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# β-LACTAMS FROM AZETIDINE CARBOXYLATES. A SYNTHESIS OF (±)-3-ANA, THE NUCLEUS OF THE NOCARDICINS

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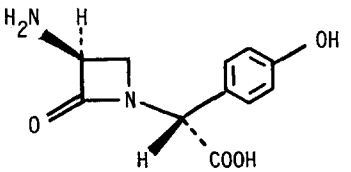
Summary: A synthesis of (±)-3-ANA is described involving oxidative decarbonylation of an azetidine carboxylic ester.

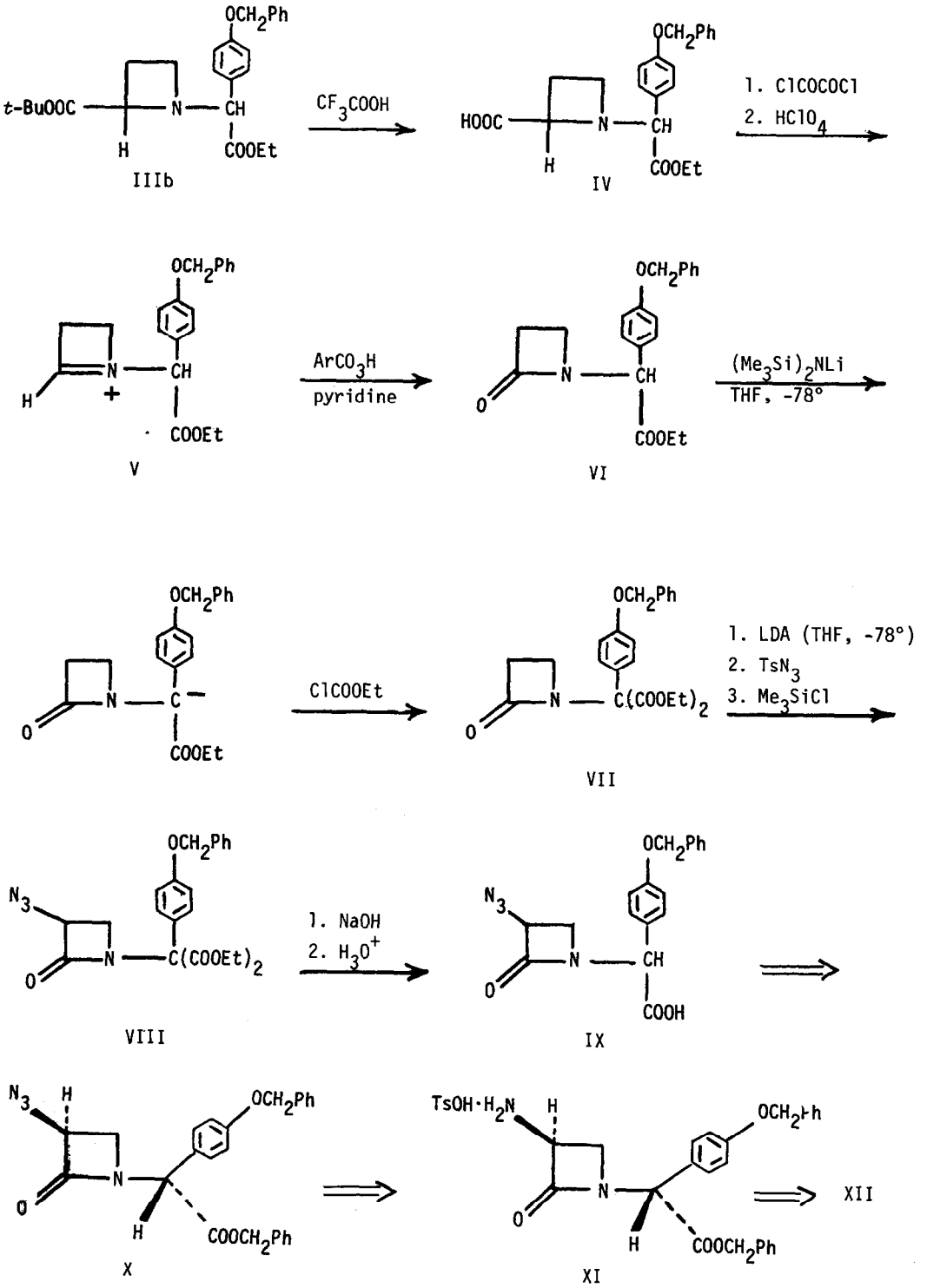
We have recently described new methods for the formation of β-lactams by the oxidative decarboxylation[1,3] or decarbonylation[2] of azetidine-2-carboxylic acids. We now report the application of one of these procedures[2] to the synthesis of (±)-3-aminonocardicinic acid (3-ANA) (XII), the nucleus of the nocardicins, β-lactam antibiotics recently isolated from a strain of Nocardia.[4,5] Our synthetic sequence outlined in Scheme I involves the preparation of the β-lactam malonate (VII) which is then converted as shown to the key acid-azide intermediate (IX).

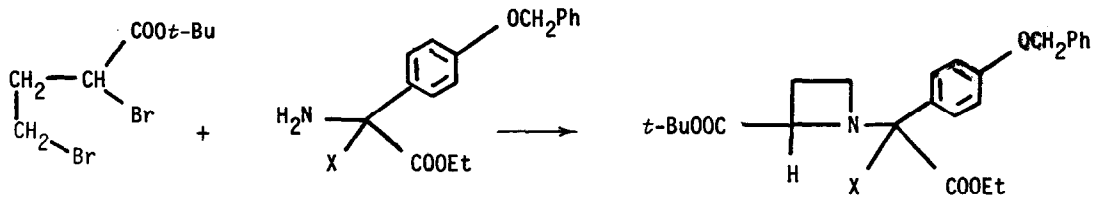



XII

In earlier reports[1,3] we have described the formation of a series of azetidine carboxylates by the reactions of primary amines with dibromo esters such as (I). Attempts to convert IIa to the azetidine (IIIa) by this method were unsuccessful due to the unfavorable steric factors in the reaction of the bulky malonate derivative with the dibromobutyrate (I).[6] However, it was possible to form the azetidine (IIIb) by warming t-butyl 2,4-dibromobutyrate (I) with the α-amino ester (IIb)[7] ($Na_2CO_3$, EtOH, 55°C, 4 days). The azetidine diester (IIIb) m.p. 108-109° was obtained as a 1:1 mixture of diastereomers (63%)[8,9].

Scheme I


t-BuOOC
OCH2Ph
CH
COOEt
H
IIIb
CF3COOH
HOOC
IV
1. ClCOCOCl
2. HClO4
V
ArCO3H
pyridine
VI
(Me3Si)2NLi
THF, -78°
ClCOOEt
C(COOEt)2
VII
1. LDA (THF, -78°)
2. TsN3
3. Me3SiCl
N3
VIII
1. NaOH
2. H3O+
COOH
IX
X
TsOH·H2N
XI
XII



I II III

a, X=COOEt
b, X=H

Selective hydrolytic cleavage of the tertiary butyl group of the diester (IIIb) was accomplished with anhydrous $CF_3COOH$ ($CH_2Cl_2$, 0°C, 2h). The intermediate azetidine carboxylic acid monoester (IV) thus formed was converted directly to the iminium salt (V) (decarbonylation) by treatment with oxalyl chloride (0°C, 2h) and then perchloric acid. Oxidation of V using 100% meta-chloroperbenzoic acid (1 equiv)[10] and pyridine (2 equiv) ($CH_2Cl_2$, 0°C, 40 min.) gave the azetidinone (VI) m.p. 61-62°C (53% overall from IIIb)[9,11,12].

Treatment of β-lactam (VI) with hexamethyldisilazide (THF, -78°C, 2h) and then with ethyl chloroformate resulted in selective carbethoxylation to yield the azetidine malonate (VII) (64%), as a colorless oil.[9,13] Introduction of the azide group at the 3-position of the β-lactam was accomplished by the procedure of Kühlein and Jensen.[14] Anion formation with LDA (THF, -78°C, 2h) was followed by the addition of p-toluenesulfonyl azide and then trimethylsilyl chloride to yield VIII (50%)[9,15]. Hydrolysis of the azide-malonate (VIII) with 1N NaOH ($CH_3OH$, 0°C, 2h) followed by acidification with 1N HCl resulted in decarboxylation and formation of IX as a 1:1 mixture of diastereomers (70%). This material was found to be completely identical (IR, NMR, and TLC) with the azide-acid diastereomeric mixture formed by an alternate route as recently reported[16]. Previous studies have described the benzylation of the mixture of azide-acids (IX)[16], separation of the diastereomers by HPLC to give X[16], reduction by $H_2S$ to (±)-dibenzyl 3-ANA hydrotosylate (XI)[16], and the final hydrogenolysis to 3-ANA (XII)[17b]. The procedure outlined here, utilizing an azetidine carboxylate as a precursor to the β-lactam system thus constitutes an alternate route to 3-ANA and to the nocardicins[17,18].

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## References and Notes

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2. H.H. Wasserman and A.W. Tremper, Tetrahedron Lett. 1449 (1977).

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5. T. Kamiya, "Recent Advances in the Chemistry of β-Lactam Antibiotics", Cambridge University Press, London, 1976.
6. Under the conditions previously employed[1,3] the reaction of IIa with a series of 2,4-dibromobutyrates gave none of the desired azetidine carboxylate.
7. p-Hydroxyphenylglycine ethyl ester was converted to the N-benzylidene derivative (benzaldehyde) and then treated with benzyl bromide in the presence of potassium carbonate to form the benzyl ether in DMF. Hydrolysis of the benzylidene derivative (10% HCl) yielded the amino ester (IIb).
8. IR ($CHCl_3$) 1735 $cm^{-1}$; NMR ($CDCl_3$) δ 7.30 (7H, m), 6.90 (2H, d, J = 9 Hz), 5.01 (2H, s), 4.21 (1H, s), 4.12 (2H, q, J = 7 Hz), 3.79 (1H, t, J = 8 Hz), 3.56-2.90 (2H, m), 2.34-2.05 (2H, m), 1.28 (9H, s), 1.17 (3H, t, J = 7 Hz); and 7.30 (7H, m), 6.88 (2H, d, J = 9 Hz), 5.01 (2H, s), 4.32 (1H, s), 4.10 (2H, q, J = 7 Hz), 3.79 (1H, t, J = 8 Hz), 3.56-2.90 (2H, m), 2.34-2.05 (2H, m), 1.40 (9H, s), 1.17 (3H, t, J = 7 Hz).
9. Yields given in this synthesis are for pure isolated products having satisfactory spectroscopic properties and either elemental analyses or high resolution mass spectra.
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11. IR ($CHCl_3$) 1740 $cm^{-1}$; NMR ($CDCl_3$) δ 7.33 (5H, m), 7.14 (2H, d, J = 8.8 Hz), 6.91 (2H,d, J = 8.8 Hz), 5.46 (1H, s), 4.99 (2H, s), 4.14 (2H, q, J = 6.6 Hz), 3.54 (1H, m), 2.99 (1H, m), 2.92 (1H, m), 2.76 (1H, m), 1.18 (3H, t, J = 6.6 Hz).
12. β-Lactam (VI) has also been prepared by the cyclization of ethyl 2-(3-bromopropionylamido)-p-benzyloxyphenyl acetate with sodium hydride in 20% DMF-$CH_2Cl_2$ (79%), H.H. Wasserman, D.J. Hlasta, A.W. Tremper, and J. Wu, Tetrahedron Lett., in press.
13. IR (neat) 1740 $cm^{-1}$; NMR ($CDCl_3$) 7.40 (5H, m), 7.33 (2H, d, J = 8.8 Hz), 6.97 (2H, d, J = 8.8 Hz), 5.06 (2H, s), 4.33 (4H, q, J = 7.0 Hz), 3.47 (2H, t, J = 4.4 Hz), 2.95 (2H, t, J = 4.4 Hz), 1.30 (6H, t, J = 7.0 Hz).
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15. IR (neat) 2130, 1775, 1750 $cm^{-1}$; NMR ($CDCl_3$) δ 7.37 (5H, m), 7.30 (2H, d, J = 8.0 Hz), 6.97 (2H, d, J = 8.9 Hz), 5.05 (2H, s), 4.57 (1H, dd, J = 5.2 Hz, J = 2.6 Hz), 4.32 (4H, q, J = 7.0 Hz), 3.78 (1H, dd, J = 6.4 Hz, J = 5.2 Hz), 3.36 (1H, dd, J = 6.4 Hz, J = 2.6 Hz), 1.29 (6H, t, J = 7.0 Hz).
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18. For recent syntheses of 3-ANA, see (a) H.H. Wasserman and D. Hlasta, ref. 16; (b) T. Kamiya, T. Oku, O. Nakaguchi, H. Takeno, and M. Hashimoto, Tetrahedron Lett., 5119 (1978).

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