

An Easy Method for the Preparation of 4-Acylisoxazoles from $C(\alpha),O$ -Dianions of Oximes (1)

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Several $C(\alpha),O$ -dilithiooximes of aromatic ketones were condensed with acyl chlorides. The presumed diacyl intermediates were not isolated, and the reaction mixtures containing them were acid-cyclized to give 4-acylisoxazoles in 22-62% yield.

J. Heterocyclic Chem., 13, 607 (1976).

A number of 4-acylisoxazoles and other products have been isolated from the reaction of O -benzoyl oximes with sodium hydride (3); however, Neber rearrangement products were also isolated, and the synthetic value of this reaction appears limited.

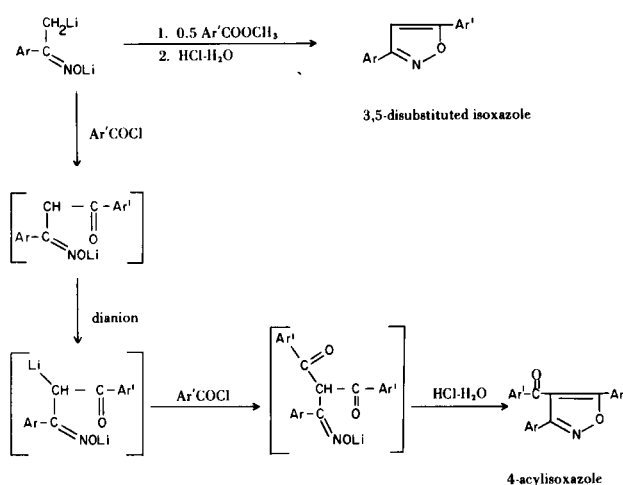
During the course of our investigations of the synthetic utility of $C(\alpha),O$ -dilithiooximes and related dianions, it was of value to condense these reactive lithio-intermediates with electrophilic reagents such as aldehydes and ketones (4), nitriles (5), and esters (6). In the case of the condensation with esters, which was followed by a routine acid-cyclization procedure, unsymmetrical 3,5-disubstituted isoxazoles were prepared. The reaction of these dilithiooximes with acid chlorides promised to be of interest because of the greater reactivity of these electrophilic reagents over esters, and offered the possibility of diacylation of the $C(\alpha)$ -anion center. This diacylated intermediate, after acid cyclization, would give the 4-acylisoxazole. The fact that we were able to prepare 4-acylpyrazoles by the condensation of $C(\alpha),N$ -dianions of phenylhydrazones followed by acid-cyclization, further suggested the feasibility of such an investigation (7).

This was in effect what resulted when the $C(\alpha),O$ -dilithiooximes of acetophenones were treated with two molar equivalents of acid chloride, followed by acid cyclization. The ratio of the reactants, and the reaction time of the multiple anion with the acid chloride is important for the successful synthesis of the 4-acylisoxazoles free of contamination of 3,5-disubstituted isoxazoles (see experimental). In a typical reaction one molar equivalent of oxime was treated with two molar equivalents of *n*-butyllithium, which was followed by the condensation of the dianion with one molar equivalent of acid chloride (one hour reac-

tion time). After neutralization and reflux, the desired products were isolated. The 4-acylisoxazoles are listed in the Table.

Each of these heterocyclic materials was characterized by ir spectra, which contained a C=O stretch at 1653 cm^{-1} . In addition, elemental analysis confirmed that the pure materials that were obtained were free from 3,5-disubstituted isoxazoles, many of which had melting points that were very close to the corresponding acylated isoxazole.

This new synthetic procedure has the advantage of giving the desired product in fair yields from readily available starting materials, and it involves recrystallization of products rather than vacuum sublimation and recrystallization.



Table

4-Acylisoxazoles

| Compound Number | Compound Name (-isoxazole) | Empirical Formula | Yield (a) % | M.p. C° | Analytical Data |
|-----------------|--|--|-------------|-------------|---|
| 1 | 4-benzoyl-5-phenyl-3(<i>p</i> -tosyl)- | C ₂₃ H ₁₇ NO ₂ | 62 (b) | 132-134 (h) | Calcd.: C, 81.40; H, 5.05 Found: C, 81.49; H, 5.27 |
| 2 | 4(<i>p</i> -chlorobenzoyl)-5(<i>p</i> -chlorophenyl)-3-phenyl | C ₂₂ H ₁₃ Cl ₂ NO ₂ | 52 (c) | 187-189 (i) | Calcd.: C, 67.02; H, 3.32 Found: C, 67.14; H, 3.58 |
| 3 | 3-phenyl-4(<i>p</i> -toluoyl)-5(<i>p</i> -tosyl)- | C ₂₄ H ₁₉ NO ₂ | 54 (d) | 138-139 (h) | Calcd.: C, 67.66; H, 3.70 Found: C, 67.44; H, 3.60 |
| 4 | 4(<i>p</i> -chlorobenzoyl)-3,5-di(<i>p</i> -chlorophenyl) | C ₂₂ H ₁₂ Cl ₃ NO ₂ | 49 (e) | 186-187 (i) | Calcd.: C, 61.64; H, 2.82 Found: C, 61.63; H, 3.03 |
| 5 | 4-benzoyl-1,3-diphenyl- | C ₂₂ H ₁₅ NO | 22 (f) | 153-154 (h) | Calcd.: C, 81.21; H, 4.65 Found: C, 81.49; H, 4.80 |
| 6 | 3(<i>p</i> -chlorophenyl)-4(<i>p</i> -fluorobenzoyl)-5(<i>p</i> -fluorophenyl)- | C ₂₂ H ₁₂ ClF ₂ NO ₂ | 36 (g) | 157-158 (h) | Calcd.: C, 66.76; H, 3.06 Found: C, 66.81; H, 3.11 |

(a) The yields for those 4-acylisoxazoles reported (3) were not given. We estimate that they were between 1-3%. (b) Lit. m.p. 134-135°, See reference (3). (c) Lit. m.p. 191-192°, See reference (3). (d) Lit. m.p. 134-135°, See reference (3). (e) Lit. m.p. 189-190°, See reference (3). (f) Lit. m.p. 153-155°, See reference (3). (g) *Anal.* Calcd. for C₂₂H₁₂ClF₂NO₂: N, 3.54. Found: N, 3.48. (h) Recrystallized from 95% ethanol. (i) Recrystallized from xylene-ethanol.

EXPERIMENTAL

Combustion analyses were performed by Robertson Laboratory, Florham Park, New Jersey. Infrared spectra were obtained on a Perkin-Elmer Model 700 Spectrometer. Melting points were taken in open capillary tubes with a Thomas-Hoover melting point apparatus and are uncorrected. Tetrahydrofuran (THF) was taken from a newly-opened bottle (Matheson-Coleman-Bell). The *n*-butyllithium was obtained from the Lithium Corporation of America, Bessemer City, North Carolina. The oximes were prepared by a standard procedure (8).

General Procedure for Preparation of 4-Acylisoxazoles.

To a stirred solution of 0.02 mole of oxime dissolved in 100 ml. of dry THF, which was blanketed by nitrogen and cooled to 0°, was added 0.042 mole of *n*-butyllithium during 5-10 minutes. The resulting mixture was stirred 30-45 minutes; 0.025 mole of acid chloride dissolved in 50 ml. of THF was added during 5-10 minutes, and the resulting mixture was stirred for at least 1 hour. The mixture was then neutralized with 100 ml. of 3*N* hydrochloric acid, and the mixture was well stirred and heated under reflux for 1 hour and cooled. The mixture was placed in a large flask with approximately 100 ml. of ether and carefully neutralized with sodium bicarbonate. The layers were separated, and the aqueous layer was extracted with two 50-ml. portions of ether. The organic layers were combined, dried (magnesium sulfate), filtered, concentrated, and the resulting oil or residue was immediately crystallized and/or recrystallized from the appropriate solvent (see Table).

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