

INTRAMOLECULAR CYCLIZATIONS OF α -KETOIMIDOYL HALIDES

DERIVED FROM ORGANIC ISONITRILES. AN EXPEDIENT APPROACH TO THE

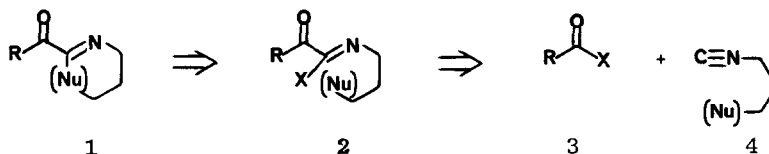
SYNTHESIS OF 1-ACYL-3,4-DIHYDROISOQUINOLINES

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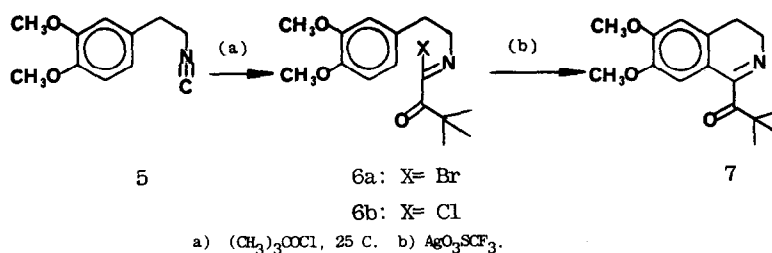
Summary. Dihydroisoquinolines are formed in high yield via the cyclization of α -ketoimidoyl halides prepared by the reaction of phenethyl isocyanides with acyl halides.

Intramolecular cyclization reactions involving carbon centered nucleophiles and nitrogen stabilized carbocations have recently played an increasingly crucial role for the elaboration of alkaloids and their structural prototypes. The numerous variations of these annulation processes include the intramolecular Mannich,¹ Pictet-Spengler,² Bischler-Napieralski,³ and acyliminium ion-olefin⁴ cyclizations among others. Recently, we required a general and exceedingly mild method for the construction of nitrogenous heterocycles of variable ring size. In principle, this objective could be met in a highly convergent manner by invoking the cyclization of an α -ketoimidoyl halide (e.g., 2) bearing an internal carbon nucleophile. These intermediates, in turn, were expected to be readily accessible by the reaction of an acyl halide 3 with the requisite isonitrile 4 (Scheme I). In this communication we wish to describe the first examples of this novel approach to heterocycle synthesis.



SCHEME I

Accounts concerned with the reactions of isonitriles with electrophilic species have remained surprisingly few in number.^{5,6} We have found that acyl bromides and chlorides react with representative isonitriles to provide the corresponding α -ketoimidoyl halides in c.a. 90% yield at temperatures as low as 0°C.^{7a,b} As expected, acyl bromides were found to react with somewhat greater facility than acyl chlorides in the above context.⁸ Accordingly, treatment of 3,4-dimethoxyphenethyl isocyanide **5** in CH_2Cl_2 solution with either trimethylacetyl bromide (0°C, 0.5h) or trimethylacetyl chloride (25°C, 18h) afforded the anticipated imidoyl halides **6a** or **b** in quantitative yield. The cyclization of **6a** or **6b** to the dihydroisoquinoline **7** could be easily accomplished under several sets of reaction conditions. Under the mildest of these, the crude adducts **6a** or **6b** formed in the above manner were treated directly with 1.1 equiv. of silver trifluoromethanesulfonate (CH_2Cl_2 , -20°C + 20°C, 12h) to afford the dihydroisoquinoline **7** (82% overall from **5**). Significantly, no detectable quantity (HPLC, Capillary G.C.) of the isomeric 1-acyl-7,8-dimethoxydihydroisoquinoline was formed under these reaction conditions. Alternatively, the cyclization of **6b** could be achieved in lower yield in the presence of a catalytic quantity of $\text{CF}_3\text{SO}_3\text{H}$ (CH_2Cl_2 , 0°C) or SnCl_4 (1 equiv., CH_2Cl_2 , (-78°C + 0°C).



The generality of the foregoing annulation sequence was subsequently examined by the utilization of a variety of acyl chlorides (e.g., **8a-e**). The results of this study are summarized in Table I.⁹

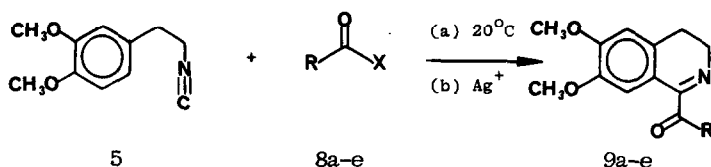
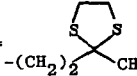


TABLE I

| Acyl Chloride | Cyclization Conditions | Isolated % Yield |
|--|---------------------------------------|------------------|
| a) R = $-\text{C}(\text{CH}_3)_3$ | $\text{Ag}^+\text{O}_3\text{SCF}_3^-$ | 82 |
| " | HO_3SCF_3 | 71 |
| " | SnCl_4 | 31 |
| b) R = $-(\text{CH}_2)_3\text{CH}=\text{CH}_2$ | $\text{Ag}^+\text{O}_3\text{SCF}_3^-$ | 87 |
| c) R = $-(\text{CH}_2)_3\text{C}\equiv\text{CH}$ | $\text{Ag}^+\text{O}_3\text{SCF}_3^-$ | 75 |
| d) R =  | Ag^+BF_4^- | 61 |
| e) R = $-\text{SC}_2\text{H}_5^1$ | $\text{Ag}^+\text{O}_3\text{SCF}_3^-$ | 57 |
| f) R = $-\text{OCH}_3^2$ | ----- | 0 |

- 1) In this instance it was necessary to employ an excess of the pure acyl chloride to achieve the preparation of the imidoyl chloride.
- 2) The formation of imidoyl chloride was not observed even when this acyl chloride was employed as the reaction solvent.

Heterocycle annulations reliant upon the nucleophilic interception of chemically activated α -ketoimidoyl halides should facilitate the synthesis of numerous alkaloids. The execution of this type of cyclization involving alternative carbon based nucleophiles (e.g., indole and other heteroaromatic nuclei as well as electron rich double bonds) is currently underway. The further application of this methodology to natural product synthesis will be the topic of future reports from these laboratories.

Acknowledgement:

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*This communication is dedicated to the memory of Professor Robert V. Stevens.

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7. The first example of this reaction in which α -ketoimidoyl chlorides were isolated was reported by Ugi.^{7b} The reaction conditions employed in this early account were far harsher than necessary (benzene, reflux) and the product yields were lowered as a consequence. 7b. Ugi, I.; Fetzer, U. Chem. Ber., 1961, 94, 1116.
8. The greater reactivity of acyl bromides permits the desired insertion reactions to be conducted at temperatures as low as 0°C. In some instances this characteristic has proven advantageous.
9. All new compounds exhibited satisfactory NMR, and I.R. spectra as well as elemental (C,H) analyses.
10. The following represents a typical experimental procedure for the synthesis of a dihydroisoquinoline. A dried three necked flask fitted with a magnetic stirring bar, rubber septum, thermometer, and nitrogen inlet, was charged with 1.00 g 3,4-dimethoxyphenethyl isocyanide¹¹ (5.2 mmol) in 15 mL dry CH₂Cl₂. To this solution was added 0.70 mL 5-hexenoyl chloride (5.2 mmol) at 0°C and the reaction mixture was then allowed to warm to 25°C. After stirring for 18 h, the reaction mixture was cooled to 0°C and treated with 1.48 g silver trifluoromethanesulfonate (5.8 mmol). After stirring at this temperature for 4 h, 15 mL of 10% KHCO₃ was added and the aqueous phase was extracted with CH₂Cl₂ (3x25 mL). The organic phases were combined, washed with brine and dried over 4A powdered molecular sieves. The solvent was evaporated under reduced pressure and the crude mixture was chromatographed on 230-400 mesh silica gel with 30% ethyl acetate hexane for elution to yield 1.30 g (87 %) of the dihydroisoquinoline **9b** as a crystalline solid: M.P. 54-56°C.; NMR (CDCl₃/Me₄Si) δ 1.79 (2H, apparent t of t, J = 7.4 Hz, CH₂) 2.14 (2H, broad d of t, J = 6.53, 6.75 Hz, CH₂), 2.66 (2H, m, CH₂), 3.02 (2H, t, J = 7.4 Hz, CH₂), 3.42 (2H, m, CH₂), 3.89 (3H, s, CH₃O), 3.92 (3H, s, CH₃O), 4.98 (1H, m, vinyl), 5.04 (1H, m, vinyl), 5.83 (1H, m, vinyl), 6.69 (1H, s, aromatic), 7.39 (1H, s, aromatic); IR (CCl₄) cm⁻¹ 3010-2810 (CH envelope), 1710 (C=O), 1610 (C=N); Anal. Calcd. for C₁₇H₂₁O₃N: C, 71.06; H, 7.36. Found: C, 70.93; H, 7.24.
11. Prepared by the dehydration method: Org. Syn., 1961, 41, 13.

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