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THE QUESTION OF INSERTION-ALKYLATION OF α-LACTAMS

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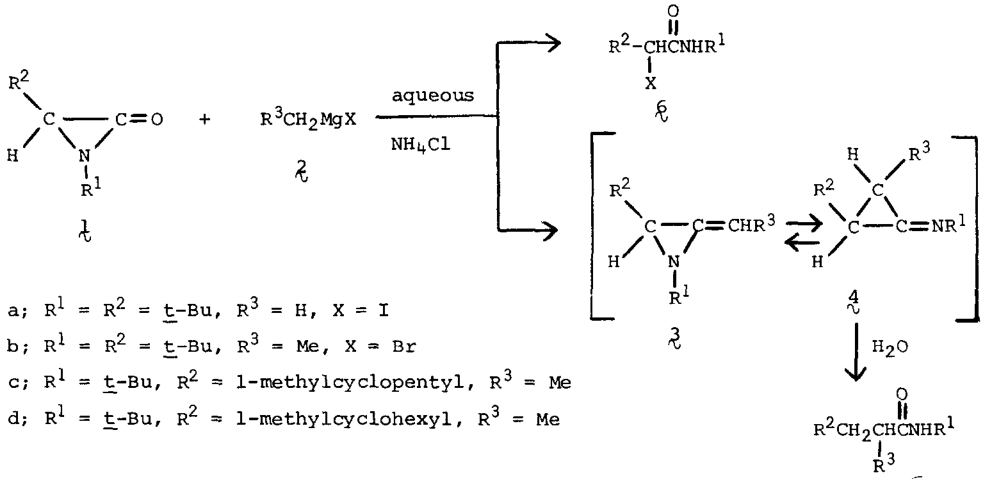
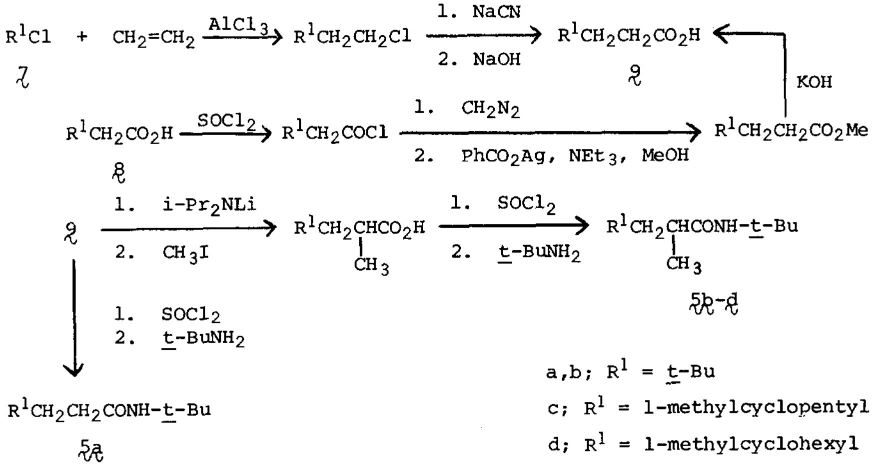
The reaction of α-lactams with alkylmagnesium halides has been claimed to produce amides by a novel, insertion-type alkylation of the acyl group,[1] a claim that has been hailed in a recent text-book[2] as an example of the construction and subsequent destruction of a heterocyclic ring as a useful synthetic tool. Thus, the reaction of 1,3-di-t-butylaziridinone(**1a**) with MeMgI(**2a**) in ether was reported to afford a compound(**5a**) by a path involving **3a** and **4a**. Neither of these intermediates was isolated, and the structure of the product was based on spectral evidence. Corresponding products (**5b**-**d**) were postulated to result from the reaction of ethylmagnesium bromide(**2b**) with the α-lactams **1b**-**1d**.



a; $R^1 = R^2 = $ t-Bu, $R^3 = H$, X = I
b; $R^1 = R^2 = $ t-Bu, $R^3 = Me$, X = Br
c; $R^1 = $ t-Bu, $R^2 = $ 1-methylcyclopentyl, $R^3 = Me$
d; $R^1 = $ t-Bu, $R^2 = $ 1-methylcyclohexyl, $R^3 = Me$

Attempts to reproduce the preparation of **5a** from **1a** by the above method have been made on four separate occasions in the present authors' laboratory, and each time there has been no evidence of the presence of **5a** even in the crude reaction mixture. Instead, the principal set of products consists of an α-iodo amide(**6a**)[3a] along with varying amounts of substances derived from this halo amide by various processes, e.g., reduction,[3b] a result[3c] that is in complete agreement with that of another group.[4] The question still remains whether this failure to obtain **5a** from **1a** reflects an inability to duplicate adventitious reaction conditions or whether other factors have been overlooked. The entire work[1] summarized on the previous page has now been repeated by the current authors, and all the products (**5a**-**5d**) reported therein have been synthesized by independent procedures.

The desired amides (**5a**-**5d**) were obtained by one of two straightforward routes commencing from the tertiary-alkyl chloride **7** or the tertiary-alkylacetic acid **8**, both involving the acid **9** (Scheme).[5] Compound **9a**, b.p. 104-105°/8 mm., was prepared by both routes and found to be identical in all respects [i.r. (CCl_4):3485-2350 (broad), 1719 cm^{-1}; 60 MHz p.m.r. (CCl_4): δ 0.92 (9H, s), 1.38-2.46 (4H, m), 11.22 (1H, s)].[6] The viability of both routes for the synthesis of one β-tertiary-alkylpropionic acid (**9a**) having been thus established,[7] other members (**9c**, **9d**) of this class of acids were synthesized only by the route starting from the corresponding substituted acetic acids (**8c**, **8d**). Compound **5a** had a m.p. and spectral features entirely



SCHEME

different from those described previously,[1] and discrepancies were also observed in the case of **5b** (Table). No properties of **5c** or **5d** were reported;[1] hence, these compounds are not included in the Table. Key features of the reported n.m.r. spectra,[1] which are missing in the spectra recorded in the Table, are two triplets and a mere doublet corresponding to the methylene protons in **5a** and **5b**, respectively. Adjacent methylene groups in compounds very similar to **5a** usually exhibit not first-order splitting patterns but patterns ranging from AA'XX' to AA'BB',[8] a feature observed by the present authors in the spectra of all such compounds shown in the Scheme.[9] The methylene group in **5b** is adjacent to a chiral carbon atom, and assignment of a doublet splitting to this group ignores the possibility of these protons being anisochronous, a possibility fully realized for all such compounds synthesized in the current authors' laboratory (Scheme). A prime evidence cited in support of structure **5a** was a prominent McLafferty rearrangement of the parent ion,[1] but a peak (m/e 129) corresponding to this process was found to be very weak in the present work. Thus, it is highly unlikely that insertion-alkylation of **1a** to **5a** occurs during its reaction with **2a**. An examination of the reactions of α-lactams

TABLE. Comparison of observed and reported[a] characteristics[b] of "insertion-alkylation products"

	5a	**5b**
m.p.	160.5-162°C [96-97°C]	114.2-115°C [107°C]
i.r.	3295, 1644, 1555 cm^{-1} [3200, 1655, 1540 cm^{-1}]	3310, 1632, 1525 cm^{-1} [3210, 1650, 1545 cm^{-1}]
60-MHz n.m.r.	δ 0.90 (9H,s), 1.36 (9H,s), 1.49-2.32 (4H,m), 5.62-6.44 (1H, broad) [1.00 (9H,s), 1.32 (9H,s), 1.93 (2H,t), 2.17 (2H,t), 5.82 (1H, broad)]	δ 0.88 (9H,s), 1.33 (9H,s), 1.03-1.23 (3H,d--overlaps other peaks), 1.03-2.92 (3H,m, $-CH_2-$ + $-\overset{\vert}{\underset{\vert}{C}}-H$), 5.33-6.00 (1H, broad) [1.00 (9H,s), 1.33 (9H,s), 0.97 (3H,d), 1.97 (2H,d), 2.18 (1H,m), 5.33 (1H, broad)]
mass spectrum	*m/e* 185 (M^+), 128 (*M*-*t*-Bu), 129 (2.3%), 114 (*M*-*t*-$BuCH_2$) [*m/e* 185, 129 (60%)]	*m/e* 199 (M^+), 142 (*M*-*t*-Bu), 128 (*M*-*t*-$BuCH_2$) [*m/e* 199, none at 171]

[a] Values in brackets are from ref. 1. [b] All spectra were recorded under the same conditions as those reported in ref. 1. Compounds **5a** and **5b** were recrystallized from a commercial mixture of hexanes.

1b, **1c**, and **1d** with ethylmagnesium bromide by the present authors reveals the presence of more than one product in each case. Although a full analysis of the reaction mixtures has not been completed, n.m.r. spectra of the crude products do not provide any compelling evidence in favour of the insertion-alkylation products **5b**, **5c**, and **5d** independently synthesized by the processes described in the Scheme.[10]

We thank Mr. Dennis Davis for technical assistance, and the Graduate School, Wichita State University, for the award of a Research Assistantship to one of us (K.E.G.).

REFERENCES AND NOTES

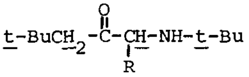
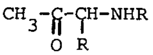
1. J. C. Sheehan and M. M. Nafissi-V, *J. Am. Chem. Soc.* **91**, 4596 (1969).
2. A. I. Meyers, 'Heterocycles in Organic Synthesis,' Wiley, New York, 1974, p. 7.
3. (a) E. R. Talaty, A. E. Dupuy, Jr., C. K. Johnson, T. P. Pirotte, W. A. Fletcher, and R. E.Thompson, *Tetrahedron Letters*, 4435 (1970), which also contains evidence for the structure of **6a**; (b) E. R. Talaty, L. M. Pankow, K. W. Knutson, and K. E. Garrett, unpublished work; (c) Meyers (ref. 2) mentions references 1 and 3(a), but states: "Although the precise nature of the intermediates has been questioned, this does not detract from the utility of the process ...." ["the process" being the preparation of **5a** from **1a**.]
4. H.E. Baumgarten, D. G. McMahan, V. J. Elia, B. I. Gold, V. W. Day, and R. O. Day, *J. Org. Chem.* **51**, 3798 (1976) and references therein.

5. The structures of all new compounds shown in the Scheme were proven by the usual techniques (spectroscopy and C,H analysis). In addition, spectral data were used to confirm the structures of known intermediates.

6. The synthesis of **9a** by the route starting from ethylene has been described by A. Brändström, *Acta Chem. Scand.* **13**, 611, 613 (1959); *ibid.* **10**, 1197 (1956). However, he did not provide any spectral data. Others have reported a partial n.m.r. spectrum (ref. 8 (a) below) and a detailed mass spectrum [N. C. Rol, *Recl. Trav. Chim. Pays-Bas* **84**, 413 (1965)] of **9a**, both of which are in agreement with the spectra obtained by us.

7. The modified Arndt-Eistert synthesis of **9a** from **8a** has not been described previously. The structure of the methyl ester [a known compound (ref. 8(a))] of **9a** is supported by spectral data [i.r. (CCl_4) 1740 cm^{-1}; 60 MHz p.m.r. (CCl_4) δ 0.90 (9H, s), 1.22-2.48 (4H, m), 3.58 (3H, s)], all of which were not reported in ref. 8(a).

8. (a) G. M. Whitesides, J. P. Sevenair, and R. W. Goetz, *J. Am. Chem. Soc.* **89**, 1135 (1967) (b) K. Mislow and M. Raban, in 'Topics in Stereochemistry,' ed. N. L. Allinger and E. L. Eliel, Wiley, New York, 1967, Vol. 1, p. 29; (c) see also J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Vol. 1, Pergamon Press, Oxford, 1965, pp. 415-416, for a different example of an unsymmetrical 1,2-disubstituted ethane that also does not exhibit a first-order spectrum.

9. A referee suggested  $\textit{t}\text{-BuC}\underline{\text{H}}_2\text{-}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{-}\underset{\text{R}}{\underset{|}{\text{C}\underline{\text{H}}}}\text{-NH-}\textit{t}\text{-Bu}$ (R = H or CH_3) as alternative structures with which our n.m.r. data for **5a** or **5b** would also be consistent. This would be true if the underlined protons on either side of the carbonyl group were to be coupled to each other However, we have prepared other α-amino ketones [E. R. Talaty, L. M. Pankow, D. D. Delling and C. M. Utermoehlen, *Synth. Commun.* 143 (1974)] and have not observed any splitting (within the limits of the same spectrometer) arising from such coupling; e.g.,  $\text{CH}_3\text{-}\underset{\text{O}}{\underset{\|}{\text{C}}}\text{-}\underset{\text{R}}{\underset{|}{\text{CH}}}\text{-NHR}$ (R = 1-adamantyl) exhibits only singlet signals that can be assigned to the methyl and methine protons.

10. This is probably the result of overlapping peaks of various products.

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