4-Acyl-3-aryl-1,2-oxazoles

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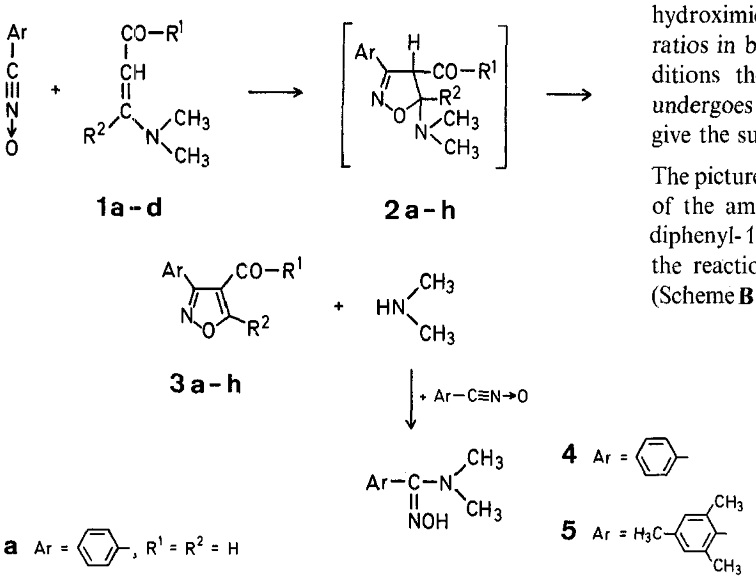
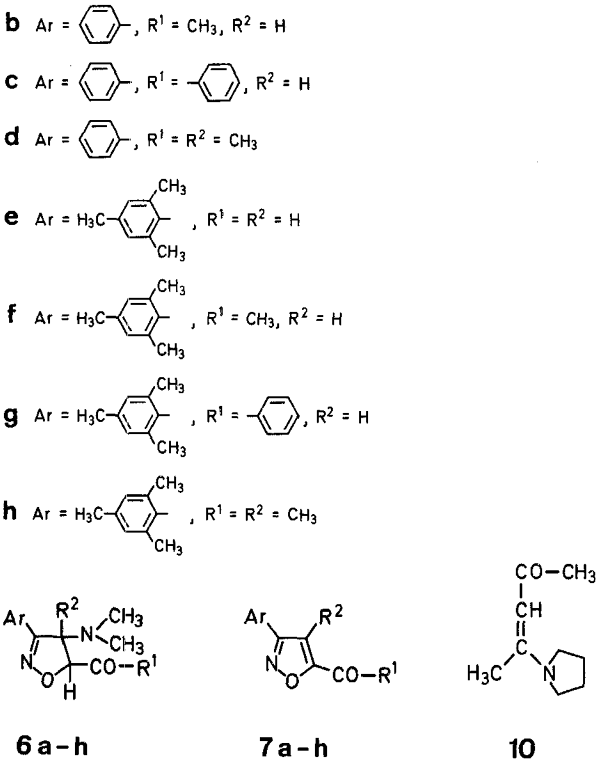
We wish to report the synthesis of 4-acyl-3-aryl-1,2-oxazoles from benzonitrile oxides and β-acylenamines. 4-Acyl-1,2-oxazoles are generally prepared by cyclocondensation of hydroximic acid chlorides and the alkali metal salts of β-dicarbonyl compounds[1]. Aside from this well-known reaction, little information on other methods is found in the literature. The reaction of nitrile oxides with β-enamino ketones[2,3], β-enamino esters[4], or β-enamino nitriles[5] may be employed to advantage in the synthesis of 1,2-oxazole-4-carbonyl derivatives. However, application of this method to the preparation of 4-acyl-3-aryl-1,2-oxazoles gives relatively poor yields when the reaction is performed employing a 1:1 ratio of the reactants. Thus, in the reaction of benzonitrile oxide with an equimolar amount of 4-oxo-2-pyrrolidino-2-pentene (**10**) we recovered more than 50% of unreacted enamine. The efficiency of the reaction may be considerably improved, however, by altering the reaction conditions.

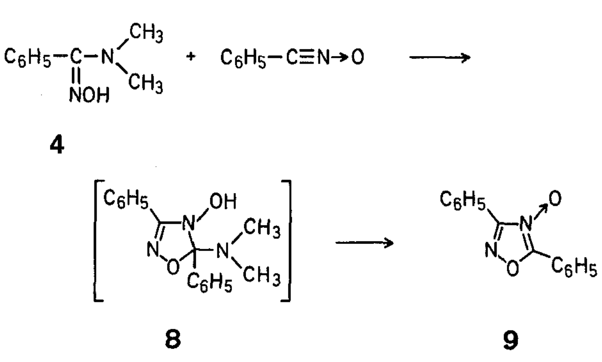




Scheme **A**

The reaction of equimolar amounts of benzonitrile oxide (generated *in situ*) and 1-dimethylamino-3-oxo-3-phenylpropene (**1c**) in benzene afforded a mixture of **1c**, 4-benzoyl-3-phenyl-1,2-oxazole (**3c**), and N,N-dimethylbenzamide oxime (**4**). The ratio **1c**:**3c**:**4** (as determined by N.M.R. spectrometry) was 11.5:9:5.7 when benzhydroximic acid chloride was added to a solution of **1c** and triethylamine in benzene, and it was 10:9:6 when a solution of **1c** and triethylamine in benzene was added to a solution of benzhydroximic acid chloride in benzene. The nearly identical ratios in both cases point out that under the reaction conditions the intermediate **2c** loses dimethylamine which undergoes an addition reaction with benzonitrile oxide to give the substituted carboxamide oxime **4** (Scheme **A**).

The picture is further complicated by the subsequent reaction of the amidoxime **4** with benzonitrile oxide to yield 3,5-diphenyl-1,2,4-oxadiazole 4-oxide (**9**), whose presence in the reaction mixtures has been ascertained in some cases (Scheme **B**).



Scheme **B**

The dipolarophilic reactivity of amidoximes toward nitrile oxides has recently been demonstrated[6].

The reaction of **1c** with two equivalents of benzonitrile oxide yielded a mixture of **1c**, **3c**, and **4** in the ratio 7:16:9. The absence of N.M.R. signals between 4 and 6.5τ (with the exception of the doublet of the starting *trans*-**1c** at 4.38τ, $J = 12.7$ Hz) excludes the presence of the 1,2-oxazolines **2c** and **6c** in the product mixture obtained; T.L.C. analysis of the mixture shows the absence of 5-benzoyl-3-phenyl-1,2-oxazole (**7c**). Thus, the reaction is regiospecific, whereas the cycloaddition of benzonitrile oxide and benzoylacetylene yields the two regioisomers **3c** and **7c** in a ratio of 1:6 (as evidenced by N.M.R. spectrometry).

Column chromatography of the reaction mixture afforded 4-benzoyl-3-phenyl-1,2-oxazole (**3c**), 3,5-diphenyl-1,2,4-oxadiazole-4-oxide (**9**), and N,N-dimethylbenzamide oxime (**4**) in 65%, 10%, and 46% yields, respectively (based on **1c**).

The 1,2-oxazoles **3a**, **3b**, and **3d** were prepared in an analogous manner.

From the reaction of the stable and less reactive 2,4,6-trimethylbenzonitrile oxide with an equimolar amount of **1c** in benzene, a 1:1:1 mixture (determined by N.M.R. spectrometry) of **1c**, **3g**, and **5** was obtained. Monitoring of the reaction by I.R. showed an increasing carbonyl absorption (of **3g**) at 1665 cm^{-1} but no other peaks which might be assignable to the 1,2-oxazoline **2g**. Column chromatography afforded the 1,2-oxazole **3g** and the amide oxime **5** in 41% and 40% yield, respectively. The 1,2-oxazoles **3e**, **3f**, and **3h** were prepared in an analogous manner.

Table 1. 4-Acyl-3-aryl-1,2-oxazoles (**3**) prepared from Benzonitrile Oxides and N,N-Dimethyl-β-enamino Carbonyl Compounds (**1**)[a, b]

Compound	Method	Yield[c] %	m.p.	Solvent used for recrystallization	N.M.R.[d] (CDCl$_3$)	
					R^1	R^2
3a	A	49	44[e]	petroleum ether	−0.2(s)	0.92(s)
3b	A	58	82[f]	methanol	7.60(s)	1.02(s)
3c	A	65	82[g]	methanol	2–2.7(m)	1.20(s)
3d	A	56	58–59[h]	methanol/water	7.91(s)	7.30(s)
3e	B	20	68–69	petroleum ether	0.37(s)	0.90(s)
3f	B	48	89	ethanol/water	7.68(s)	0.92(s)
3g	B	41	116	methanol/water	2.1–2.5(m)	1.12(s)
3h	B	41	93–94	methanol	8.2(s)	7.37(s)

[a] Satisfactory elemental analyses were obtained for all new compounds.

[b] The N,N-dimethyl-β-enamino carbonyl compounds **1a–d** were prepared following known procedures.

[c] Yields are based on compounds **1a–d**.

[d] R-12 Perkin Elmer spectrometer, TMS used as internal standard, τ values.

[e] b.p. 180° (bath)/2 mm.

[f] Ref.[10], m.p. 82°.

[g] Ref.[11], m.p. 83–84°.

[h] Ref.[9], m.p. 60°.

The structural assignments of the 5-unsubstituted 4-acyl-1,2-oxazoles **3** are based on N.M.R. data. The C-5 ring proton signal is found at $\tau = 1$, whereas the C-4 ring-proton signals of **7b**[7] and **7c**[8] appear at $\tau = 2.80$ and 2.77, respectively. Compound **3d** was identical with a specimen prepared according to Ref.[9] and the structure of **3h** was established by analogy to the other compounds **3**.

Preparation of 4-Acyl-3-aryl-1,2-oxazoles; General Procedure:

Method A. To a stirred solution of the N,N-dimethyl-β-enamino carbonyl compound (**1a–d**; 5 mmol) and triethylamine (10 mmol) in absolute benzene (25 ml), a solution of benzhydroximic acid chloride (10 mmol) in benzene is added dropwise over a period of 30 min. The reaction mixture is allowed to stand overnight. Triethylamine hydrochloride is then filtered off, the solvent is removed, and the residue chromatographed on silica gel, cyclohexane/ethyl acetate (7:3) serving as the eluent.

Method B. A solution of 2,4,6-trimethylbenzonitrile oxide (2 mmol) and the N,N-dimethyl-β-enamino carbonyl compound (**1a–d**; 2 mmol) in absolute benzene (4 ml) is allowed to stand at room temperature for 7 days (in the case of **1a**, 1 month). The solvent is then evaporated and the residue chromatographed as described above.

Cycloaddition of Benzonitrile Oxide and Benzoylacetylene; Preparation of 5-Benzoyl-3-phenyl-1,2-oxazole (7c):

To a stirred solution of benzoylacetylene (5 mmol) and benzhydroximic acid chloride (5 mmol) in absolute benzene (25 ml) is slowly added a solution of triethylamine (5 mmol) in benzene (20 ml). The reaction mixture is allowed to stand overnight, triethylamine hydrochloride filtered off, the solvent evaporated, and the residue chromatographed on silica gel using cyclohexane/ethyl acetate as the eluent; yield: 70% of **7c**, m.p. 73° (Ref.[8], m.p. 73°), and 12% of **3c**.

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