CHEMISTRY LETTERS, pp. 369 - 370, 1984. © The Chemical Society of Japan 1984

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

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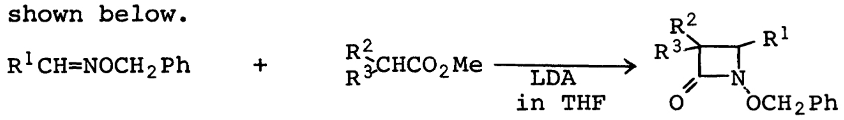
N-Benzyloxyimines have been shown to react with lithiated carboxylic esters to give N-benzyloxy-β-lactams in moderate to good yields.

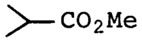
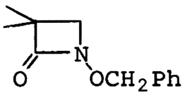
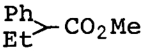
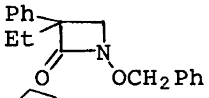
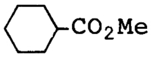
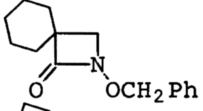
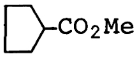
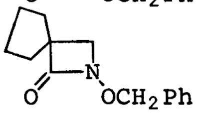
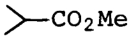
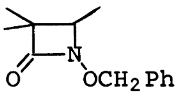
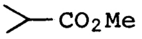
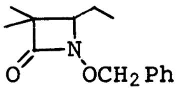
Monocyclic β-lactams such as nocardicin,[1)] monobactams,[2)] and monosulfactams[3)] have recently drawn a world-wide attention as chemotherapeutics of a new generation, because of their biological activities against a broad spectrum of Gram-negative bacteria. A number of new methods have been developed 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	$CH_2=NOCH_2Ph$			67
2	$CH_2=NOCH_2Ph$			82
3	$CH_2=NOCH_2Ph$			65
4	$CH_2=NOCH_2Ph$			49
5	$CH_3CH=NOCH_2Ph$			48
6	$C_2H_5CH=NOCH_2Ph$			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)]

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(Received December 8, 1983)