SYNTHESIS OF 1-ARYL-3-PYRROLIN-2-ONE DERIVATIVES

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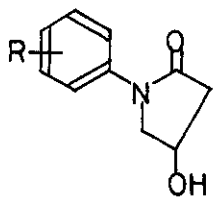
Abstract --- 1-Aryl-3-pyrrolin-2-one derivatives (6a-e) were obtained from the corresponding γ-bromoacetoacetanilide derivatives (1a-e) in the overall yields of 31 - 48% through the reduction of the β-carbonyl group, acetylation of the hydroxyl group, and subsequent cyclization and elimination to the 3-pyrrolin-2-one structure.

In the preceeding paper, we reported a new method for the preparation of 1-aryl-4-hydroxypyrrolidin-2-one derivatives (3) from the corresponding γ-bromoacetoacetanilide derivatives (1) via 4-bromo-3-hydroxybutananilide derivatives (2).[1] In connection with this experiment, we have interested in the structure of these γ-lactams as preliminary intermediate of the synthesis of mitomycin and related compounds, since we can see a similarity between these γ-lactams and certain features of the mitomycin antibiotics.[2] The present report deals with the synthesis of one of such intermediates, 1-aryl-3-pyrrolin-2-one derivatives (6).



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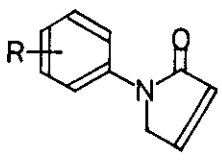

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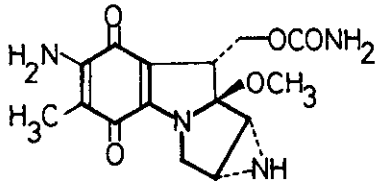


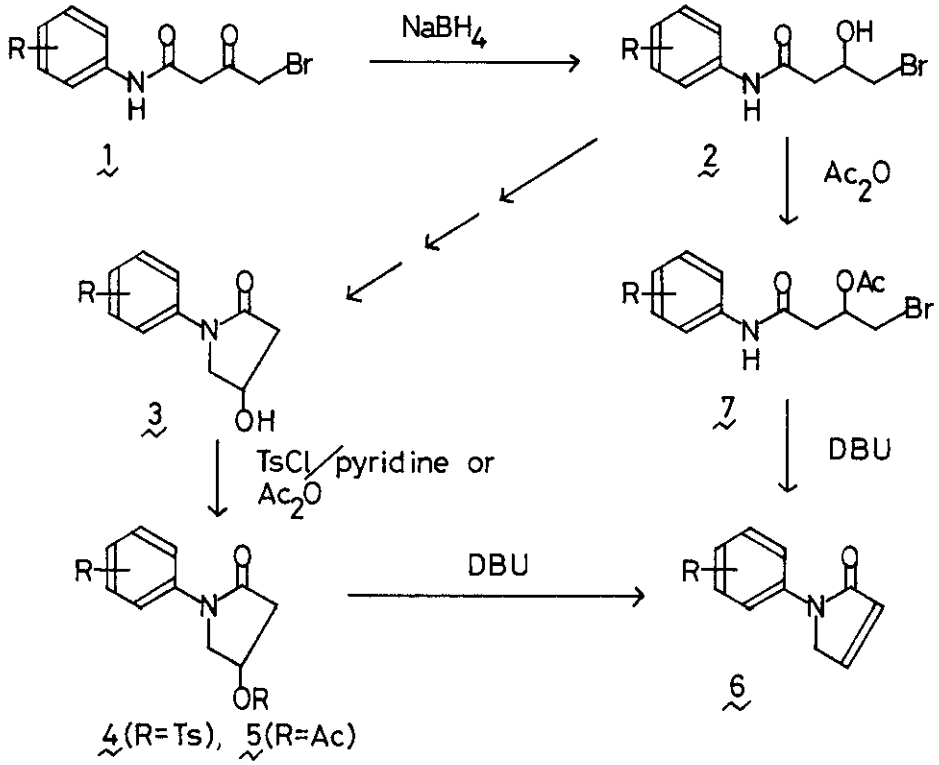
Mitomycin C

It is well known that N-substituted γ-lactams are prepared but in rather low yield from the corresponding N-substituted succinimides through the partial reduction of the carbonyl groups, protection of the hydroxyl group, and subsequent elimination of the ether or ester moiety.[3]

First we tried the elimination of 4-hydroxy-1-phenylpyrrolidin-2-one (3a) to form 3-pyrrolin-2-one structure. On treatment with p-toluenesulfonyl (tosyl) chloride in dry pyridine at room temperature, compound 3a did not give the objective 3-pyrrolin-2-one derivative but gave its O-tosylate, 1-phenyl-4-tosyloxypyrrolidin-2-one (4a), $C_{17}H_{17}NO_4S$,[4,5] as colorless needles (from benzene) of mp 96° in 85% yield. When acetic anhydride was used as acylating agent, compound 3a afforded 4-acetoxy-1-phenylpyrrolidin-2-one (5a), $C_{12}H_{13}NO_3$,[6] as colorless viscous oil in 92% yield.

Compounds 4a and 5a were treated with 1,8-diazabicyclo[5,4,0]-7-undecene (DBU) in dry THF at room temperature giving 1-phenyl-3-pyrrolin-2-one (6a), $C_{10}H_9NO$,[7] as colorless needles (from ethanol) of mp 86° in 95% and 82% yields, respectively.

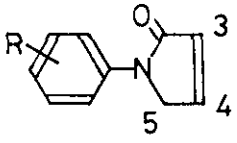
In the similar manner, 4-hydroxy-1-(2,5-dimethoxyphenyl)pyrrolidin-2-one (3e) was treated with acetic anhydride and subsequently with DBU to afford 1-(2,5-dimethoxyphenyl)pyrrolin-2-one (6e), $C_{12}H_{13}NO_3$,[8] as colorless needles (from benzene) of mp 90° in 63% yield.



Since compound 3a was obtained in about 50% yield from 1a following the method mentioned in our previous report, the overall yield of 6a from 1a is estimated to be 38 - 40%. Therefore, we tried direct cyclization of 3-acetoxy-4-bromobutananilide (7a) in order to improve the synthetic process. However, cyclization of 2-(3-acetoxy-4-bromobutanamido)pyridine was unsuccessful under treatment with DBU.

4-Bromo-3-hydroxybutananilide (2a) which was derived from compound 1a in 70% yield was treated with acetic anhydride giving 3-acetoxy-4-bromobutananilide (7a), $C_{12}H_{13}BrNO_3$,[8] as colorless viscous oil in 95% yield. Compound 7a was treated with DBU in dry THF at room temperature for 4 hrs affording 6a in 69% yield. Four kinds of 1-aryl-3-pyrrolin-2-one derivatives (6b-e) were also prepared from the corresponding γ-bromoacetoacetanilide derivatives (1b-e) by the similar manner as described above in the overall yields of 31 - 48%. The mps, yields, and spectral data are listed in Table I.

Table I. Mps, Yields, and Spectral Data of 6a-e



6	R	Mp (°C)	Yield[a] (%)	IR ν (KBr) cm^{-1} (amide C=O)	NMR δ ($CDCl_3$) ppm H-3[b]	H-4[b]	H-5[c]
a	H	86	48.3	1690	6.20	7.09	4.18
b	p-OCH_3	103	32.9	1678	6.20	7.10	4.35
c	p-CH_3	95	41.5	1682	6.20	7.08	4.35
d	m-CH_3	91	31.0	1678	6.20	7.04	4.39
e	2,5-di OCH_3	90	46.6	1670	6.25	7.17	4.40

a) based on γ-bromoacetoacetanilide derivatives (1a-e)

b) 1H, multiplet

c) 2H, multiplet

From the above results, the present method involving cyclization of 3-acetoxy-4-bromobutananilide derivatives (7) was found to be more favourable for the preparation of 1-aryl-3-pyrrolin-2-one derivatives (6). The synthetic approach to mitomycin structure from compound 6 is now in progress.

References and Notes

1) K. Tabei, H. Ito, and T. Takada, Heterocycles, 14, 1779 (1980).

2) R. W. Franck and J. Auerbach, J. Org. Chem., 36, 31 (1971).

3) J. B. P. A. Wijnberg, J. J. J. de Boer, and W. N. Speckamp, Recueil. J of the Royal Netherland Chem. Soc., 97, 227 (1978) and the literature cited therein.

4) All new compounds reported herein gave satisfactory elemental analyses and the mass numbers (m/e) of the parent peaks in agreement with the proposed structure.

5) IR ν (KBr) cm^{-1}: 1698 (C=O). NMR δ (DMSO-d_6) ppm: 2.47 (3H, s, tosyl CH_3), 2.50 - 3.00 (2H, ABX-octet, H-3), 3.90 - 4.24 (2H, ABX-octet, H-5), 5.23 (1H, m, H-4), 7.1 - 7.8 (9H, m, aromatic H). Mass (m/e): 331 (M^+), 159, 130, 106

6) IR ν ($CHCl_3$) cm^{-1}: 1735 (acetyl C=O), 1705 (amide C=O). NMR δ ($CDCl_3$) ppm: 2.10 (3H, s, acetyl CH_3), 2.50 - 3.10 (2H, ABX-octet, H-3), 3.70 - 4.30 (2H, ABX-octet, H-5), 5.35 (1H, m, H-4), 7.10 - 7.65 (5H, m, aromatic H). Mass (m/e): 219 (M^+), 159, 130, 106.

7) Lit. mp 89 - 90°; J. B. P. A. Wijnberg et al., Recueil. J. of the Royal Netherland Chem. Soc., 97, 227 (1978).

8) IR ν (KBr) cm^{-1}: 1735 (acetyl C=O), 1670 (amide C=O). NMR δ ($CDCl_3$) ppm: 2.08 (3H, s, acetyl CH_3), 2.78 (2H, d, J = 8 Hz, changed to singlet at 2.72 ppm on irradiation at 5.35 ppm, H-4), 3.60 (2H, m, changed to AB-quartet centred at 3.45 and 3.65 ppm on irradiation at 5.35 ppm, H-2), 5.35 (1H, m, H-3), 7.00 - 7.50 (5H, m, aromatic H), 7.80 (1H, broad s, disappeared by addition of D_2O, NH). Mass (m/e): 299 (M^+), 159, 130.

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