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REACTION OF N-BENZYLOXYIMINES WITH LITHIATED ALKYL CARBOXYLATES. CONVENIENT SYNTHESIS OF N-BENZYLOXY-β-LACTAMS

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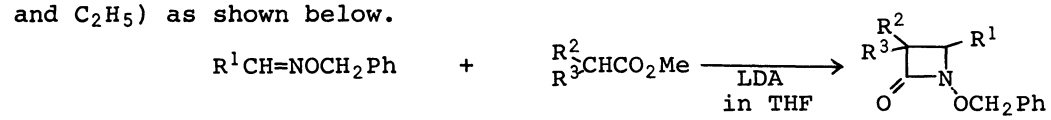
N-Benzyloxyimines have been shown to react with lithiated carboxylic esters to give N-benzyloxy-β-lactams in moderate to good yields.

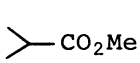
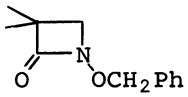
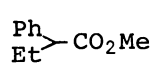
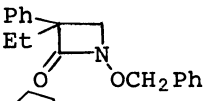
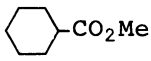
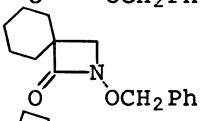
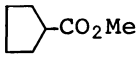
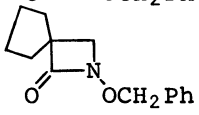
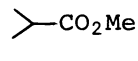
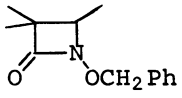
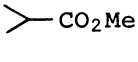
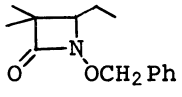
Monocyclic β-lactams such as nocardicin,[1] monobactams,[2] and monosulfactams[3] have recently drawn a world-wide attention as chemotherapeutics of a new generation, because of their biological activities against a broad spectrum of Gram-negative bacteria. A number of new methods have been developed for the construction of their β-lactam rings having suitable substituents.[1-4]

Although the reaction of imines with lithiated carboxylic esters was exploited as one of the potentially useful methods for the synthesis of the β-lactam ring, the applicable imines were limited to only nonisomerizable arylimines and alkylimines which have no hydrogen atom in the α-position to prevent their crucial isomerization to enamines. Therefore, this methodology was applicable only to the synthesis of 4-arylated and 4-t-alkylated β-lactams.[5] To overcome the critical limitation of this methodology, N-benzyloxyimines (or O-benzyloximes) were anticipated to be the most suitable alkylimine derivatives with less tendency of imine-to-enamine isomerization owing to the imine bond deactivation interacted by the lone pair electrons on the oxygen atom and would produce biologically important 4-alkylated β-lactams[2] by reaction with lithiated carboxylic esters. We wish to describe here the realized reaction of N-benzyloxyimines with lithiated carboxylic esters, yielding 4-unsubstituted and 4-alkylated N-benzyloxy-β-lactams (R^1=H, CH_3, and C_2H_5) as shown below.



A typical experiment (entry 5 in Table 1) is as follows. A solution of methyl isobutyrate (5 mmol) in dry THF (1 ml) was added to a solution of LDA (6 mmol) in dry THF (10 ml) dropwise with stirring at -78 °C. After 1 h, a solution of acetaldoxime-O-benzylether (5 mmol) in dry THF (1 ml) was added dropwise. Stirring was continued at -78 °C for 1 h and then at room temperature for a while. The solvent was then evaporated under reduced pressure and an ethereal solution of the residue was washed with 3 M aqueous hydrochloric acid, 10% aqueous potassium hydrogencarbonate and dried over anhydrous magnesium sulfate. Removal of the ether gave the crude product which was submitted to distillation under reduced pressure to give 1-benzyloxy-3,3-dimethyl-4-methyl-2-azetidinone in 48% yield. A liquid: 116 °C (0.05 mmHg); IR(film) 1768 cm^{-1} (β-lactam C=O).

Table 1. Production of N-Benzyloxy-β-lactams[a)]

Entry	N-Benzyloxyimine	Ester	Product[b)]	Yield/%[c)]
1	CH_2=NOCH$_2$Ph			67
2	CH_2=NOCH$_2$Ph			82
3	CH_2=NOCH$_2$Ph			65
4	CH_2=NOCH$_2$Ph			49
5	CH_3CH=NOCH$_2$Ph			48
6	C_2H_5CH=NOCH$_2$Ph			40

a) LDA : Ester : N-Benzyloxyimine = 1.2 : 1.0 : 1.0 (molar proportion). b) All products gave satisfactory elemental analyses and their spectral data were consistent with the proposed structures. The products of entries 2, 5 and 6 are NMR spectrometrically single isomers. c) Based on the product actually isolated.

Table 1 indicates clearly that all the reactions proceed smoothly to give the corresponding β-lactams in moderate to good yields.[6)] This finding shows the distinct contrast to the previous papers[5)] where the corresponding N-arylimines and N-silylimines were failed to react with lithiated carboxylic esters.

It is also noted that N-benzyloxy-β-lactams thus obtained may be easily convertible to N-hydroxy-β-lactams[7)] and then to N-unsubstituted ones.[8)] These products are related to monosulfactams, monobactams and also some 3,3-dialkyl-β-lactams which have been found to have a biological activity.[9)]

References

1) T. Kamiya, H. Aoki, and Y. Mine, "Chemistry and Biology of β-lactam Antibiotics," ed by R. B. Morin and M. Gorman, Academic Press(1982), Vol. 2, pp. 166-226.
2) W. H. Koster, C. M. Cimarusti, and R. B. Sykes, "Chemistry and Biology of β-Lactam Antibiotics," ed by R. B. Morin and M. Gorman, Academic Press(1982), Vol. 3, pp. 339-375.
3) E. M. Gordon, M. A. Ondetti, J. Pluscec, C. M. Cimarusti, D. P. Bonner, and R. B. Sykes, J. Am. Chem. Soc., 104, 6053(1982).
4) K. Ikeda, K. Achiwa, and M. Sekiya, Tetrahedron Lett., 24, 4707(1983) and references cited therein.
5) A. K. Bose, M. S. Khajavi, and M. S. Manhas, Synthesis, 1982, 407; D. J. Hart, K. Kanai, D. G. Thomas, and T. K. Yang, J. Org. Chem., 48, 289(1983).
6) Under these reaction conditions, only lithiated α,α-dialkylcarboxylic esters react to give the β-lactams.
7) P. G. Mattingly, J. F. Kerwin, Jr., and M. J. Miller, J. Am. Chem. Soc., 101, 3983(1979).
8) P. G. Mattingly and M. J. Miller, J. Org. Chem., 45, 410(1980).
9) R. F. Abdulla and K. H. Fuhr, J. Med. Chem., 18, 625(1975).

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