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A SIMPLE BIS-ANNELATION ROUTE TO 3,4,5,6-TETRAHYDROPYRIDO[3,2-c]QUINOLIN-2-ONES

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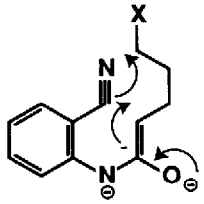
Abstract : A short, novel synthesis of the title ring system is descibed involving the intramolecular reaction of an amide dianion with a nitrile followed by *in situ* N-alkylation of the resultant intermediate.

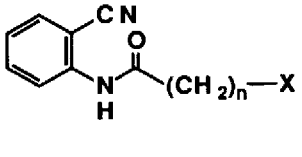
We recently required gram quantities of the unknown compound, 3,4,5,6-tetrahydropyrido[3,2-c]quinolin-2-one (**1**) which was postulated to be the stucture of a major metabolite of a bioactive material. Although N-methyl analog **2** had been prepared in two steps/13% overall yield, it was reported that the same

1 : R = H
2 : R = CH_3

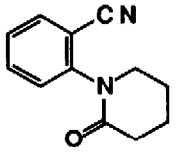


A

methodology could not be used to synthesize **1** itself.[1] We reasoned that **1** might be readily available *via* a bis-annelation reaction involving dianion **A**.[2] Accordingly, bromoamide **3**[3] was treated with 2.5 equivalents of lithium diisopropylamide (LDA) in THF at -78°. No reaction was observed at this temperature, but at 0° (1h) **1** was indeed formed in very low yield, the major product being lactam **4**. However, when the reaction was run at -



3 : n = 4, X = Br
6 : n = 4, X = Cl
8 : n = 5, X = Cl
9 : n = 3, X = Cl



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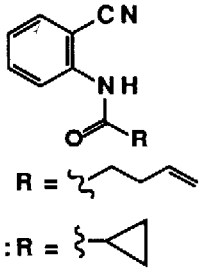


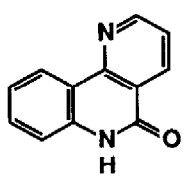
5 : R =

11 : R =

20°, we were able to isolate **1** in 45% yield [4] together with **4** and dehydrohalogenation product **5**.

In order to suppress intramolecular alkylation even further, chloroamide **6**[3] was prepared. Treatment of **6** with 2.5 equivalents of LDA in THF as previously described afforded **1** in 50% isolated yield; **4** was not obtained at all. However, a metastable material which appeared to contain diisopropylamine was produced in significant quantity. Therefore, we replaced LDA with the more hindered base, lithium 2,2,6,6-tetramethylpiperidide (LTMP) and, as anticipated, the isolated yield of **1** increased to 73%.

Chemical proof of the structure of **1** was achieved by oxidation to pyridoquinolinone **7**.[4] This



7

10

transformation could be cleanly effected by heating an intimate mixture of **1**, 10 equivalents of sodium carbonate and 4 equivalents of silver tetrafluoroborate at 275° under high vacuum for 8 hours.

The scope and limitations of the bis-annelation reaction were briefly explored. Attempted cyclization of **8**[3] with 2.5 equivalents of LTMP afforded **10**[4] (45% isolated yield). However, the dianion of **9**[3] reacted to give cyclopropyl amide **11** in 67% isolated yield.

A representative experimental procedure is given below :

To a stirred solution of 0.84 ml (5 mmol) of 2,2,6,6-tetramethylpiperidine in 10 ml of dry THF (-20°, N_2 atmosphere) was added 2 ml (5 mmol) of 2.5 M n-BuLi. After 10 min, 473 mg (2 mmol) of **6** dissolved in 5 ml of THF was added dropwise. The resulting dark yellow solution was stirred at -20° for 30 min. Water was then added and the pH adjusted to 9 with 1N HCl, after which **1** precipitated from solution. The product was collected by filtration, washed with water and ethyl acetate, and dried (yield 248 mg). Additional product was obtained from the filtrate after extraction with methylene chloride and purification by flash chromatography on silica gel (94:5:1 CH_2Cl_2/MeOH/NH_4OH). The overall isolated yield of pure **1** was 293 mg (73%).

In summary, we have illustrated that the uncommon 3,4,5,6-tetrahydropyrido[3,2-c]quinolin-2-one ring system, exemplified by **1**, can be prepared in good yield *via* a novel one step amide dianion cyclization. This bis-annelation strategy also is useful for synthesizing certain related fused ring systems, e.g., **10**.

Acknowledgements : We thank Mr. Richard Ware (HRMS), Ms. Diane Rescek (NMR) and Mr. Stephen Day (LRMS) for their technical assistance.

References and Notes

1. F. Eiden and E. Baumann, *Archiv. Pharmazie*, **316**, 897 (1983).
2. Intramolecular N-alkylation of in situ-generated imine anions to give cyclic products is precedented. See C. A. Hergrueter, P. D. Brewer, J. Tagat and P. Helquist, *Tet. Lett.*, 4145 (1977).
3. Anthranilonitrile (1.0 equivalent) was reacted with the appropriate acid chloride (1.2 equivalents) in pyridine in the presence of 2 mole % 4-dimethylaminopyridine (0-25°/1h). The desired amides were obtained in 70-80% isolated yields.
4. Characteristic spectral data for compounds **1**, **4**, **7**, **10** and **11** are given below :

1 : m.p. 265-268°; ^{1}H-NMR (300MHz, DMSO-d_6, δ) 1.76-1.80 (m, 2H); 2.43 (t, 2H), 3.26-3.30 (m, 2H), 6.89 (bs, 1H), 7.05 (t, 1H), 7.18 (d, 1H), 7.38 (t, 1H), 7.75 (d, 1H), 10.75 (bs, 1H); IR (KBr) 1638, 1629 cm^{-1}; MS m/e 200 (M^+).

4 : m.p. 120-122°; IR(KBr) 2225, 1642 cm^{-1}; MS m/e 200 (M^+).

7 : ^{1}H-NMR (300MHz, DMSO-d_6, δ) 7.28 (t, 1H), 7.38 (d, 1H, J = 9 Hz), 7.58 (t, 1H), 7.61-7.68 (m, 1H), 8.58-8.62 (m, 2H), 9.04-9.06 (m, 1H), 11.88 (bs, 1H); IR (KBr) 1675 cm^{-1}; MS m/e 196 (M^+).

10 : ^{1}H-NMR (300MHz, DMSO-d_6, δ) 1.47-1.48 (m, 2H), 1.50-1.53 (m, 2H), 2.45-2.52 (m, 2H), 3.29-3.33 (t, 2H), 3.61-3.67 (m, 2H), 6.17 (bs, 1H), 7.05 (t, 1H), 7.16 (d, 1H, J = 8Hz), 7.34 (t, 1H), 7.90 (d, 1H, J = 8 Hz), 10.81 (bs, 1H); IR (KBr) 1648, 1626 cm^{-1}; MS m/e 214 (M^+).

11 : m.p. 162-164°; ^{1}H-NMR (300MHz, $CDCl_3$, δ) 0.88-0.95 (m, 2H), 1.08-1.13 (m, 1H), 1.58-1.63 (m,1H); IR(KBr) 2224, 1660 cm^{-1}.

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