Pergamon

Tetrahedron Letters, Vol. 37, No. 13, pp. 2281-2284, 1996

0040-4039/96 $15.00 + 0.00

S0040-4039(96)00243-2

A New Facile Procedure for the Preparation of Pyrrolo[2,1-*c*][1,4]benzodiazepines : Synthesis of the Antibiotic DC-81 and its Thio Analogue

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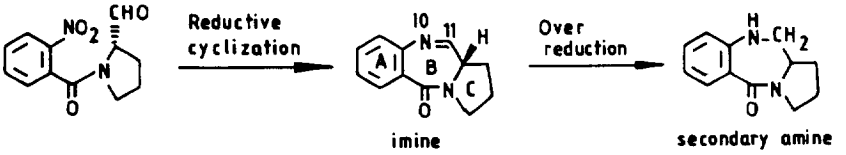
Abstract : An efficient synthesis of the imine form of the pyrrolo[2,1-*c*][1,4] benzodiazepine ring system based on a new reductive cyclization procedure is described. The naturally occuring antibiotic DC-81(5c) and its 5-thio analogue (7c) have also been synthesized to illustrate the usefulness of this methodology.

The carbinolamine-containing pyrrolo[2,1-*c*][1,4] benzodiazepine (PBD) family of antitumour antibiotics is produced by various *streptomyces* species, and well known members include anthramycin, tomaymycin and DC-81.[1] These compounds exert their biological activity by covalently binding to the N2 of guanine in the minor groove of DNA, via an electrophilic N10-C11 imine or carbinolamine functionality. The resulting DNA-adduct leads to a number of biological effects including inhibition of DNA replication.[2] Various approaches to the synthesis of these compounds have been investigated over the past few years.[3,4] These methods meet with varying degrees of success and have different limitations.[4]

Herein, we wish to report an efficient and convenient method of synthesis of PBD imines by reductive cyclization of acyclic nitroaldehydes. Earlier studies[3b] using this route generally gave large amounts of the secondary amine along with the desired carbinolamine, methyl ether or imine in moderate yields. In the present method employing iron powder in acetic acid-THF(1:1), the imine form can be obtained in high yields with no by products utilizing a simple and rapid work up procedure. In earlier investigations[5] iron has been employed for the cyclization to benzo[1,4]diazepine system which lacks the C-ring of the PBD. Further, iron complexes such iron(II)sulphate heptahydrate has also been used for the preparation of 5H-imidazo[2,1-*c*][1,4]benzodi azepine.[6]



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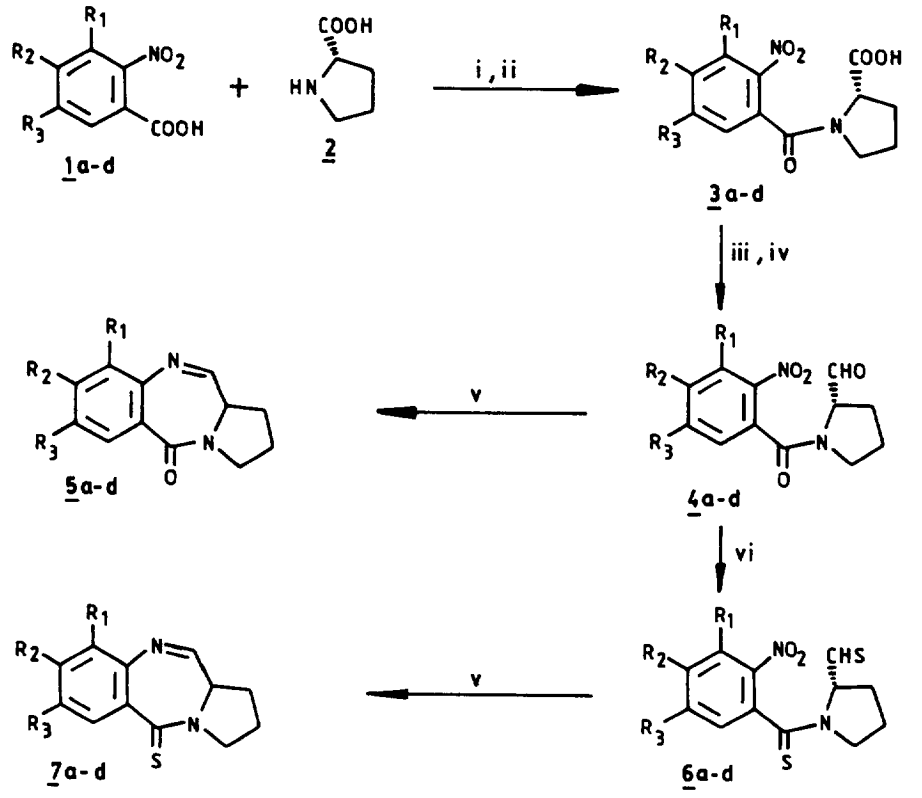

Scheme: i) $SOCl_2$ / C_6H_6 / RT / 3-4h ; ii) Et_3N / THF / 0°C / 1h ; iii) H^+ / CH_3OH / Δh / 2-3h ; iv) DIBAL-H / CH_2Cl_2 / -78° C / 45 min. ; v) Fe / CH_3COOH / THF / RT / 3-6h ; vi) $(p\text{-}CH_3OC_6H_4PS_2)_2$ / Toluene / 80°C / 2-3h

The starting materials were synthesized from coupling the appropriate 2-nitrobenzoic acids (**1**) via their acid chlorides with (2S) - proline (**2**) to afford the (2S)-N-(2-nitrobenzoyl) pyrrolidine-2-carboxylic acids (**3**). Esterification followed by reduction with DIBAL-H gave the (2S)-N-(2-nitrobenzoyl) pyrrolidine-2-carboxaldehydes (**4**). Finally, reductive cyclization with iron and acetic acid in THF afforded the PBD imine of type **5** in good yields (73-75%). This methodology has also been applied to the synthesis of the natural product DC-81. It is to be noted that in this methodology PBD imine is produced with an optical rotation value somewhat lower than the product obtained through the diethylthioacetal deprotective cyclization route.[7] This is due to the racemization taking place to some extent in the acidic reaction conditions.[8]

Further, we have been interested in the synthesis of 5-thio PBD imines which are thought to be attractive synthetic targets due to a likely improvement in their lipophilicity compared to the existing PBD antitumour antibiotics. We have previously synthesized 5-thio abbeymycin by employing the iminothioether approach.[9] However, this method has not been successful for the preparation of various other 5-thio PBD imines as large amounts of side-products such as overreduced secondary amines, PBD 5-thio-11-ones and 5,11-diones are isolated. Initially, versatile method involving the deprotective cyclization of amino diethylthioacetals[8] (**8** - **9**) was utilized for the synthesis of 5-thio PBD imines. Unfortunately, this method proved to be unsuccessful as (11aS)-1,2,3,11a-tetrahydro-5H-pyrrolo[2,1-*c*][1,4]benzodiazepine-5-one (**10**) was obtained instead of (11aS)-1,2,3,11a-tetrahydro-5H-pyrrolo[2,1-*c*][1,4]benzodiazepine-5-thione (**9**) due to desulphurization of the C5-thiocarbonyl

8

9 X = S

10 X = O

functionality. However, the present method can be used to produce 5-thio PBD imines. The precursor (2S)-N-(2-nitrothiobenzoyl)pyrrolidine-2-thiocarboxaldehyde(**6**)[10] were prepared by thiation of nitro aldehydes (**4**) with Lawesson's reagent.[11] Reductive cyclization with iron and acetic acid in THF afforded the desired 5-thio PBD imines of type 7 in good yields (70%)[12].

In a typical reduction procedure, iron powder (250 mg) was added to a solution of a precursur **4** (158 mg: 0.128 mmol) in THF (5 ml) and acetic acid (5 ml) at ice cold temperature. The reaction was allowed to warm to ambient temperature and stirred for 3-6 h until TLC indicated completion; or as soon as any traces of secondary amine was observed. The reaction mixture was diluted with water (10 ml) and extracted with chloroform. The organic phase was washed with saturated $NaHCO_3$ solution and brine, and then dried (anhydrous Na_2SO_4). Evaporation in vacuo afforded the crude product which was purified by column chromatography (silica gel) employing ethyl acetate as an eluent to obtain 65-75% yields of a product of type **5a-d**. Analytical and spectroscopic data were satisfactory.[8,12]

In summary, this simple new reductive cyclization procedure is capable of producing good yields of the DNA-interactive PBDs in their imine form, without production of **N10-C11** secondary amine side product. Further, this method is useful in the synthesis of 5-thio PBD imines which are difficult to access by other routes. These features make the present method a useful approach for the synthesis of various naturally occuring PBDs and their 5-thio analogues.

Acknowledgement:

One of the authors (BSPR) thanks CSIR, New Delhi for the award of a Senior Research Fellowship.

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7. **5a**: By diethylthioacetal deprotective cyclization method the $[\alpha]_D^{28}$=309° (c=0.25, $CHCl_3$) while by the present method: $[\alpha]_D^{28}$=217° (c=0.25, $CHCl_3$)

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10. Spectral data for **6a**: ^{1}H NMR (200 MHz, $CDCl_3$): 1.92-2.31 (m, 4H), 3.32-3.52 (m, 2H), 4.82 (m, 1H), 7.31-7.42 (m,1H), 7.51-7.82 (m,2H), 8.12 (d, 1H, J = 6.2Hz), 9.90 (d, 1H, J = 3.2 Hz).; ^{13}C NMR ($CDCl_3$); 24.6, 26.1, 47.9, 56.6, 109.2, 109.4, 126.9, 128.2, 137.4, 144.2, 149.1, 192.8, 209.6.MS (EI) m/e : 280 ($M^{+\cdot}$, 20).

11. Typical procedure: To a solution of nitroaldehyde **5a** (500mg) in toluene (15ml) was added an equimolar amount of Lawesson's reagent (630mg) and the mixture was heated to70-80^{0}C for 2-3h. After reaction was complete by TLC, the toluene was evaparated in vacuo. The residue was purified by flash chromatography using ethyl acetate: hexane (1:1) on silica gel column to yield 70% of **6a.**

12. Spectral data for **7a**: ^{1}H NMR (200 MHz, $CDCl_3$): 1.81-2.12 (m. 3H). 2.50-2.73 (m,1H), 3.31-3.67(m,2H), 4.12 (d, 1H, J=2.2Hz), 6.98 (d, 1H, J=4.2Hz), 7.19-7.61 (m, 3H), 7.82 (d, 1H, J=2.1Hz);^{13}C NMR ($CDCl_3$): 25.2, 27.1, 47.3, 57.6,121.2,124.3,125.1, 128.2, 130.6, 131.2, 152.6, 192.1.; MS (EI) m/e 216 ($M^{+\cdot}$, 30).

(*Received in UK* 5 *December* 1995; *revised* 8 *February* 1996; *accepted* 9 *February* 1996)