

THE REACTION OF α -LACTAMS WITH GRIGNARD REAGENTS: A CORRECTION OF THE LITERATURE¹

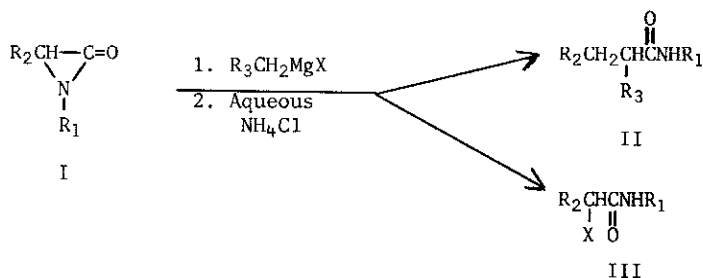
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The reaction of α -lactams (Ia) with alkylmagnesium halides has been claimed by Sheehan and Nafissi² to afford a secondary amide (IIa) by a novel, insertion-type alkylation of the acyl group (Scheme I). We have examined the reaction of 1,3-di-tert-butylaziridinone (Ib) with methylmagnesium iodide, and we are unable to confirm either the structure of the product (IIb) or the experimental data cited by these investigators, despite repeated attempts by three independent groups of co-workers under a variety of conditions. An examination of the crude reaction mixtures suggests the presence of at least three products, the principal set of products being an α -iodo amide (IIIb) along with varying amounts of compounds derived from this halo amide by coupling or reduction;³ but in no case did we detect any evidence of the presence of IIb. An entirely different type of product has been reported in the reaction of phenylmagnesium bromide with 1-(1-adamantyl)-3-tert-butylaziridinone (IV) by Lengyel, Mark and Troise⁴

Scheme I



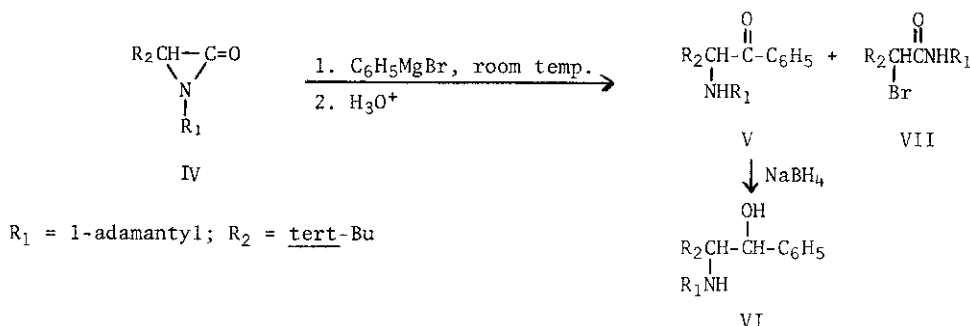
a, $\text{R}_1 = \text{R}_2 = \text{tert-alkyl}$; $\text{R}_3 = \text{CH}_3$ or H

b, $\text{R}_1 = \text{R}_2 = \text{tert-Bu}$; $\text{R}_3 = \text{H}$; $\text{X} = \text{I}$

(Scheme II), who concluded on the basis of spectral data that this product is an α -amino ketone (V). Reduction of V to an amino alcohol (VI) by sodium borohydride in ethanol was also reported by these investigators as additional proof of the structure of V.

In the present communication, we describe our experience with the reactions reported by Lengyel and his co-workers which leads us to assign different structures to the products believed by them to be V and VI. Moreover, we have prepared and characterized a sample of V and found that it does not undergo reduction to VI under the conditions mentioned by these workers.

Scheme II



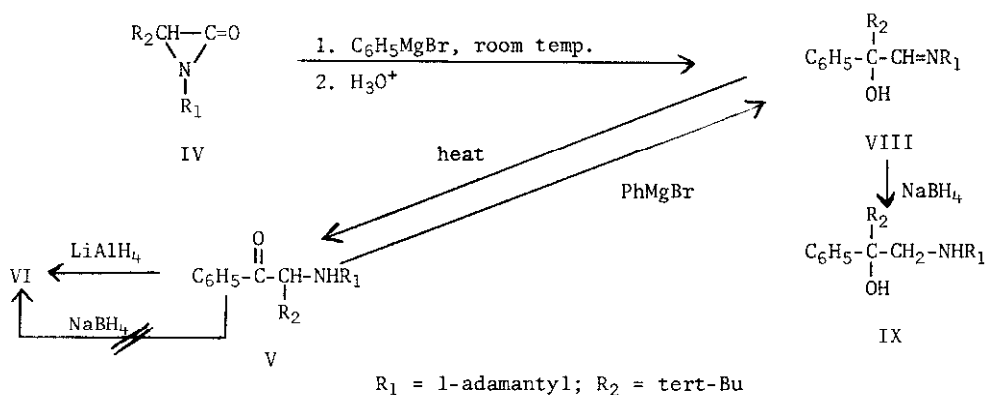
Treatment of IV with phenylmagnesium bromide in ether (1:0.9 molar ratio), initially at 0° and then for 12 hr. at room temperature, afforded a compound, mp 82-84°, exhibiting essentially the same spectral features as those reported by Lengyel and his co-workers.⁴ The crude reaction mixture also contained biphenyl and the α -bromo amide (VII).^{4,5} We have found that the proportion of VII as a contaminant in the crude reaction mixture can be greatly reduced by the use of up to 400% excess of the Grignard reagent. Lengyel and his co-workers attributed the signal seen at the lowest field ($\delta = 8.33$) in the pmr spectrum of the principal product to the N-H proton of V, without any justification for the unusually low-field position nor any indication that this proton undergoes an H-D exchange in the presence of D₂O. In fact, it is the hydrogen atom exhibiting a signal at $\delta 5.12$, believed by Lengyel to be the methine hydrogen of V, that is easily exchanged. Moreover, the nmr signal for the phenyl protons is not split into two distinct groups (o- and m- + p-) as would be expected for a benzoyl group. Therefore, we reject structure V as the true structure of the principal product and instead propose that this compound is the isomeric α -hydroxy imine VIII (Scheme III). On this basis, the signals at $\delta 8.33$ and 5.12 (in CCl₄) can be readily attributed to the CH=N and OH groups, respectively. The presence of these two groups is confirmed by the observation of bands at 1667 and 3367 cm⁻¹ in the ir (CCl₄) spectrum. The low frequency of the latter band, believed by Lengyel to be an NH band, coupled with the invariance of its position upon dilution, suggests an intramolecular hydrogen bond between the hydroxyl group and the nitrogen atom. Further proof of the structure of VIII is provided by its reduction by sodium borohydride in ethanol to IX (mp 93-94°), a compound considered by Lengyel and his co-workers⁴ to be VI. They assigned two sets of doublets, reportedly centered at $\delta 2.20$ and 2.70 in the pmr spectrum, to the methine hydrogen atoms of VI. We observed similar doublets, centered at approximately $\delta 3.2$ ⁷ and 2.7, which we consider to be the AB pattern produced by the anisochronous protons of the methylene group⁸ that is adjacent to the benzylic carbon atom. The chemical shift corresponding to either doublet is inconsistent with that to be expected for structure VI; thus, in ephedrine [PhCH(OH)CH(CH₃)NHCH₃],

the resonance of the benzylic proton is encountered at a considerably lower field ($\delta = 5.15$), and the coupling constant between the two methine protons is only 4 Hz.⁹ The peak at m/e 164 in the mass spectrum (the base peak in our spectrum) can be easily interpreted in terms of fragmentation adjacent to the benzylic carbon atom in IX, whereas structure VI would require a different explanation.

The α -hydroxy imine VIII undergoes quantitative rearrangement to the α -amino ketone V, mp 105.5-107°, when heated at 119° for 10 hr. under argon.¹⁰ Compound V exhibits ir bands (CCl₄) at 3300 and 1672 cm⁻¹; nmr (CCl₄) signals at δ 0.85 (s, 9 H), 1.82 (m, 16 H, adamantyl + NH), 4.03 (s, 1 H), and 7.68 (m, 5 H, two distinct groups of lines about 0.6 ppm apart); and peaks in the mass spectrum (80 eV) at m/e 325 (M⁺), 220 (M-C₆H₅CO, base peak), 135 (adamantyl) and 105 (C₆H₅CO), the other peaks considered by Lengyel to be prominent peaks being either absent or present to the extent of less than 4% of the base peak. Treatment of V with sodium borohydride failed to yield VI under the conditions described by Lengyel. However, this reduction could be effected by lithium aluminum hydride (molar ratio of LiAlH₄ to V = 3:1) in boiling ether after 15 hr. to give a solid, mp 74.5-77°, [hydrochloride, mp 237-240°(dec.)], in 81% yield, and having physical properties quite different from those reported by Lengyel. Thus, its ir spectrum (CCl₄) exhibited a broad band centered at 3385 cm⁻¹ (shoulder at 3570 cm⁻¹) and the pmr signals (CCl₄) besides those for NH and OH protons appeared at δ 0.73 (s, tert-butyl), 1.33-2.33 (m, adamantyl), 2.98 [d, $J = 3.5$ Hz, CH(NH)], 4.83 [d, CH(OH)], and 7.25 (m, phenyl). Peaks in its mass spectrum (80 eV) at m/e 327 (M⁺), 270 (M-C₄H₉), 220 (M-C₆H₅CHOH, base peak), 135 (C₁₀H₁₅), and 107 (C₆H₅CHOH) further corroborate structure VI assigned to this compound.

The conversion of the α -lactam IV into the α -hydroxy imine VIII probably involves an initial cleavage of the acyl-nitrogen bond of IV by the Grignard reagent to afford the magnesium

Scheme III



salt (or a complex) of V, followed by rearrangement of this intermediate to a metallic derivative of VIII. Although other pathways are not excluded, evidence in favor of the proposed mechanism is the actual detection of V in the crude reaction mixture when IV is allowed to react with phenylmagnesium bromide at -78°C., and the rearrangement of pure V to VIII in the

presence of phenylmagnesium bromide.¹¹

REFERENCES AND NOTES

1. This communication is being dedicated to Professor Robert B. Woodward of Harvard University, Cambridge, Massachusetts, on the occasion of his sixtieth birthday, and in appreciation of one of the most exciting periods in the life of one of us (E.R.T.).
2. J. C. Sheehan and M. M. Nafissi-V., J. Am. Chem. Soc., **91**, 4596 (1969).
3. (a) E. R. Talaty, A. E. Dupuy, Jr., C. K. Johnson, T. P. Pirotte, W. A. Fletcher, and R. E. Thompson, Tetrahedron Lett., 4435 (1970); (b) E. R. Talaty, L. M. Pankow, K. W. Knutson, and K. E. Garrett, unpublished results.
4. I. Lengyel, R. V. Mark, and C. A. Troise, Synthetic Commun., **1**, 153 (1971).
5. The formation of α -halo amides by the reaction of α -lactams and Grignard reagents (ref. 3a) or magnesium halides (ref. 6) has been reported by us; however, contrary to a statement made in ref. 4, we have never claimed in ref. 3a that α -halo amides are the sole products in all reactions involving Grignard reagents.
6. E. R. Talaty, A. E. Dupuy, Jr., and C. M. Utermoehlen, Chem. Commun., 16 (1971)
7. The discrepancy in the position of one doublet could be attributed to a typographical error in Lengyel's manuscript. Except for this difference, the remaining features of the spectra described by Lengyel for this product are essentially in accord with our observations.
8. When analyzed as an AB pattern, the chemical shifts of the protons are δ 2.73 and δ 3.23 ($J = 11$ Hz).
9. J. Reisch, H. Alfes, and H. Möllmann, Fresenius' Z. Anal. Chem., **238**, 29 (1968).
10. This type of rearrangement is well known: for example, S. Yamada, H. Mizuno, and S. Terashima, Chem. Commun., 1058 (1967); C. L. Stevens, P. M. Pillai, M. E. Munk, and K. G. Taylor in "Mechanism of Molecular Migrations", Vol. 3, B. S. Thyagarajan, Ed., Wiley-Interscience, New York, N. Y., 1971, p. 271.
11. The rearrangement of α -amino ketones to α -hydroxy imines in the presence of Grignard reagents has not been reported previously.