N,N-Dibenzyloxycarbonylglycyl Chloride as Useful Ketene Equivalent in the Synthesis of Azetidin-2-ones

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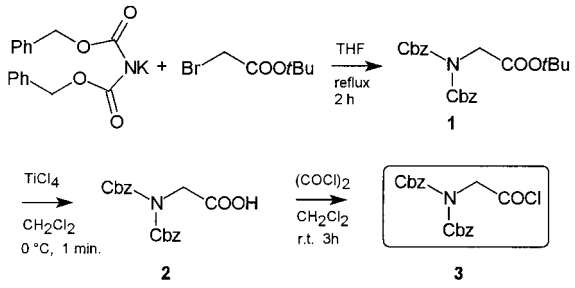
Received 12 March 1998

Abstract: *N,N*-3-Dibenzyloxycarbonylaminoazetidin-2-ones have been conveniently prepared from *N,N*-dibenzyloxycarbonylglycyl chloride and imines or hexahydrotriazines. The β-lactams thus obtained could be monodeprotected by mild hydrogenolysis with Pd on carbon.

Penicillins, cephalosporins and other major β-lactam antibiotics are characterized by the presence of a 3-aminoazetidin-2-one unit. Their synthesis was performed either *via* Staudinger reaction[1] or *via* the ester-enolate imine route.[2] In the former, in order to have a nitrogen bonded to the C-3 position, azidoacetyl chloride (Bose reaction) or phthalimidoacetyl chloride were the most utilized reagents, while in the latter the enolate of 1-(ethoxycarbonylmethyl)-2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopentane (STABASE) was largely employed.

Recently, we reported a synthesis of the 3-amino-4-acetoxyazetidin-2-one through a C-4 oxidation by ruthenium catalysts.[3] We emphasized the urgency to have a C-3 full protected nitrogen atom in order for the C-4 oxidation to be successful. In this perspective, the phthalimido group works well, but suffers by the need of a difficult cleavage.[4] The yield of this hydrolysis depends strongly on the substrate and, in general, the conditions required are too drastic for azetidinones.

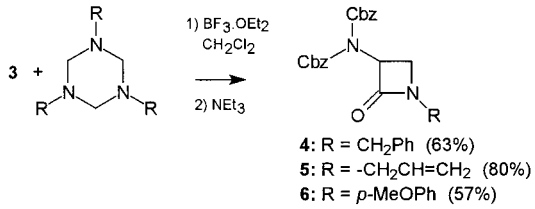
In connection with our ongoing interest in exploring new synthetic routes for β-lactams, we now report an easy and convenient method, starting from *N,N*-dibenzyloxycarbonylglycyl chloride**,** to prepare *N,N*-3-dibenzyloxycarbonylaminoazetidin-2-ones and deprotect them under mild conditions to the *N*-benzyloxycarbonylamino derivatives.



Scheme 1

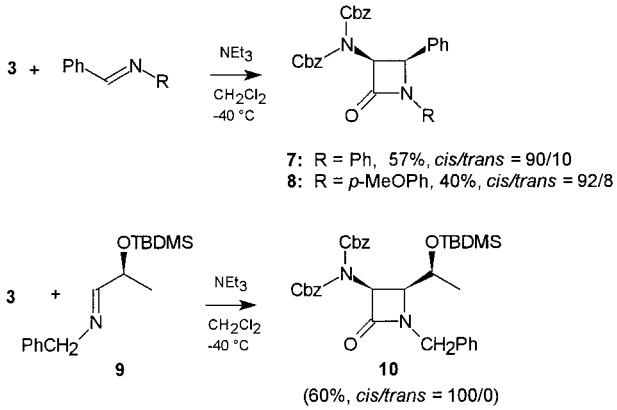
The *N,N*-dibenzyloxycarbonylglycine **2** was obtained in a 60% overall yield through alkylation of potassium dibenzyl iminodicarboxylate with *tert*-butyl bromoacetate[5] to give **1** and subsequent deprotection of *tert*-butyl group with $TiCl_4$ (1.5 eq., CH_2Cl_2, 0°C, 1 min).[6] The new ketene equivalent **3** was formed *in situ* by adding oxalyl chloride to the corresponding glycine derivative **2** (1.5 eq., CH_2Cl_2, rt, 3h) (Scheme 1). *N,N*-Dibenzyloxycarbonylglycyl chloride **3** in the presence of NEt_3 reacts with imines[7] or hexahydrotriazines affording β-lactams **4-8** and **10** in satisfactory yields.[8]

N-Allyl, *N*-benzyl, and *N-p*-methoxyphenylhexahydrotriazines were previously treated with BF_3•OEt_2 in CH_2Cl_2 according to a modified Kamiya procedure[9] and then added at -40 °C to a dichloromethane solution of **3** and Et_3N to afford β-lactams **4-6** (Scheme 2). In this approach, hexahydrotriazines served as a useful equivalent of the elusive



Scheme 2

formaldehyde imines for the preparation of monocyclic 4-unsubstituted β-lactams.[10]

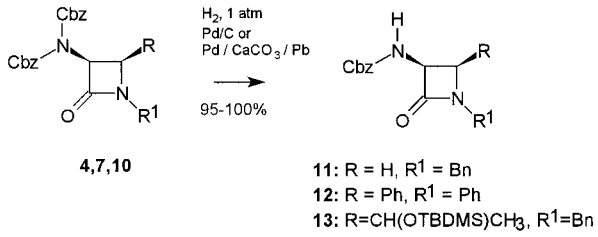


Scheme 3

When the *N,N*-dibenzyloxycarbonylglycyl chloride **3** was treated with imines, C_4 substituted azetidinones **7-10** were obtained (Scheme 3). The simple diastereoselectivity plays in favor of the *cis* isomer. The relative *cis/trans* stereochemistry was unequivocally determined by ^1H NMR spectroscopy on the basis of the coupling constants (*cis:* $J_{3,4}$ = 5.7-5.9 Hz and *trans:* $J_{3,4}$ = 2.5-3.0 Hz). It is noteworthy that we preferentially obtained *cis* azetidinones also with *N*-phenylbenzaldimine while it is known that the reaction of phthalimidoacetyl chloride with the same imine gives the corresponding *trans* β-lactam.[11] The *N*-benzylimine of (2*S*)-lactal **9**[12] furnished, in this approach, the optically active *cis* azetidinone **7** as a single isomer ($[\alpha]_D^{20}$ = +16.7, c = 0.936, $CHCl_3$). The stereochemistry of this product was determined by analogy with known compounds.[13] The total *cis-syn* asymmetric induction observed in this case, is particularly noteworthy when compared with the *trans-syn* one obtained with the STABASE enolate imine cycloaddition.[13] This stereochemical result implies that the natural (*S*)-C3 configuration could be obtained starting from the easily available (2*S*)-lactal.

Exposure of β-lactams **4, 7, 10** to H_2 (1 atm) in THF at room temperature in the presence of a catalytic amount of Pd (10% on C for short reaction time or Lindlar catalyst) provided the corresponding monobenzyloxycarbonylamino derivatives in almost quantitative yields (Scheme 4).[14]

In conclusion, we have demonstrated that the *N,N*-dibenzyloxycarbonylglycyl chloride constitutes a useful ketene equivalent for the synthesis of C4-unsubstituted 3-aminoazetidin-2-ones and *cis* C-4 substituted as well. The selective hydrogenolysis to mono



4,7,10

11: R = H, R^1 = Bn
12: R = Ph, R^1 = Ph
13: R=CH(OTBDMS)CH_3, R^1=Bn

Scheme 4

benzyloxycarbonylamino derivatives, largely employed as β-lactam antibiotic intermediates, is mild and quantitative.

Acknowledgment: Financial support was provided by MURST (Fondi 40% and 60%) and C.N.R.

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(7) The mono *N*-Cbz glycyl chloride has been previously applied in cycloaddition reactions with acyclic imines but with very low yields (11-22%). See for instance Bose, A.K.; Manhas, M.S.; Chawla, H.P.S.; Dayal, B. *J. Chem. Soc., Perkin Trans. I* **1975**, 1880.

(8) A representative procedure is as follows:
To a solution of *N,N*-dibenzyloxycarbonyl glycine (343 mg, 1 mmol) in CH_2Cl_2 (10 mL) at room temperature, oxalyl chloride (1.5 mmol, 0.13 mL) was added. After the mixture was stirred for 3 h, the temperature was brought to –40 °C and Et_3N (6 mmol, 0.84 mL) was slowly added dropwise into the mixture. The solution became yellow and then orange confirming that the ketene was formed. After 30 min at low temperature one equivalent of the appropriate imine in CH_2Cl_2 (3 mL) or a previously mixed solution of hexahydrotriazine (0.33 mmol) and BF_3•OEt_2 (1 mmol) in CH_2Cl_2 (5 mL) at room temperature, was added dropwise. The mixture was allowed to slowly warm to room temperature overnight. The resulting brown solution was diluted with CH_2Cl_2 and washed with HCl (1 M, 20 mL). The aqueous washes were re-extracted with CH_2Cl_2 (2 x 20 mL) and the combined organic layers were dried and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (cyclohexane / AcOEt = 8 / 2).
4: IR ($CHCl_3$): 1800, 1759, 1700. ^{1}H NMR ($CDCl_3$, 300 MHz): 3.29 (dd, 1H, *J* = 3.0 and *J* = 5.1 Hz); 3.35 (dd, 1H, *J* = 5.4 and *J* = 5.1 Hz); 4.02 (d, 1H, *J* = 15.0 Hz); 4.4 (d, 1H, *J* = 15 Hz); 5.21 (m, 4H); 5.55 (dd, 1H, *J* = 3.0 and *J* = 5.4 Hz); 7.2-7.4 (m, 15H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): 166.8; 152.4; 135.0; 134.5; 128.6; 128.5; 128.4; 128.2; 128.1; 127.9; 69.4; 59.9; 45.8; 45.7.
10: $[\alpha]_D^{20}$ = +16.7 ($CHCl_3$, c = 0.936). IR ($CHCl_3$): 1790, 1760, 1710, 1244. ^{1}H NMR ($CDCl_3$, 300 MHz): -0.02 (s, 3H); -0.01 (s, 3H); 0.84 (d, 3H, *J* = 6.0 Hz); 0.89 (s, 9H); 3.46 (dd, 1H, *J* = 5.3 Hz, *J* = 9.5 Hz); 4.11 (d, 1H, *J* = 14.6 Hz); 4.13 (dq, 1H, *J* = 6.0 and *J* = 9.5 Hz); 4.86 (d, 1H, *J* = 14.6 Hz); 5.25 (m, 3H); 7.2-7.5 (m, 5H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): 166.1; 153.2; 152.7; 135.8; 134.4; 128.6; 128.5; 128.4; 127.5; 69.6; 68.5; 51.7; 51.6; 45.5; 25.9; 20.8; 17.8; -4.3; -4.6.

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(10) For a recent study on 4-unsubstituted β-lactams see:
Palomo, C.; Aizpurua, J.M.; Legido, M.; Galarza, R. *J. Chem. Soc., Chem. Comun.* **1997**, 233. Alcaide, B.; Rodriguez-Vincente, A.; Sierra, M.A. *Tetrahedron Lett.* **1998**, *39*, 163.

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(12) To a stirred solution of benzyl amine (1mmol) in dry CH_2Cl_2 (5 mL) under an inert atmosphere at rt were successively added $MgSO_4$ (2 mmol) and the (2*S*)-*t*-butyldimethylsilyloxylactal **9** (1mmol). The resulting mixture was stirred at room temperature until the starting aldehyde was consumed (GC-monitoring). The filtered solution was evaporated to give the crude imine.

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(14) A representative procedure is as follows:
To a solution of β-lactam **4, 7, 10** (0.17 mmol) in THF (5 mL), 5 mg of 10% Pd on activated charcoal were added. The reaction flask was connected to a balloon containing H_2 at the pressure of 1 atm and the reaction was monitored by TLC each 15 min. After total consumption of the starting material (30-60 min) the Pd was filtered off and the solution was concentrated *in vacuo* to afford the monodeprotected β-lactam **11, 12, 13**. When the reaction time was extended, total deprotection was achieved.
With the same procedure 100 mg (0.23 mmol) of β-lactam **4** were deprotected using 10 mg of 5% Pd on $CaCO_3$ poisoned with Pb to afford β-lactam **11**. In this case no further deprotection was detected even with extended reaction time.
11: IR ($CHCl_3$,): 3400, 1732, 1708. ^{1}H NMR ($CDCl_3$, 300 MHz): 3.18 (dd, 1H, *J* = 1.9 Hz, *J* = 5.4 Hz); 3.42 (dd, 1H, *J* = 5.2 Hz, *J* = 5.2 Hz); 4.39 (m, 2H); 4.83 (m, 1H); 5.08 (s, 2H); 6.12 (m, 1H); 7.2-7.4 (m, 10H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): 166.9; 155.6; 135.9; 134.7; 128.7; 128.4; 128.0; 127.7; 67.0; 57.3; 48.1; 45.9.
13: IR ($CHCl_3$,): 3300, 1761, 1749, 1725, 1253. $[\alpha]_D^{20}$ = + 44.3 ($CHCl_3$, c = 3.93). ^{1}H NMR ($CDCl_3$, 300 MHz): 0.012 (s, 6H); 0.93 (s, 9H); 1.14 (d, 3H, *J* = 6.5 Hz); 3.53 (dd, 1H, *J* = 4.7 Hz, *J* = 4.4 Hz); 3.97 (dq, 1H, *J* = 6.5 Hz, *J* = 4.4 Hz); 4.14 (d, 1H, *J* = 15.3 Hz); 4.89 (d, 1H, *J* = 15.3 Hz); 5.08 (dd, 1H, *J* = 9.6 and *J* = 4.7 Hz); 5.12 (m, 2H); 5.64 (d, 1H, *J* = 9.6 Hz); 7.1-7.4 (m, 5H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): 167.5; 155.7; 136.0; 135.4; 128.8; 128.5; 128.4; 128.1; 127.6; 67.7; 67.2; 61.7; 58.5; 45.7; 25.9; 21.9; 17.9; -3.3; -4.5.