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SIMPLE N-PROTECTING GROUPS FOR β-LACTAM SYNTHESIS

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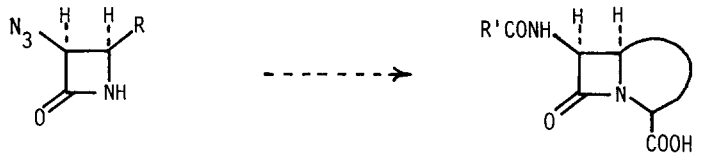
Abstract: Allyl and 2,2-diethoxyethyl groups on β-lactam nitrogen can be removed via the enol acetate to give N-unsubstituted β-lactam under mild conditions.

N-Unsubstituted β-lactam 1 is a useful synthetic intermediate for the preparation of a variety of analogues of β-lactam antibiotics.[1] Although Bose's procedure is widely used for β-lactam synthesis,[2] only a handful of amines have been devised to synthesize the N-unsubstituted β-lactams.[1d, 3] In connection with our synthetic studies on naphthyridinomycin,[4] we needed to find a β-lactam N-protecting group which can be deprotected under mild conditions. We now wish to report herein that commercially available allylamine and aminoacetaldehyde diethyl acetal can be added to this narrow group of amines.



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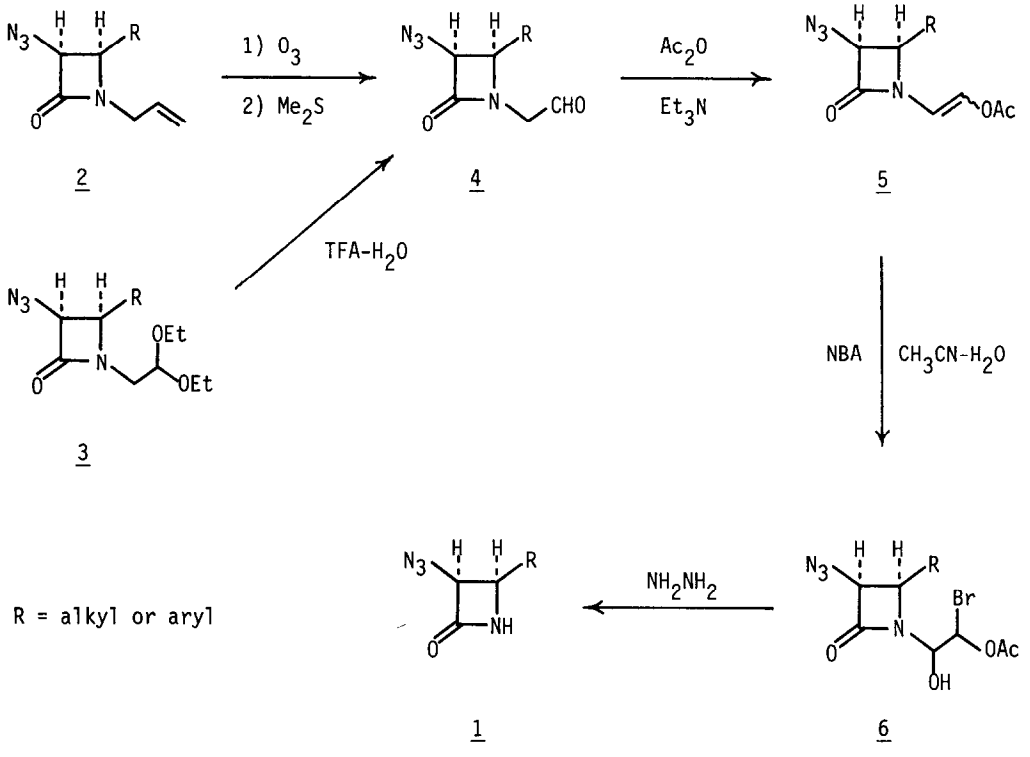
The aldehyde 4, obtained either by ozonolysis of the N-allyl compound 2 or by acid hydrolysis of the corresponding diethyl acetal 3, underwent unusually facile enol acetate

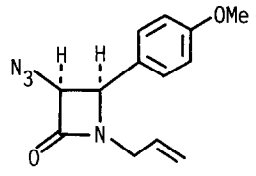
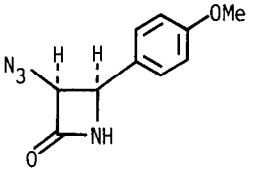
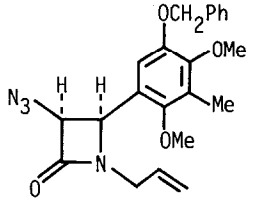
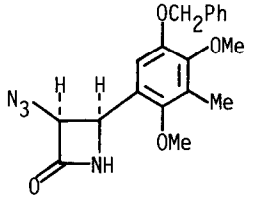
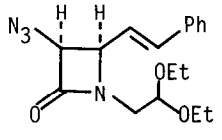
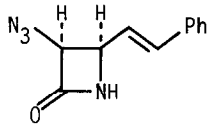
formation upon treatment with acetic anhydride and triethylamine in dichloromethane at room temperature. Oxidation of the resultant enol acetate 5 with N-bromoacetamide (NBA) in aqueous acetonitrile gave the bromohydrin 6, which was subsequently treated with hydrazine to afford the N-unsubstituted β-lactam 1. No tedious separation of the intermediates is necessary. Selected examples, which clearly demonstrate general applicability of our method, are shown in the Table.



A representative experimental procedure is as follows: Ozone was passed through a solution of 7a (305 mg, 1.18 mmol) in 20 ml of methanol-dichloromethane (1:1) at -78° until the blue color of ozone persisted. After excess ozone was purged by argon, 3 ml of dimethyl sulfide was added and the solution was allowed to warm to room temperature. After 30 minutes, the solution was evaporated under reduced pressure. Traces of methanol were azeotropically removed by addition and evaporation in vacuo of three 10-ml portions of toluene. To a solution of this crude aldehyde in 5 ml of dichloromethane were added 1 ml each of acetic anhydride and triethylamine. After standing at room temperature for 30

minutes, the mixture was evaporated to a small volume and partitioned between ether and saturated $NaHCO_3$ solution. The ethereal layer was dried over anhydrous $MgSO_4$, evaporated to give a cis and trans mixture (2:1) of enol acetates. To a stirred solution of the crude enol acetates in 5 ml of acetonitrile-H_2O (4:1) was added 163 mg (1.18 mmol) of N-bromoacetamide. After stirring for 10 minutes at room temperature, 188 µl (5.9 mmol) of hydrazine was added and stirring was continued for an additional 10 minutes. The solution was then poured into saturated $NaHCO_3$ solution, extracted with ethyl acetate, dried ($MgSO_4$), and evaporated. Chromatographic separation (MPLC) afforded pure N-unsubstituted β-lactam 8a (186 mg, 72% overall yield).

TABLE

Starting Material[5]		Product		Yield
	7a		8a[6]	72%
	7b		8b[7]	74%
	7c[8]		8c[9]	66%

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References and Notes

1. (a) M. Ihara, Y. Haga, M. Yonekura, T. Ohsawa, K. Fukumoto, and T. Kametani, J. Am. Chem. Soc., 105, 7345 (1983); (b) J. V. Heck, M. J. Szymonifka, and B. G. Christensen, Tetrahedron Lett., 1519 (1982); (c) J. G. Gleason, T. F. Buckley, K. G. Holden, D. B. Bryan, and P. Siler, J. Am. Chem. Soc., 101, 4730 (1979); (d) D. B. Bryan, R. F. Hall, K. G. Holden, W. F. Huffman, and J. G. Gleason, J. Am. Chem. Soc., 99, 2353 (1977).

2. A. K. Bose, M. S. Manhas, B. Anjaneyulu, and S. K. Bhattacharya, Tetrahedron, 23, 4769 (1967).

3. (a) T. Fukuyama, R. K. Frank, and C. F. Jewell, Jr., J. Am. Chem. Soc., 102, 2122 (1980); (b) J. V. Heck and B. G. Christensen, Tetrahedron Lett., 5027 (1981); (c) D. R. Kronenthal, C. Y. Han, and M. K. Taylor, J. Org. Chem., 47, 2765 (1982).

4. J. Sygusch, F. Brisse, S. Hanessian, and D. Kluepfel, Tetrahedron Lett., 4021 (1974).

5. Prepared in 55-72% yield from the corresponding aldehydes using A. K. Bose's procedure (ref. 2).

6. 8a: ^{1}H NMR ($CDCl_3$) δ 3.84 (3H, s), 4.8-5.0 (2H, m), 6.52 (1H, br s), 6.95 (2H, d, J = 9 Hz), 7.26 (2H, d, J = 9 Hz); IR (CH_2Cl_2) 3412, 2118, 1788 cm^{-1}; mp (EtOAc-hexane) 127-128°.

7. 8b: ^{1}H NMR ($CDCl_3$) δ 2.24 (3H, s), 3.69 (3H, s), 3.87 (3H, s), 4.89 (1H, dd, J = 2.5, 5 Hz), 5.07 (2H, s), 5.23 (1H, d, J = 5 Hz), 6.13 (1H, br s), 6.80 (1H, s), 7.20-7.52 (5H, m); IR (CH_2Cl_2) 3410, 2115, 1786 cm^{-1}; mp (Et_2O) 111°.

8. The acetal of 7c was deprotected by treatment with trifluoroacetic acid- H_2O (4:1) at room temperature for 10 minutes.

9. 8c: ^{1}H NMR ($CDCl_3$) δ 4.49 (1H, dd, J = 5.5, 7 Hz), 4.80 (1H, dd, J = 2, 5.5 Hz), 6.18 (1H, dd, J = 7, 16 Hz), 6.66 (1H, d, J = 16 Hz), 6.87 (1H, br s), 7.20-7.52 (5H, m); IR (CH_2Cl_2) 3415, 2112, 1789 cm^{-1}; mp (Et_2O) 105°.

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