Tetrahedron Letters,Vol.30,No.28,pp 3625-3628,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Maxwell Pergamon Macmillan plc

THE AZA-ROBINSON ANNULATION: AN APPLICATION TO THE SYNTHESIS OF ISO-A58365A

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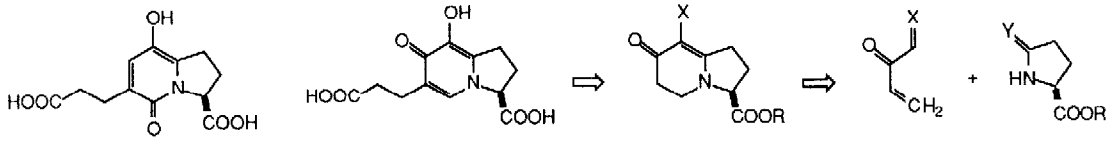
Abstract. Annulation of diazomethylvinylketone (**4a**) with a variety of secondary thiolactams provides a novel route to dihydro-γ-pyridones. This approach has been applied to the synthesis of iso-A58365A (**2**), the γ-pyridone analog of the ACE inhibitor, A58365A (**1**).

We have recently described a novel route to 5-hydroxy-2-pyridones in the context of the total synthesis of the angiotensin converting enzyme (ACE) inhibitor, A58365A (**1**).[2] In order to gain some insight into the structural features of **1** which are pertinent to its biological activity, the synthesis of several variants was undertaken. A particularly interesting target was the isomeric 4-pyridone (**2**). The biological evaluation of this analog could provide information regarding the importance of the proximal lactam-dicarboxylate array in determining the ACE inhibitory activity of **1**. In this Letter we describe a new and general route to dihydro-γ-pyridones and the application of this methodology to the synthesis of **2**.

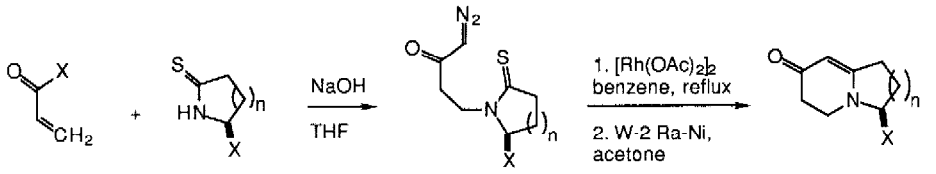


1 A58365A 2 iso-A58365A 3 4 5

Dihydropyridone **3** was seen to be a potentially useful intermediate for the synthesis of **2** via addition of a propionate side chain and dehydrogenation. An aza-Robinson annulation type process for the construction of **3** (cf. **4** + **5** to **3**) was pursued.[3] Crucial to the successful realization of this strategy would be the feasibility of the amide olefination reaction. A recent finding in our laboratories indicated that a diazo-thioamide coupling reaction would be particularly well suited for achieving this process.[4] With this result in mind, diazomethylvinylketone(**4**, $X=N_2$) [5] and thiopyroglutamate (**5**, Y=S, R=t-Bu) [6] were selected as the annulation components.

Addition of a freshly prepared solution of **4** (0.1M in THF) to a solution of **5a** (0.5M in THF at room temperature in the presence of a catalytic amount of solid sodium hydroxide followed by stirring for 1h produced a 95% yield of Michael adduct **6a**. A solution of **6a** (0.1 M in benzene) was added to a refluxing suspension of rhodium(II) acetate dimer in benzene. The crude cyclization product (*vide infra*) was taken up in acetone and added to a stirred suspension of partially deactivated[7] W-2 Raney nickel in acetone. Dihydropyridone **7a** was

obtained in 65% yield following flash chromatography. The scope and limitations of this process were explored in substrates **5b, c, d,** and **e**. The results are shown in table 1.



4 a X=CHN_2
4 b X=OMe

5 a X=CO_2tBu, n=1
5 b X=CO_2Me, n=1
5 c X=H, n=1
5 d X=H, n=2
5 e X=H, n=3

6 a X=CO_2tBu, n=1
6 b X=CO_2Me, n=1
6 c X=H, n=1
6 d X=H, n=2
6 e X=H, n=3

7 a X=CO_2tBu, n=1
7 b X=CO_2Me, n=1
7 c X=H, n=1
7 d X=H, n=2
7 e X=H, n=3

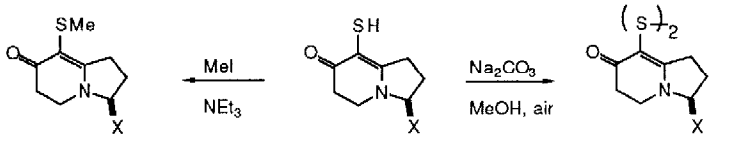
Table 1 Aza-Robinson annulation of thiolactams

Michael acceptor	Thiolactam	Procedure[a]	Michael adduct (%)[b]	Dihydropyridone(%)[b]
4a	**5a**	A	**6a** (95)	**7a** (68)
4b	**5a**	B	**6a** (75)	
4a	**5b**	A	**6b** (85)	**7b** (65)
4b	**5b**	B	**6b** (73)	
4a	**5c**	A	**6c** (42)	**7c** (68)
4b	**5c**	B	**6c** (71)	
4a	**5d**	A	**6d** (28)	**7d** (70)
4b	**5d**	B	**6d** (70)	
4a	**5e**	A	**6e** (12)	**7e** (73)
4b	**5e**	B	**6e** (71)	

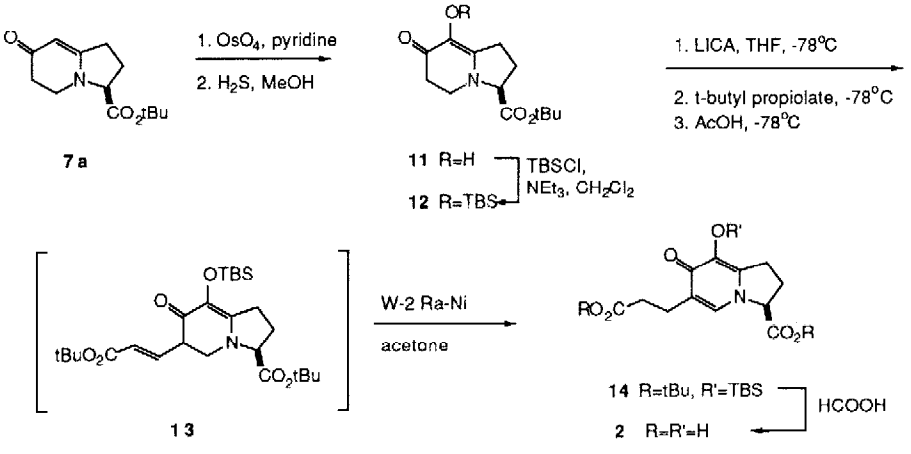
[a] procedure A: NaOH (cat.), THF. procedure B: (i) NaOH (cat.), THF (ii) 1 N NaOH, MeOH (iii) $ClCO_2Et$, CH_2Cl_2 (iv) CH_2N_2, Et_2O. [b] isolated yields following flash column chromatography

With this series of substrates, the Michael addition of diazomethylvinylketone (**4a**) to thiolactams (giving rise to **6**) proceeds well in only two cases (**5a** and **5b**). In the other examples (**5c, d,** and **e**) varying amounts of starting material **5** are obtained in addition to product **6**. Fortunately, a stepwise procedure using methyl acrylate (**4b**) as the Michael acceptor (see proc. B), though longer proved to be more general.[8] The Michael adducts were subjected to hydrolysis, mixed anhydride formation, and conversion to the diazoketone **6**.The ring closure process generates bicyclic dihydropyridones **7** in 65 to 73 % yield.

The intermediate in the transformation of **6** to **7** prior to treatment with W-2 Raney nickel was identified as enethiol **8** for two of the substrates (**6b** and **6c**). These unstable species (**8a, 8b**) could be methylated (methyl iodide, triethylamine) or oxidatively dimerized (methanol, sodium carbonate, air) to produce thiomethyl ethers **9a,b** (58%, 60%) or disulfides **10a,b** (48%,51%).



Treatment of **7a** with osmium tetroxide in pyridine followed by reductive workup afforded hydroxy dihydropyridone **11** in 51% yield. Protection of the hydroxyl group as a t-butyl dimethylsilyl ether gave **12** in 92% yield. Regioselective deprotonation of **12** with lithium isopropylcyclohexylamide (LICA) in THF at -78 followed by addition of t-butyl propiolate and quenching with glacial acetic acid gave a crude reaction mixture containing Michael adduct **13** along with several regio- and stereoisomers. Direct treatment of the crude mixture with W-2 Raney nickel in acetone provided pyridone **14** in 35 % overall yield in a process which apparently involves migration of the acrylate double bond into the pyridone ring.[9] Removal of the protecting groups by treatment of **14** with formic acid provided iso-A58365A (**2**) in quantitative yield. Evaluation of iso-A58365A (**2**) showed it to be virtually inactive as an ACE inhibitor in protocols where **1** showed strong activity.[10] This result, although of a negative sort, suggests that the proximity of the lactam carbonyl group with both carboxyl functions might be an important source of activity. Experiments to probe this point are being readied.



In summary, the utility of diazomethylvinylketone or a synthetically equivalent scheme for an annulation of thiolactams leading to γ-dihydropyridones has been demonstrated. Using this chemistry, a synthesis of iso-A58365A (**2**) was achieved. Further applications of this methodology towards the synthesis of other biologically interesting alkaloids will be described in due course.

Acknowledgements. This research was supported by PHS Grant CA 28824. A Kent Fellowship (Yale University) to FGF is gratefully acknowledged. NMR spectra were obtained through the auspices of the Northeast Regional NSF/NMR facility at Yale University, which was supported by NSF Chemistry Division Grant CHE 7916210.

Notes and References

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7 W-2 Raney nickel was partially deactivated by stirring in refluxing acetone for 1h.

8 The adducts of methyl acrylate (**4a**) with thiolactams **5a-e** were obtained in greater than 95% yield in all cases. These products were fully characterized (^{1}H NMR, IR, MS, HRMS and or elemental analysis).

9 The dihydro version of **13** (the adduct of **12** and **4a**) failed to give **14** upon treatment with W-2 Ra-Ni.

10 Descriptions of the protocols and test results for the biological evaluations of compounds **1** and **2** and derivatives of these systems will be disclosed separately.

11 All new compounds were fully characterized. The data for selected compounds is: **10a** (mp 208-210°C); $[\alpha]_D$ +165.2° (MeOH, c 0.37); IR ν_{max} (CH_2Cl_2) 1739, 1627, 1542, 1460, 1163 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.37 (dd, J=8.8, 4.7 Hz, 2H, 2(NCH)), 3.79 (s, 6H, 2(OCH_3)), 3.67-3.27 and 3.16-3.02 (m, 8H, 4(CH_2)), 2.62 (t, J=7.6 Hz, 4H, 2(CH_2)), 2.56-2.45 and 2.25.2.13 (m, 4H, 2(CH_2)). MS m/e (%) 454 (1.9), 453 (3.8), 241 (16.9), 228 (24.4), 227 (5.7), 226 (100), 196 (11.5),184 (16.8), 182 (45.1), 168 (66.8); HRMS Calcd. for $C_{20}H_{24}N_2O_6S_2$: 452.1077, obsd 452.1064. **9a** (mp 115-116°C); $[\alpha]_D$ -99.1° (MeOH, c 0.32); IR ν_{max} ($CDCl_3$) 1735, 1627, 1549, 1460, 1160 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.28 (dd, J=8.7, 4.4 Hz, 1H, NCH), 3.80 (s, 3H, OCH_3), 3.69-3.57 and 3.46-3.35 (m, 2H, CH_2), 3.07 (t, J=8.6 Hz, CH_2), 2.69-2.61 (m, 2H, CH_2), 2.52-2.37 and 2.24-2.11 (m, 2H, CH_2), 2.14 (s, 3H, SCH_3). MS m/e (%) 243 (6.1), 242 (13.0), 241 (100), 208 (17.6), 184 (10.9), 183 (11.5), 182 (99.4). **7b** (mp 75-77°C); $[\alpha]_D$ -147.4° (EtOAc, c 0.77); IR ν_{max} ($CDCl_3$) 1738, 1623, 1578 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.04 (s, 1H, C=CH), 4.18 (dd, J=8.5, 4.3 Hz, 1H, NCH), 3.79 (s, 3H, OCH_3), 3.78-3.58 and 3.46-3.36 (m, 2H, CH_2), 2.86-2.12 (m, 6H, 3(CH_2)); MS m/e (%) 196 (3.7), 195 (26.8), 137 (8.7), 136 (100), 109 (1.8) 108 (25.5); HRMS Calcd. for $C_{10}H_{13}NO_3$: 195.0896, obsd 195.0890. **6b** $[\alpha]_D$ +100.3° ($CHCl_3$, c 3.35); IR ν_{max} ($CDCl_3$) 2100, 1735, 1635, 1480, 1375, 1325, 1210, 1170 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.34 (bs, 1H, N_2CH), 4.78 (dd, J=9.4, 2.9 Hz, 1H, NCH), 4.24-4.14 and 3.87-3.76 (m, 2H, CH_2), 3.79 (s, 3H, OCH_3), 3.13-2.99 and 2.75-2.67 (m, 4H, 2(CH_2)), 2.46-2.10 (m, 2H, CH_2); MS m/e (%) 229 (1.0), 228 (2.9), 227 (10.9), 196 (2.0), 195 (12.3), 194 (100), 184 (27.6), 168 (60.1), 166 (12.8), 140 (52.8), 136 (12.4), 134 (21.7), 126 (28.1), 114 (27.4), 112 (19.4).

(Received in USA 20 April 1989)