Reactions with 4-Substituted-2-Isoxazolin-5-ones

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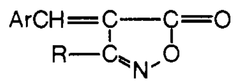
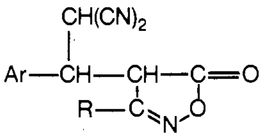
The reactivity of 4-arylidene-3-substituted-2-isoxazolin-5-ones as Michael acceptors toward a variety of Michael addenda, namely, malononitrile, acetylacetone, and thioglycolic acid is reported. Treatment of the 4-acyl derivatives of 2-methyl-3-phenyl-2-isoxazolin-5-one with Grignard reagents results only in addition of the reagent to the exocyclic carbonyl group. On the other hand, the hetero-ring of the 4-arylazo derivatives is cleaved upon treatment with the same reagents.

Treatment of 4-arylidene-3-methyl (or phenyl)-2-isoxazolin-5-ones (I) with Grignard reagents (*6, 7, 9*) or with aromatic hydrocarbons in the presence of aluminum chloride (*7*) effects the addition of the reagent to the exocyclic double bond with the formation of 4-disubstituted methyl derivatives. Also, cyclopropane derivatives are formed upon the addition of 9-diazofluorene (*5*) and bromomalononitrile (*14*) to the carbon-carbon double bond in I. This marked reactivity of the exocyclic double bond in I, together with the fact that the isoxazolone ring is found in several active compounds (*13*), prompted us to investigate the behavior of I toward a variety of other nucleophilic reagents.

When the colored Ia–d were refluxed in ethanol with malononitrile in the presence of piperidine, a Michael-type addition took place with formation of the colorless products IIa–d, respectively. The infrared spectra of IIa–d show strong carbonyl absorption which is split into two partially resolved bands at around 1670–1690 cm^{-1} [cf. carbonyl absorption of 4-benzhydryl-3-phenyl-2-isoxazolin-5-ones (*7*)] and a weak cyano band at around 2230 cm^{-1}.



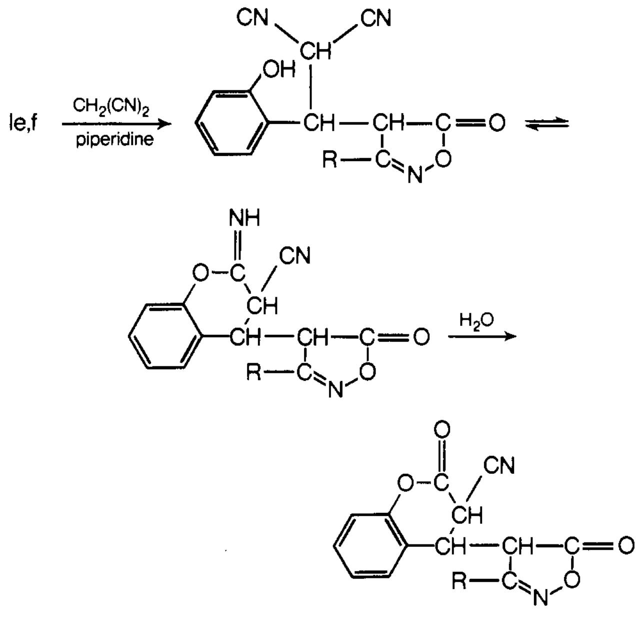
Ia. Ar = C_6H_5; R = CH_3
b. Ar = R = C_6H_5
c. Ar = C_6H_4OH-*m*; R = CH_3
d. Ar = C_6H_4OH-*m*; R = C_6H_5
e. Ar = C_6H_4OH-*o*; R = CH_3
f. Ar = C_6H_4OH-*o*; R = C_6H_5



IIa. Ar = C_6H_5; R = CH_3
b. Ar = R = C_6H_5
c. Ar = C_6H_4OH-*m*; R = CH_3
d. Ar = C_6H_4OH-*m*; R = C_6H_5

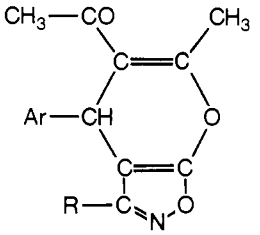
Similar behavior has been recently reported (*4*) for alkylmalononitriles. The uv spectrum of IIa, taken as an example, shows maxima at 235 and 255 nm; these maxima are comparable with those reported (*1*) for 3,4,4-trimethyl-2-isoxazolin-5-one.

Treatment of the 4-salicylidene derivatives Ie,f with malononitrile, under the same conditions described above, afforded colorless products, the analytical data of which agree well with the hydrocoumarin structure IIIa,b. The formation of IIIa,b may proceed via the route illustrated in chart I. The ir spectra of IIIa,b show absorption at 2225 cm^{-1} (CN) and two CO absorption at 1725 and 1690 cm^{-1}; the former was considered to be due to γ-lactone CO and the latter for the isoxazolone carbonyl group.



IIIa. R = CH_3
b. R = C_6H_5

The reaction of Ia–c with acetylacetone in the presence of piperidine afforded the pyranoisoxazole derivatives IVa–c. The formation of the latter compounds may involve addition of acetylacetone to the exocyclic double bond in I followed by cyclodehydration of the Michael adducts to yield IV. In addition to the correct analytical data of IVa–c, their ir spectra show single CO absorption at around 1700 cm^{-1} for acetyl CO and reveal no absorption for the hydroxyl group.



IVa. Ar = C_6H_5, R = CH_3
b. Ar = R = C_6H_5
c. Ar = C_6H_4OH-*m*; R = CH_3

Attempted addition of thiophenol or *p*-thiocresol to Ia in the presence of piperidine afforded colorless products which were readily decomposed on crystallization with regeneration of Ia. On the other hand, treatment of Ia–d with thioglycolic acid in the presence of a trace of piperidine yielded colorless stable crystalline products for which structure V is proposed. The assignment of the latter structure is based on the well-established structure for the addition of thiols to α,β-unsaturated ketones (*10,*

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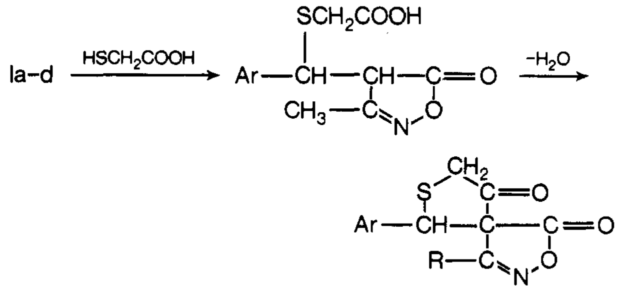
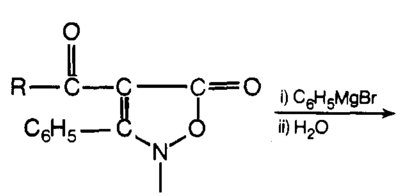
11). That cyclodehydration has also occurred is evident from correct analytical data, the insolubility of the products in carbonate solution, and the ir spectra which show two CO absorption at 1640 and 1650 cm^{-1} and reveal no absorption for carboxylic acid.



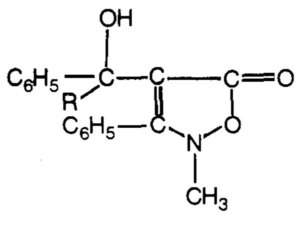
Va. Ar = C_6H_5; R = CH_3
b. Ar = R = C_6H_5
c. Ar = C_6H_4OH-*m*; R = CH_3
d. Ar = C_6H_4OH-*m*; R = C_6H_5

Recently, the reaction of 4-acyl- (*2, 12*) and 4-aryl-azo (*2*) derivatives of antipyrine (3-dimethyl-1-phenyl-3-pyrazolin-5-one) with Grignard reagents has been reported to yield 4-dialkylhydroxymethyl-2,3-dimethyl-1-phenyl-3-pyrazolin-5-ones and 4-arylazo-1-phenyl-3,5,5-triarylpyrazolidine. It seemed worthwhile to investigate the behavior of the oxygen analogs of these compounds, namely, 4-acyl (VI) and 4-arylazo (VII) derivatives of 2,3-dimethyl-3-isoxazolin-5-one toward the action of the same reagents. In analogy with the behavior of acylantipyrines, treatment of VIa,b with an excess of phenylmagnesium bromide effected the addition of one molecule of the reagent to the exocyclic CO to yield, after hydrolysis, the carbinols VIIIa,b, respectively. Oxidation of VIIIb with chromic acid afforded among the oxidation products benzophenone.

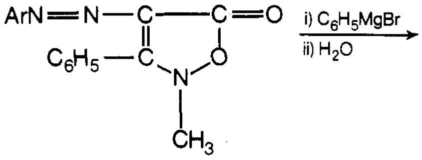
On the other hand, when 4-arylazo-2-methyl-3-phenyl-2-isoxazolin-5-ones (VIIa,b) were treated with phenylmagnesium bromide, cleavage of the heterocyclic ring took place with the formation of the carbinols IXa,b which were identical with authentic samples, prepared after Mustafa et al. (*8*), via the action of phenylmagnesium bromide on 1,3-diphenylpropan-1,2,3-trione-2-arylhydrazones. This behavior is in analogy with the reaction of 3,4-diphenyl-2-methyl-3-isoxazolin-5-one with the same reagents to yield α,β-diphenylbenzalacetophenone (*3*).



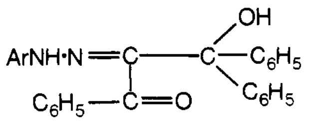
VIa. R = CH_3
b. R = C_6H_5



VIIIa. R = CH_3
b. R = C_6H_5



VIIa. Ar = C_6H_5
b. Ar = $C_6H_4CH_3$-*o*



IXa. Ar = C_6H_5
b. Ar = $C_6H_4CH_3$-*o*

Experimental

All melting points are uncorrected. Ir spectra were determined on a Perkin-Elmer Infracord Model 137B using the KBr wafer technique. Uv spectra were obtained in ethanol on a Beckman DK-2A spectrophotometer.

Michael reaction with 4-arylidene-3-methyl (or phenyl)-2-isoxazolin-5-ones (Ia–f) (general procedure). To a suspension of each of Ia–f (0.1 mole) in ethanol (100 ml), the appropriate Michael addendum (0.1 mole) and one drop of piperidine were added. The reaction mixture was heated under reflux until the yellow color of the arylidene disappeared (time ranges from 10 min to 3 hr). The solvent was then removed by vacuum, and the remaining oily product was triturated with a little water and then acidified with concentrated hydrochloric acid. The resulting solid products, listed in Table I, were collected by filtration and crystallized from ethanol.

Reaction of VIa,b with Grignard reagents. To a Grignard solution (prepared from 1.0 gram magnesium and 9.0 grams bromobenzene in 100 ml dry ether), a suspension of each of VIa,b (2.0 grams) in dry ether (100 ml) was added. The reaction mixture was kept aside at room temperature for 2 hr and then decomposed with saturated aqueous ammonium chloride solution. The ethereal layer was separated, washed several times with water, and dried with Na_2SO_4. The oily residue obtained upon evaporation of the ether was triturated with ethanol, and the resulting solid was crystallized from ethanol.

4-(1-Hydroxy-1-phenylethyl)-2-methyl-3-phenyl-3-isoxazolin-5-one (VIIIa) formed colorless crystals, mp 193°; yield 66% (Found: C, 73.41; H, 5.58; N, 4.64%. Calcd for $C_{18}H_{17}O_3N$: C, 73.22; H, 5.75; N, 4.74%).

4-(Diphenylhydroxymethyl)-2-methyl-3-phenyl-3-isoxazolin-5-one (VIIIb) formed colorless crystals, mp 176°; yield 62%. (Found: C, 77.60; H, 5.00; N, 3.70%. Calcd for $C_{23}H_{19}O_3N$: C, 77.31; H, 5.32; N, 3.92%).

Oxidation of VIIIb. A suspension of VIIIb (0.5 gram) and chromium trioxide (1.0 gram) in acetic acid (20 ml) was warmed on a boiling water bath for 1 hr. The reaction mixture was cooled, poured into ice-cold water, and then extracted with ether. The oily residue, obtained after evaporation of the ether layer, was treated with 2,4-dinitrophenylhydrazine, and the resulting product proved to be benzophenone-2,4-dinitrophenylhydrazone (mp and mmp).

3-Hydroxy-1,3,3-triphenyl-1,2-dione-2-arylhydrazones (IXa,b). Each of VIIa,b was treated with phenylmagnesium bromide using the experimental conditions described above, and the resulting product was crystallized from benzene–petroleum ether (bp 80–100°) and proved (mp and mmp) to be identical with the corresponding Grignard products prepared after Mustafa et al. (*8*).

Table I. List of Michael Products of Reaction with 4-Arylidene 3-Methyl or Phenyl-2-isoxazolin-5-one (II–V)

				Carbon, %		Analysis hydrogen, %		Nitrogen, %	
Compound	Yield, %	MP	Formula	Found	Calcd	Found	Calcd	Found	Calcd
IIa	68	142	$C_{14}H_{11}N_3O$ (253.25)	66.32	66.39	4.27	4.38	16.70	16.59
IIb	65	155	$C_{19}H_{13}N_3O_2$ (315.32)	72.82	72.37	4.20	4.16	13.11	13.33
IIc	62	145	$C_{14}H_{11}N_3O_3$ (269.25)	62.24	62.45	4.30	4.12	15.70	15.60
IId	64	170	$C_{19}H_{13}N_3O_3$ (331.32)	68.69	68.87	3.81	3.96	12.39	12.68
IIIa	58	182	$C_{14}H_{10}N_2O_3$ (254.24)	66.23	66.13	3.96	3.93	10.64	11.02
IIIb	60	180	$C_{19}H_{12}N_2O_3$ (316.30)	72.21	72.14	3.80	3.82	8.76	8.86
IVa	55	122	$C_{16}H_{15}NO_3$ (269.29)	70.90	71.36	5.25	5.61	4.85	5.20
IVb	50	182	$C_{21}H_{17}NO_3$ (331.35)	76.50	76.12	4.82	5.17	4.71	4.23
IVc	50	228	$C_{16}H_{15}NO_4$ (285.29)	67.12	67.36	5.34	5.30	5.21	4.91
Va	45	175	$C_{13}H_{11}NO_3S$ (261.23)	59.76	59.77	4.24	4.21	5.80	5.36
Vb	50	181	$C_{18}H_{13}NO_3S$ (323.29)	66.77	66.87	4.02	4.05	4.53	4.33
Vc	46	225	$C_{13}H_{11}NO_4S$ (277.23)	56.31	56.32	4.36	4.00	5.31	5.05
Vd	43	165	$C_{18}H_{13}NO_4S$ (339.37)	63.65	63.72	3.74	3.86	4.43	4.13

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