH_3CN	IV (OH)	96
	CH_3OH	V (OCH_3)	87
	CH_3CO_2H (a)	VI ($OCOCH_3$)	23
		VII (Cl)	68
II (*m*-NO_2)	CH_3CN	VIII (OH)	98
	CH_3OH	IX (OCH_3)	97
	CH_3CO_2H (a)	X ($OCOCH_3$)	18
		XI (Cl)	54
III (*o*-NO_2)	CH_3OH	XII (OCH_3)	68
		XV	19

(a) These were separated by alumina column chromatography using *n*-hexane as eluent.

On the contrary, when *o*-nitrobenzylideneacetylacetone (III) was treated with hydroxylamine hydrochloride in acetonitrile or glacial acetic acid at 50°, pale yellow needles of m.p. 162.5-163°, $C_{12}H_9N_2O_2Cl$ (XV), were obtained in 93-94% yield beside the formation of a trace *o*-nitrobenzaldoxime, which was presumably obtained by a retro Knoevenagel reaction of III followed by reaction with hydroxylamine. The ir spectrum of XV showed the absence of a nitro group and the presence of a >C=N absorption of 1645 cm^{-1}. The nmr spectrum showed two methyl protons at δ 2.30 and 2.60, and three aromatic protons as shown in Figure I.

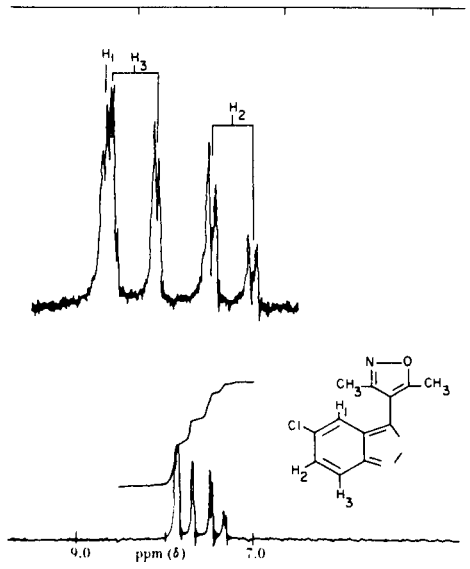
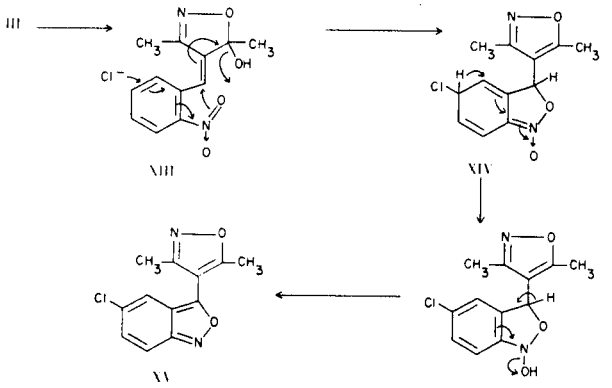


Figure 1. Nmr 60 MHz spectrum of XV in deuteriodimethylsulfoxide.

The ultraviolet (uv) spectrum showed the absorption maximum at 337 nm (log ϵ 4.07). These data suggested that the structure of XV is the chloroanthranil.

It is well known that the formation of anthranils in general from *o*-nitrobenzene derivatives is catalyzed by acids (3). Recently we reported a novel synthesis of 3-(1′-acetyl-3′,5′-dimethylpyrazolo)-5-chloroanthranil by reaction of 4-(*o*-nitrobenzylidene)-3,5-dimethylisopyrazole with acetyl chloride (4). Therefore the new compound XV proved to be, based on comparison of spectroscopic data, 3-(3′,5′-dimethylisoxazolo)-5-chloroanthranil. The following mechanism proposes that after the formation of 3-benzylideneisoxazolidine (XIII), cyclization of the nitro group and nucleophilic attack by chloride ion at the *para*-position occurs to give the cyclic intermediate XIV, followed by rearomatization and dehydration to yield XV, as depicted in Scheme II.

Scheme II



A similar reaction, however, of III in methanol gave a mixture of 4-(α-methoxy-*o*-nitrobenzyl)-3,5-dimethylisoxazole (XII) in a yield of 68% and XV in 19%.

EXPERIMENTAL

Melting points were not corrected. Ir and uv spectra were taken with a JASCO Model IRA-1 and a Schimadzu UV-200 spectrophotometers; nmr spectra were recorded with a Hitachi R-24A, mass spectra with a Hitachi Mass Spectrometer RMU-7L.

General Procedure of the Reaction of Substituted Benzylideneacetylacetones with Hydroxylamine Hydrochloride.

To a solution of α,β-unsaturated β-diketone (0.02 mole) in the appropriate solvent (100 ml.) was added with stirring, hydroxylamine hydrochloride (0.02 mole), and stirring was continued at 50° until the disappearance of starting material on thin layer chromatography. The solvent was evaporated *in vacuo*, and the residue was dissolved in chloroform. The chloroform solution was washed with saturated sodium bicarbonate solution, dried (sodium sulfate) and evaporated. The residue was recrystallized from a suitable solvent (except for compound XI).

Table I

Isoxazole Derivatives

Compound No.	M.p. °C.	Recrystallization Solvent (a)	Formula	Analyses Calcd. C	H	N	Found C	H	N
IV	103-104	L	$C_{12}H_{12}ClNO_2$	60.63	5.09	5.89	60.82	5.17	6.07
V	38-39	P.E	$C_{12}H_{14}ClNO_2$	60.12	5.88	5.84	59.99	5.60	6.01
VI	82-83	L	$C_{14}H_{14}ClNO_3$	60.11	5.04	5.00	60.14	5.11	5.16
VII	42-43	P.E	$C_{12}H_{11}Cl_2NO$	56.26	4.32	5.46	56.24	4.28	5.70
VIII	135-136	B	$C_{12}H_{12}N_2O_4$	58.06	4.87	11.29	58.32	4.84	11.25
IX	91-92	L	$C_{13}H_{14}N_2O_4$	59.53	5.38	10.68	59.81	5.26	10.64
X	93.5-95	L	$C_{14}H_{14}N_2O_5$	57.93	4.86	9.65	58.00	4.72	9.76
XI	oil								
XII	97-98	L	$C_{13}H_{14}N_2O_4$	59.53	5.38	10.68	59.72	5.55	10.82

(a) Legend: L, ligroin; P.E, petroleum ether; B, benzene.

4-(α-Hydroxy-*o*-chlorobenzyl)-3,5-dimethylisoxazole (IV).

This compound had ir ν max (potassium bromide): 3320 cm^{-1} (OH); nmr δ (deuteriochloroform): 2.09 and 2.20 (each 3H, each s, C_3- and C_5-CH_3), 3.15 (1H, d, J = 4 Hz, OH), 5.95 (1H, d, J = 4 Hz, CH).

4-(α-Methoxy-*o*-chlorobenzyl)-3,5-dimethylisoxazole (V).

This compound had ir ν max (chloroform): 1100 cm^{-1} (OCH_3); nmr δ (deuteriochloroform): 2.15 and 2.30 (each 3H, each s, C_3- and C_5-CH_3), 3.40 (3H, s, OCH_3), 5.45 (1H, s, CH).

4-(α-Acetoxy-*o*-chlorobenzyl)-3,5-dimethylisoxazole (VI).

This compound had ir ν max (potassium bromide): 1750 cm^{-1} (CO); nmr δ (deuteriochloroform): 2.10, 2.12 and 2.22 (each 3H, each s, C_3- and C_5-CH_3, $OCOCH_3$), 6.95 (1H, s, CH).

4-(α-Chloro-*o*-chlorobenzyl)3,5-dimethylisoxazole (VII).

This compound had nmr δ (deuteriochloroform): 2.22 and 2.28 (each 3H, each s, C_3- and C_5-CH_3), 6.40 (1H, s, CH).

4-(α-Hydroxy-*m*-nitrobenzyl)-3,5-dimethylisoxazole (VIII).

This compound had ir ν max (potassium bromide): 3360 cm^{-1} (OH); nmr δ (deuteriodimethylsulfoxide): 2.05 and 2.45 (each 3H, each s, C_3- and C_5-CH_3), 5.40 (1H, s, CH), 6.15 (1H, bs, OH).

4-(α-Methoxy-*m*-nitrobenzyl)-3,5-dimethylisoxazole (IX).

This compound had ir ν max (potassium bromide): 1120 cm^{-1} (OCH_3); nmr δ (deuteriochloroform): 2,05 and 2.40 (each 3H, each s, C_3- and C_5-CH_3), 3.38 (3H, s, OCH_3), 5.25 (1H, s, CH).

4-(α-Acetoxy-*m*-nitrobenzyl)-3,5-dimethylisoxazole (X).

This compound had ir ν max (potassium bromide): 1745 cm^{-1} (CO); nmr δ (deuteriochloroform): 2.10, 2.22 and 2.45 (C_3- and C_5-CH_3, $OCOCH_3$), 6.90 (1H, s, CH).

4-(α-Chloro-*m*-nitrobenzyl)-3,5-dimethylisoxazole (XI).

This compound had δ (deuteriochloroform): 2.15 and 2.40 (each 3H, each s, C_3- and C_5-CH_3), 6.15 (1H, s, CH); mass: m/e 235 (M^+-35).

4-(α-Methoxy-*o*-nitrobenzyl)-3,5-dimethylisoxazole (XII).

This compound had ir ν max (potassium bromide): 1150 cm^{-1} (OCH_3); nmr δ (deuteriochloroform): 2.02 and 2.25 (each 3H, each s, C_3- and C_5-CH_3), 3.35 (3H, s, OCH_3), 5.87 (1H, s, CH).

3-(3′,5′-Dimethylisoxazolo)-5-chloroanthranil (XV).

A mixture of III (2.33 g., 0.01 mole) and hydroxylamine hydrochloride (0.7 g., 0.01 mole) in glacial acetic acid (50 ml.) was heated at 50° for 20 hours. The solvent was evaporated *in vacuo*, and the residue was neutralized with saturated sodium bicarbonate solution and extracted with chloroform. The extract was washed with water, dried (sodium sulfate) and evaporated. The crystalline residue was recrystallized from ligroin to give pale yellow needles (2.33 g., 94%); m.p. 162.5-163°; ir ν max (potassium bromide): 1640 cm^{-1} (C=N); uv λ max (ethanol): 337 nm (log ε 4.07); nmr δ (deuteriochloroform): 2.40 and 2.60 (each 3H, each s, C'_3- and C'_5-CH_3), 7.40 (1H, d of d, J = 3 and 8 Hz, C_4-H), 7.75 (1H, d of d, J = 1 and 8 Hz, C_7-H), 7.85 (1H, m, C_4-H); mass: m/e 248 (M^+).

Anal. Calcd. for $C_{12}HCl_9N_2O_2$: C, 57.95; H, 3.64; N, 11.29. Found: C, 57.80; H, 3.71; N, 11.19.

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