Pergamon

Tetrahedron Letters 39 (1998) 4667–4670

TETRAHEDRON
LETTERS

Synthesis of Spirolactams from Tyrosine Amides and Related Substances

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Received 16 March 1998; accepted 22 April 1998

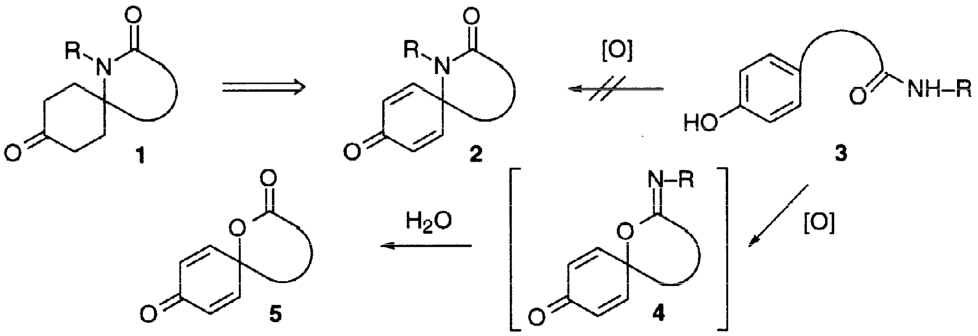
Abstract

Oxidation of oxazolines derived from phenolic ω-arylalkanoic acids such as tyrosine with iodobenzene diacetate leads to spirocyclic amides in moderate yields. This reaction was heretofore unknown due to the propensity of free amide analogs of the oxazolines to furnish lactones upon oxidation. © 1998 Elsevier Science Ltd. All rights reserved.

Keywords: *oxazolines, spiro compounds, cyclization, oxidation*

Spirolactams of type **1** are useful intermediates in the synthesis of natural azaspirocyclic compounds. An appealing route to these heterocycles may be visualized in terms of oxidative spirocyclization of phenolic amides **3**, followed by hydrogenation of the resulting dienone **2** (Scheme 1) [1-3]. Unfortunately, this transformation fails due to the propensity of the nucleophilic oxygen atom of the amide to intercept the electrophilic intermediate arising through activation of the phenol. Thus, oxidation of **3** with $PhI(OCOCF_3)_2$ (= PIFA) leads to lactone **5**, probably by way of iminoether **4**, which is readily hydrolyzed during isolation [4,5]. Work by Knapp [6] suggested that the effects responsible for the nucleophilicity of the oxygen atom of an amide should operate in favor of the nitrogen atom in imino derivatives

Scheme 1



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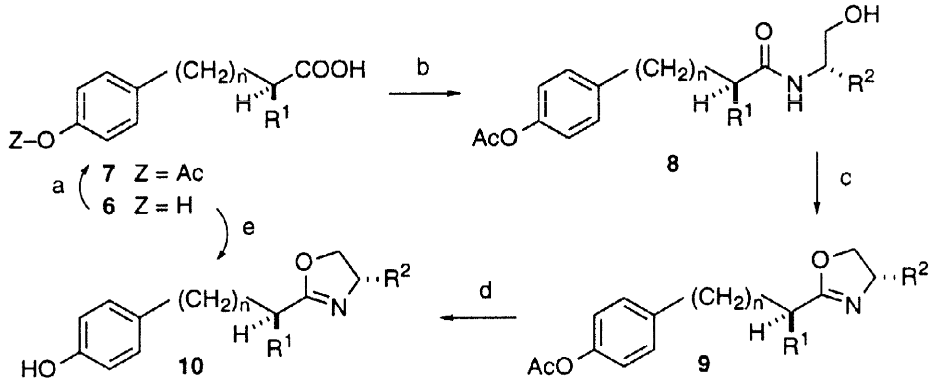
PII: S0040-4039(98)00874-0

Scheme 2



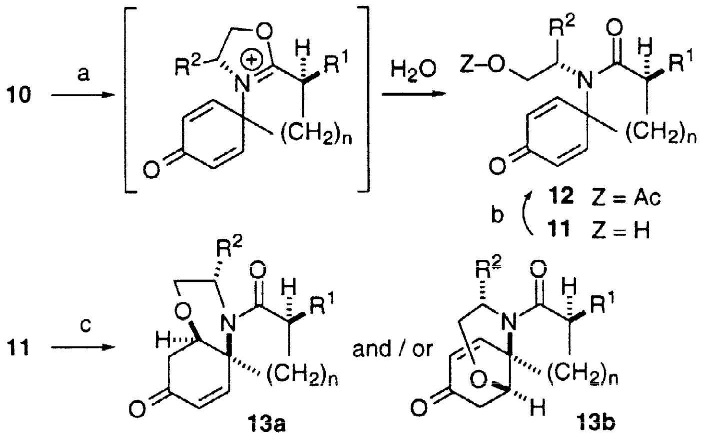
(a) Ac_2O, 15% aq. NaOH, 93-95%; (b) aminoalcohol (see Table 1), BOP-Cl, CH_2Cl_2, Et_3N, 72-82%; (c) Burgess reagent, THF, 70°C, sealed tube, 68-74%; (d) K_2CO_3, MeOH, 73-81%; (e) PPh_3, CCl_4, Et_3N, 1:1 pyridine - MeCN, aminoalcohol (see Table 1), 44-68%.

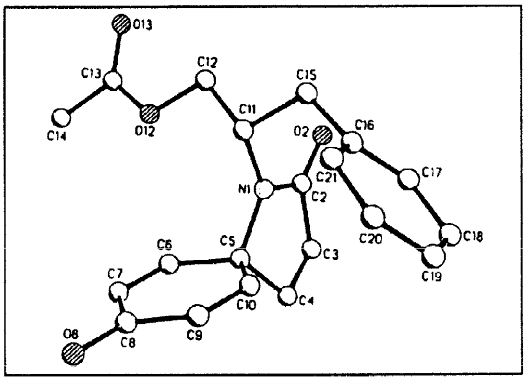
thereof. We now report that the heretofore unknown transformation **3**→**2** may indeed be achieved by oxidative cyclization of 2-oxazolines [7] derived from amides **3**.

Oxazolines **10** were made either by dehydration [8] of the preformed amides **8** [9] with the Burgess reagent [10] (method A), or, more conveniently, by condensation of phenolic acids **6** with suitable ethanolamines as described by Vorbrüggen [11] (method B, Scheme 2 and Table 1). It is necessary to protect the phenol as an acetate during oxazoline formation by method A. Seemingly, condensation of the Burgess reagent with the phenolic OH results in polar byproducts that lower the yield of desired **10**. No need for protection exists when method B is used.

Reaction of oxazolines **10** with iodobenzene diacetate under Kita-like conditions [4] provided the desired spirolactams **11**. These were prone to undergo Michael-type cyclization to heterocycles **13a** and/or **13b**. Consequently, the crude **11** were converted immediately to the corresponding acetates **12** (Scheme 3). Interestingly, oxidation of **10** with PIFA produced mixtures containing only small amounts of desired **11**. Probably the CF_3COOH liberated during these reactions damaged the acid-sensitive dienones. It is conceivable that the use of suitable acid traps (e.g. propylene oxide) in conjunction with PIFA might correct the

Scheme 3

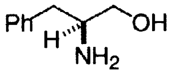
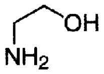
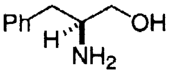
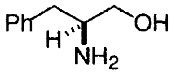
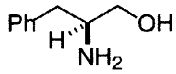




X-ray structure of **12a**

(a) $PhI(OAc)_2$, CF_3CH_2OH; (b) Ac_2O, pyridine, DMAP, (Table 1); (c) standing.

Table 1: representative formation and cyclization reactions of oxazolines **10**

Entry	**a**	**b**	**c**	**d**	**e**
Acid **6**	n = 1 R^1= H	n = 1 R^1= H	n = 1 R^1= NHTs	n = 1 R^1= NHBOC	n = 2 R^1= H
Amino-alcohol					
Method	**A**	**B**	**B**	**A**	**A**
Cpds. **10 / 12**	n = 1 R^1 = H; R^2 = Bn	n = 1 R^1 = R^2 = H	n = 1 R^1 = NHTs; R^2 = Bn	n = 1 R^1 = NHBOC; R^2 = Bn	n = 2 R^1 = H; R^2 = Bn
Yield % of **12**[a]	47	42	41	22	17

[a]Representative procedure for the cyclization of oxazolines **10**. A solution of $PhI(OAc)_2$ (1.1 mmol) in trifluoroethanol (5 mL) is added to a solution of oxazoline (1.0 mmol) in trifluoroethanol (5 mL) at rt. The mixture was stirred for 30 min, then solid $NaHCO_3$ was added to the solution and the mixture was filtered and concentrated. Standard acylation conditions (Ac_2O, pyridine, DMAP, rt) provided **12**.

problem; however, experiments in this direction have not yet been conducted. The structure of **12a** was confirmed by single crystal X-ray diffractometry.[1] A summary of representative experiments appears in Table 1, wherein the reported yields refer to purified acetates **12**.[2] In general, cyclization of oxazolines leading to a spiro[4.5] system proceeds in fair yields (40-50%), whereas the reaction of those giving a spiro[5.5] product is much less efficient (entry **e**). Tyrosine derivatives are good substrates for the new process, provided that the α-amino functionality is blocked as a sulfonamide (cf. entry **c**). In tyrosine *carbamates* (e.g., *N*-BOC compound **10d**), by contrast, the carbamate carbonyl competes effectively with the oxazoline nitrogen for capture of the electrophilic intermediate obtained by activation of the phenol. This results in several byproducts and in significantly lowered yields of **11** / **12**. Scrutiny of NMR spectra of crude **11** shows no evidence of byproducts resulting from aromatization of the oxazoline to an oxazole. The moderate yields of **11** / **12** seem to be rather attributable to

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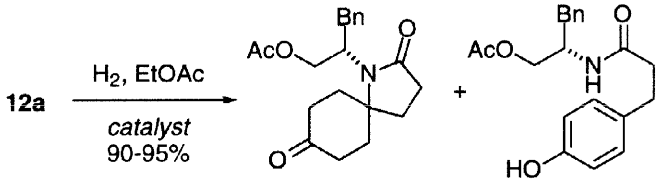
[1] Crystal data for **12a** ($C_{20}H_{21}NO_4$; M = 339.39). Crystal dimension 0.25 x 0.25 x 1.4 mm; colorless needle; orthorhombic, space group $P2_12_12_1$, a = 1008.8(1), b = 1102.5(1), c = 1610.3(3) pm, V = 1791.0(4) x 10^6 pm^3, Z = 4, d (calcd) = 1.295 g x cm^{-3}, μ(Mo $K\alpha$) = 0.09 mm^{-1}, λ = 0.71073, $2\theta_{max}$ = 55°, 5564 reflections measured, 4124 unique and 2858 with $F > 3\sigma(F)$. Full matrix LSQ. Empirical absorption correction by ψ scans. Hydrogen positions of riding model with fixed isotopic U. R(F) and $R_w(F)$ = 0.066 and 0.061, respectively. Further details of the crystal structure may be obtained from the Director of the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EW (UK), by quoting the full journal citation.

[2] All compounds were fully characterized [^1H, ^{13}C NMR ($CDCl_3$), IR, MS, $[\alpha]_D^{20}$ ($CHCl_3$), HRMS]. Data for representative compounds: **8a**: colorless crystals, mp 96 - 98 °C. ^1H: 2.29 (s, 3H), 2.28 - 2.47 (m, 2H), 2.77 (d, 7.6 Hz, 2H), 2.88 - 2.95 (m, 2H), 3.39 (dd, 3.5, 10.8 Hz, 1H), 3.45 (dd, 4.0, 10.8 Hz, 1H), 4.10 (m, 1H), 5.62 (d, 7.6 Hz, 1H), 6.97 & 7.18 (d, 8.5 Hz, each 2H), 7.14 - 7.30 (m, 5H). ^{13}C: 21.1 (q), 31.3 (t), 36.8 (t), 38.8 (t), 52.2 (d), 63.5 (t), 121.7, 126.6, 128.5, 129.2 & 129.5 (d) 137.7, 138.3 & 149.0 (s), 170.2 (s), 172.1 (s). [α] = – 14.7° (c = 1.63). **10a**: colorless crystals, mp 141 - 143 °C. - ^1H (DMSO): 2.36 - 2.41 (m, 2H), 2.59 (dd, 7.1, 13.6 Hz, 1H), 2.67 - 2.72 (m, 2H), 2.80 (dd, 6.1, 13.6 Hz, 1H), 3.83 (dd, 7.3, 8.1 Hz, 1H), 4.14 (dd, 8.1, 9.4 Hz, 1H), 4.25 (m, 1H), 6.64 & 6.98 (d, 8.5 Hz, each 2H), 7.18 - 7.29 (m, 5H). ^{13}C (DMSO): 29.7 (t), 30.8 (t), 41.4 (t), 66.8 (d), 71.1 (t), 115.3, 126.3, 128.3, 129.3 & 129.4 (d), 130.6, 138.5 & 156.1 (s), 165.9 (s). [α] = – 26.8° (c = 1.16, MeOH). **12a**: colorless needles, mp 163 - 165 °C. ^1H: 1.85 - 2.07 (m, 2H), 2.05 (s, 3H), 2.48 - 2.56 (m, 2H), 2.87 (dd, 4.9, 13.2 Hz, 1H), 3.12 (m, 1H), 3.47 (dd, 10.6, 13.2 Hz, 1H), 4.38 (dd, 5.4, 11.3 Hz, 1H), 4.53 (dd, 8.1, 11.3 Hz, 1H), 5.14 (dd, 3.1, 10.1 Hz, 1H), 5.85 & 6.21 (dd, each 1H, 2.1, 10.1 Hz, 1H), 6.78 (dd, 3.1, 10.1 Hz, 1H), 7.12 - 7.32 (m, 5H). ^{13}C: 21.0 (q), 30.0 (t), 30.5 (t), 34.5 (t), 57.0 (d), 62.8 (s), 63.5 (t), 127.1 & 128.6 (d), 129.2 & 129.6 (d, C=C), 129.9 (d) 137.9 (s), 148.6 & 149.2 (d, C=C), 170.2 (s), 175.0 (s), 184.2 (s). [α] = + 31.4° (c = 0.44).

Scheme 4



14 **15**

Catalyst	5 % Rh(C)	10 % Pd(C)	1 % Pt(C)
Ratio **14 : 15**	0 : 100	60 : 40	100 : 0

polymer formation. Finally, attempts to induce oxidative cyclization in solvents other than trifluoroethanol (e.g., MeCN) have so far been unsuccessful.

As exemplified in Scheme 4 with compound **12a**, the dienone system may be hydrogenated at atmospheric pressure to give spirocycles of the type **1**; e.g., **14**. This reduction occurred cleanly in the presence of platinum on carbon or platinum oxide (Adams catalyst), whereas other hydrogenation catalysts provided also variable quantities of re-aromatized product **15.** The ratio of desired lactam **14** to amide **15** ranged from 100:0 with Pt(C) to 60:40 with Pd(C) to 0:100 with Rh(C). Aromatization presumably involves formal oxidative addition of zerovalent metal to the dienone C–N σ bond, followed by hydrogenolysis of the intermediate complex. Indeed, the extent of aromatization seems to correlate with the reduction potential of Rh (0.600 V), Pd (0.951 V) and Pt (1.118 V) [12]. A side reaction observed with Pt catalyst is hydrogenation of the ketone to an alcohol. This process, however, is slower than dienone hydrogenation, and it may be generally controlled by careful monitoring of the course of the reduction (TLC) and by avoiding prolonged reaction times.

In summary, the preparation of spirolactams **12** by oxidative cyclization of phenolic ω-arylalkanoic acids, heretofore an elusive process, may be achieved *via* oxazoline intermediates. This chemistry is likely to facilitate the synthesis of various heterocyclic natural products. Additional developments in these areas will be described in due course.

Acknowledgment: We thank the NIH (CA-55268), the NSF (CHE 95-26183), the Robert A. Welch Foundation (C-1007), the CNRS and the MESR for support of our research program. MAC is a Fellow of the Alfred P. Sloan Foundation (1994-1998).

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