Pergamon

Tetrahedron Letters, Vol. 37, No. 28, pp. 4891-4894, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01003-9

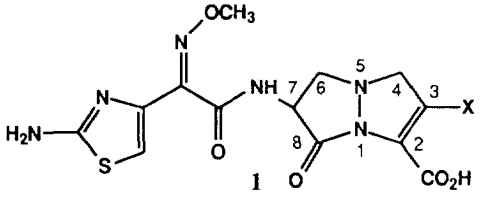
Synthesis of a 3-Keto Bicyclic Pyrazolidinone Using a Curtius Rearrangement

David A. Neel*, Richard E. Holmes and Jonathan W. Paschal

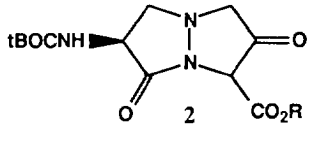
Lilly Research Laboratories
Eli Lilly and Company
Indianapolis, IN 46285

Abstract: The synthesis of bicyclic pyrazolidinone **2** is described. Traditional methods for penem and cephem ring cyclization were found to be unsuccessful and new methodology using a Curtius rearrangement was utilized. The 3-enamine **11** was hydrolysed to the desired β-keto ester **2b** without substantial loss of the t-BOC protecting group.

Our laboratories have previously reported the discovery of the bicyclic pyrazolidinones **1**, a new class of antibacterial agents.[1] Analogues with electron withdrawing substituents at C-3 (X = CN, SO_2R) have been synthesized and have shown excellent *in vitro* antibacterial activity.[2] An obvious synthetic target was the 3-keto compound **2** which would allow the synthesis of previously unattainable pyrazolidinone derivatives, particularly those with heteroatoms attached directly to the ring. Herein we describe its synthesis.



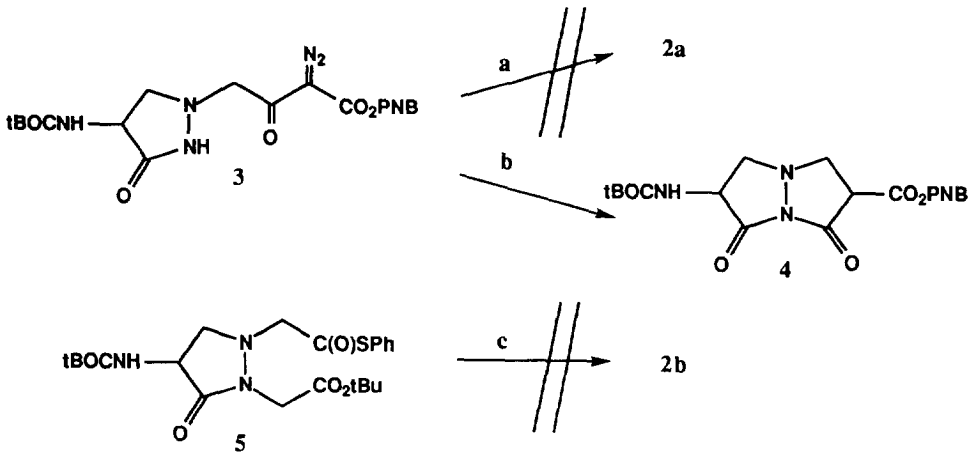
1



2

a, R = PNB
b, R = tBu

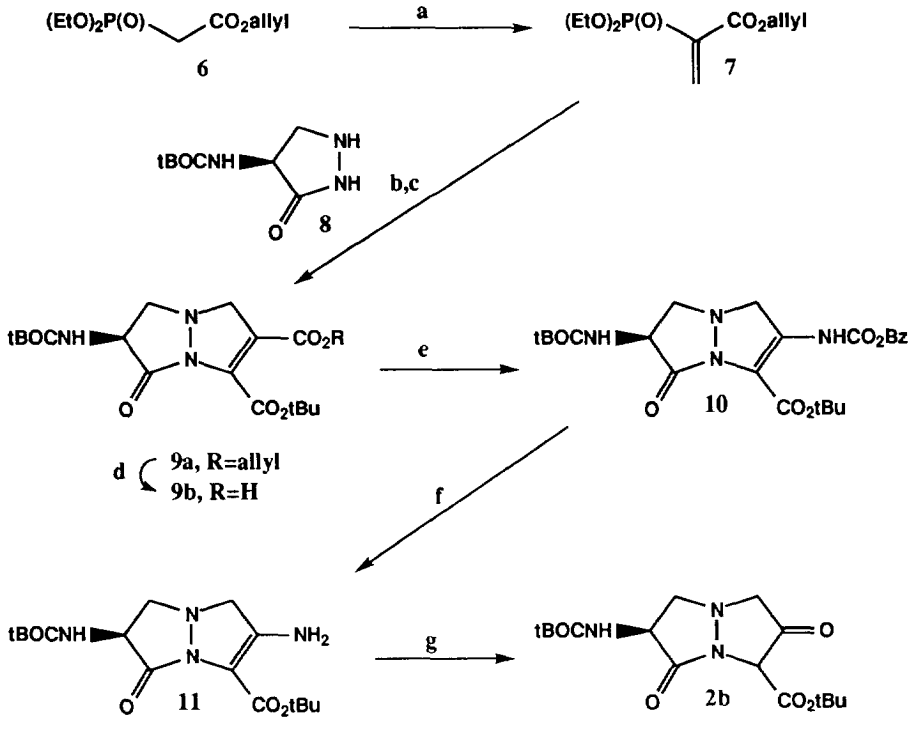
The analogous intermediates in the γ-lactam, carbapenem, and carbaceph systems have been synthesized by rhodium acetate catalyzed diazo insertion[3] or Dieckmann condensation.[4] Such chemistries were unsuccessful in the pyrazolidinone system. All attempts to achieve cyclization via the diazo insertion using a variety of conditions gave no reaction (**Scheme 1**). Thermolytic decomposition of the diazo compound **3** produced imide **4**[5] via Wolff rearrangement. The Dieckmann condensation of **5** gave a complex and inseparable mixture of products.



a) $Rh_2(OAc)_2$; b) xylene, reflux; c) THF, -78° C, $((CH_3)_3Si)_2NLi$

Scheme 1

These obstacles were circumvented by use of a Curtius rearrangement (**Scheme 2**) which had been previously applied to the 3-carboxy cephem by Spry.[6] Starting with chiral 4-(*t*-butoxycarbonylamino)-pyrazolidin-3-one **8**,[7] the diester derivative **9a** was obtained using the methodology of Ternansky and Draheim[8] with some slight modifications. Vinyl phosphonate **7** was obtained by treatment of **6** with acetic anhydride and tetramethyl diamino methane as a formaldehyde equivalent.[9] The crude vinyl phosphonate was used immediately in the Michael addition with **8**. The Michael addition was run in dichloromethane overnight followed by addition of *t*-butyl oxalyl chloride and two equivalents of Huning's base in the same pot to provide **9a** in 58% yield from **8** after chromatography. The allyl ester was deprotected using palladium catalysis to give **9b** which was purified by chromatography and subsequent trituration in ether/hexane to give 83% of an amorphous foam. Following Spry's one pot procedure,[6] **9b** was converted to the acyl azide, rearranged to the isocyanate, and trapped as the carbamate **10** with benzyl alcohol in 56% yield. Hydrogenation to the enamine **11** was accomplished in 83% yield using 5% palladium on carbon in ethyl acetate at 40 psi on a Parr shaker. **11** was purified by flash chromatography using ethyl acetate/0.25% triethyl amine as eluant. The compound was found to decompose on the column without addition of the triethylamine. Acid catalyzed hydrolysis of **11** was accomplished to give the target compound **2b** in 68% yield without substantial loss of the *t*-Boc and *t*-butyl ester protecting groups. **11** (790 mg., 2.2 mM.) was dissolved in 30 ml. of tetrahydrofuran, cooled to 5° C and treated with 60 ml. of 0.01N hydrochloric acid. The pH was carefully adjusted to 2.3 with 1N hydrochloric acid. After 12 min. the reaction was adjusted to pH = 5.5 with saturated sodium bicarbonate solution, diluted with brine and extracted five times with chloroform. The combined organics were washed with bicarbonate, 0.2N hydrochloric acid and brine and dried over magnesium sulfate to give analytically pure material as a mixture of diastereomers.[10] Subsequent elaboration of **2b** to full antibacterial compounds **1** (X = thiol heterocycle) was accomplished using standard techniques.



a) $(Ac)_2O$, $(CH_3)_2NCH_2N(CH_3)_2$; b) **8**, CH_2Cl_2; c) Hunig's base, $ClC(O)CO_2t$-Bu, CH_2Cl_2; d) $Pd(OAc)_2/Ph_3P$, Et_3SiH, CH_3CN; e) 1) $(PhO)_2P(O)N_3$, Hunig's base, CH_2Cl_2/Benzene, 2) $PhCH_2OH$; f) 5% Pd on C/[H_2]; g) THF/aqueous HCl, pH=2.3

Scheme 2

Acknowledgements: We are grateful to the physical chemistry department for providing analytical and spectral data. Large quantities of **8** were prepared by Paul Pranc.

References and Footnotes

1. (a) Jungheim, L. N.; Sigmund, S. K.; *J. Org. Chem.* **1987**, *52*, 4007-13. (b) Jungheim, L. N.; Ternansky, R. J.; Holmes, R. E.; *Drugs of the Future* **1990**, *15*, 149-157.

2. Ternansky, R. J.; Drahein, S. E.; Pike, A. J.; Ott, J. L.; "Pyrazolidinone Antibacterial Agents. Synthesis and *In Vitro* Activity of New, Highly Potent Analogues. "XXVII Interscience Conference on Antimicrobial Agents and Chemotherapy, Abstract #1213, **1987**.

3. (a) Ratliffe, R. W. ; Salzmann, T. N.; Christensen, B. G.; *Tetrahedron Lett.* **1980**, *21*, 31-34.

(b) Evans, D. A. ; Sjogren, E. B.; *Tetrahedron Lett.* **1985**, *26*, 3787-90. (c) Hashiguchi, S.; Natsugari, H.; Ochiai, M.; *J. Chem. Soc. Perkin Trans. I* **1988**, 2345-52.

4. Hatanaka, M.; Yamamoto, Y.; Nitta, H.; Ishimaru, T.; *Tetrahedron Lett.* **1981**, *22*, 3883-86.

5. Satisfactory physical data were obtained for all new compounds. **4** was obtained by alkylation of racemic **8** with $BrCH_2C(O)CH_2CO_2PNB$/lutidine/DMF and subsequent diazo transfer with $HO_2CC_6H_4SO_2N_3$. **5** was obtained by two step alkylation with $BrCH_2CO_2Bn$/NaH and $BrCH_2CO_2tBu$/NaH. Hydrogenation and DCC/HBT coupling with PhSH gave the thiol ester.

6. Spry, D. O.; *J. Chem. Soc. Chem. Commun.* **1974**, 1012-13.

7. During the course of this work an asymetric synthesis of **8** was accomplished. Holmes, R. E.; Neel, D. A.; *Tetrahedron Lett.* **1990**, *31*, 5567-70.

8. Ternansky, R. J.; Draheim, S. E.; *Tetrahedron Lett.* **1990**, *31*, 2805-2808.

9. (a) Taylor, E. C.; Shvo, Y.; *J. Org. Chem.* **1968**, *33*, 1719-27. (b) deSolms, S. J.; *J. Org. Chem.* **1976**, *41*, 2650-51.

10. At ambient temperature the resonances in the ^1H NMR were broad. Heating the solution to 50°C ($CDCl_3$) sharpened the spectrum showing two components in a 3:1 ratio. The sharpening was interpreted as averaging the possible rotational isomers around the ester and carbamate. Heating at higher temperatures in DMSO caused decomposition. The ^{13}C NMR ($CDCl_3$) was difficult to interpret due to the mixture of diastereomers. However, two ketone carbonyls were observed at 199.50 and 198.74. There were no resonances which would be assigned to an enolized carbonyl. From this, it appears that the molecule exists very predominately in the keto form. We attempted to assign the predominant diastereomer using difference NOE and ROESY experiments, but were unsuccessful.
Physical and analytical data: ^1H NMR (500 MHz, $CDCl_3$, 50°C) (major isomer): 1.45 (9H, s), 1.49 (9H, s), 2.87 (1H, t, J = 8.5 Hz), 3.16 (1H, d, J = 15.6 Hz), 3.79 (1H, d, J = 15.6 Hz), 4.28 (1H, t, J = 8.5 Hz), 4.61 (1H, m), 4.76 (1H, s), 5.18 (NH, bm); (minor isomer) 1.46 (9H, s), 1.49 (9H, s), 3.11 (1H, t, J = 8.5 Hz), 3.36 (1H, d, J = 15.6 Hz), 3.56 (1H, d, J = 15.6 Hz), 4.03 (1H, bt, J = 8.5 Hz), 4.47 (1H, s), 4.64 (1H, m), 5.18 (NH, bm); IR($CHCl_3$): 2984, 1791, 1742, 709; MS: *m/e* 355 (M^+); Anal. Calcd for $C_{16}H_{25}N_3O_6$: C, 54.07; H, 7.09; N, 11.82. Found: C, 54.31; H, 7.26; N, 11.78.

(*Received in USA* 29 *January* 1996; *revised* 14 *May* 1996; *accepted* 15 *May* 1996)