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Tetrahedron Letters
Tetrahedron Letters 47 (2006) 8911–8915

Highly diastereoselective Staudinger reaction on 5,6-dihydropyrazin-2-(1*H*)-ones. Synthesis of enantiopure fused oxopiperazino-β-lactams

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Received 11 August 2006; revised 3 October 2006; accepted 9 October 2006
Available online 30 October 2006

Abstract—The highly diastereoselective synthesis of fused oxopiperazino-β-lactams **2** by Staudinger reaction between functionalized ketenes and 5,6-dihydropyrazin-2(1*H*)-ones **1** has been carried out. Further cleavage of the β-lactam ring produced 2-oxopiperazine-3-acetic acid derivatives **7** with no epimerization and in good yields.

The oxopiperazine ring is a well established conformationally constrained peptidomimetic, therefore, many efforts have aimed to prepare these products with stereocontrol.[1] In particular, 2-oxopiperazine-3-acetic acid methyl ester has been designed as cyclic template bearing an aspartic acid side chain.[2] Furthermore, related compounds containing 2-oxopiperazine-3-acetic acid subunits have shown activity as aspartate transcarbamoylase inhibitors, and as antagonists of the glycoprotein IIb/IIIa useful for the treatment of thrombotic diseases.[3] Frequently, the enantioselective synthetic approaches to 3-substituted 2-oxopiperazines rely on natural aminoacids and are not fully useful for the straightforward synthesis of highly substituted derivatives.

β-Lactams continue to attract attention from chemists due to their antibiotic properties; in addition, in recent years the β-lactam skeleton has found broad applicability as a synthon to prepare a wide range of molecules.[4] The Staudinger reaction between imines and ketenes is one of the most efficient methods to prepare enantiopure 2-azetidinones. In particular, most of the reports on the synthesis of bicyclic β-lactams are focused on initial [2+2] cycloaddition of acyclic imines and ketenes and further cyclization of the groups pending of the β-lactam.[5] In contrast, reports focused on the diastereoselective synthesis of enantiopure β-lactams from cyclic imines are scarce and often limited to the use of enantiopure acid chlorides as the source of asymmetric induction.[6]

Within a program focused on the discovery of bioactive piperazines[7] and in connection with our studies on the development of efficient routes to highly substituted enantiopure piperazines from sulfinimines,[8] we examined the stereocontrolled addition of nucleophiles onto 5,6-dihydropyrazin-2(1*H*)-ones, **A**. A completely stereoselective and high-yielding allylation[8b] was achieved under Barbier conditions (**B**) using $CeCl_3{\cdot}7H_2O$ as additive and this would be a suitable route to an acetate group by oxidation. Encouraged by these results and seeking an alternative access to 2-oxopiperazine-3-acetic acid derivatives, we submitted substrates **A** to the parallel Reformastky procedure using methyl α-bromoacetate. However, 5,6-dihydropyrazin-2(1*H*)-ones **A** were unreactive under these conditions and the addition of preformed organozinc reagents such as 4-ethoxy-4-oxobutylzinc bromide also resulted ineffective (Scheme 1). At this point, we planned an alternative strategy for the synthesis of these compounds. We envisioned a new approach by means of a diastereoselective Staudinger reaction onto 5,6-dihydropyrazin-2(1*H*)-ones **A**, to produce fused oxo-piperazino-β-lactams **C** that could be suitable precursors to highly substituted enantiopure piperazines.

Initially we examined the reaction between **1a** and an excess of phthalimidoacetyl chloride in the presence of

Keywords: β-Lactams; Piperazines; Asymmetric synthesis.
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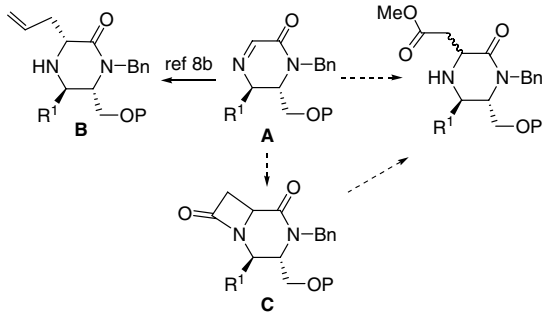
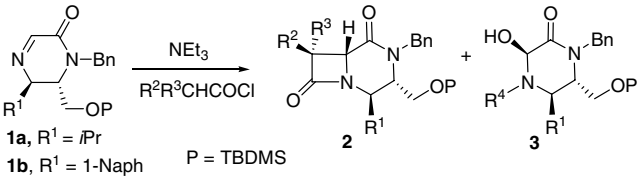
doi:10.1016/j.tetlet.2006.10.044



Scheme 1.



Scheme 2.

triethylamine, in CH_2Cl_2 and at room temperature and we found an excellent yield of β-lactam **2a** as a single diastereoisomer (Scheme 2, Table 1, entry 1).[9] Under similar reaction conditions, a good yield of acetoxy β-lactam **2b** (entry 2) was obtained, however other acetyl chlorides (benzyloxy-, chloro-, and 2,5-dimethoxyphenyl-, entries 3, 5, and 8) did not render a complete [2+2] cycloaddition yielding substantial amounts of monocyclic intermediates **3c**–**e**, each of them as a single isomer and generated by addition of water to the acyliminium intermediates during the aqueous work-up.[10]

To improve the yields of β-lactams, we changed the reaction conditions to toluene at 80 °C and good yields of chloro- and 2,5-dimethoxyphenyl β-lactams **2c** and **2e** were obtained while maintaining complete diastereoselectivity (entries 4 and 9). Upon these conditions, benzyloxyacetyl chloride led to an 82:12 mixture of diastereoisomeric β-lactams (80%) along with 14% of **3d** which incorporates two molecules of the starting acid chloride. A decrease in the reaction temperature allowed for the synthesis of **2d** as a single diastereomer but again 27% of **3d** was isolated in this experiment (entries 6 and 7). To extend the scope of this procedure, we examined the behavior of 5,6-dihydropyrazin-2(1*H*)-one **1b**, with the imine flanked by an aromatic group (R^1 = 1-naphthyl). Entries 12–14 show that **1b** underwent a highly diastereoselective Staudinger reaction providing β-lactams **2g**–**i** in good yield under these conditions.[11] Efforts to prepare 3,3-disubstituted β-lactams and 3-alkyl/vinyl

Table 1. Synthesis of piperazino-β-lactams **2a**–**i** produced via Scheme 2

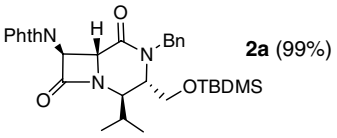
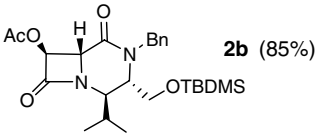
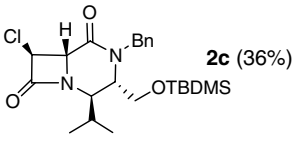
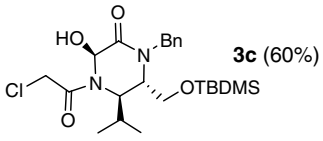
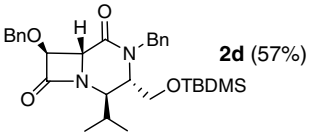
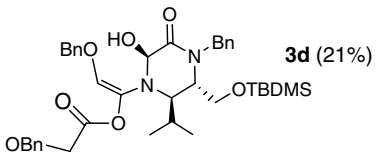
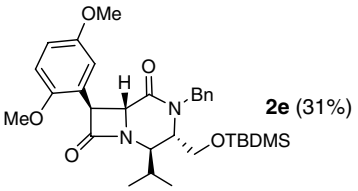
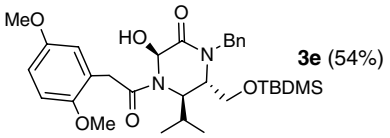
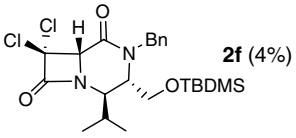
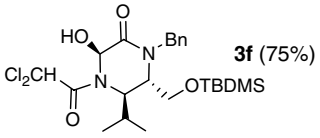
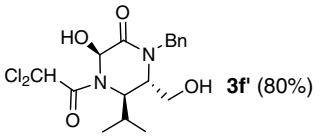
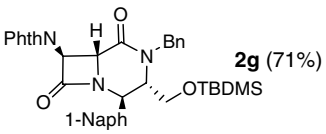
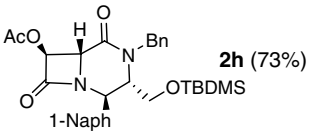
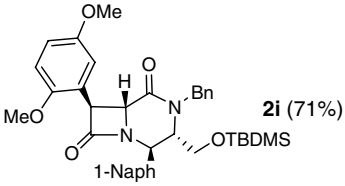
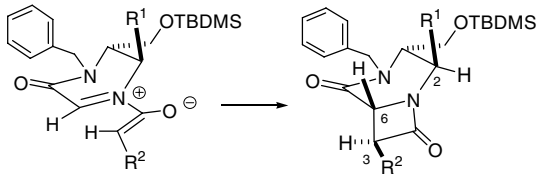
Entry	1	Conditions	2 (Yield %)	3 (Yield %)
1	**1a**	PhthNCH$_2$COCl (1.72 equiv), NEt$_3$ (4.8 equiv) CH$_2$Cl$_2$, 0 °C–rt, 15 h	 **2a** (99%)	—
2	**1a**	AcOCH$_2$COCl (2.30 equiv), NEt$_3$ (6.4 equiv) CH$_2$Cl$_2$, 0 °C–rt, 28 h	 **2b** (85%)	—
3	**1a**	ClCH$_2$COCl (1.72 equiv), NEt$_3$ (4.8 equiv) CH$_2$Cl$_2$, 0 °C–rt, 19 h	 **2c** (36%)	 **3c** (60%)
4	**1a**	Toluene, 80 °C, 4 h 30 min	**2c** (74%)	—
5	**1a**	BnOCH$_2$COCl (1.72 equiv), NEt$_3$ (4.8 equiv) CH$_2$Cl$_2$, 0 °C–rt, 18 h	 **2d** (57%)	 **3d** (21%)
6	**1a**	Toluene, 40–80 °C, 4 h	**2d** (60%)	**3d** (27%)
7	**1a**	Toluene, 80 °C, 1 h	**2d** (82:12, 80%)	**3d** (14%)

Table 1 (*continued*)

Entry	1	Conditions	2 (Yield %)	3 (Yield %)
8	**1a**	2,5-$(CH_3O)_2$-$C_6H_3CH_2COCl$ (1.72 equiv), NEt_3 (4.8 equiv) CH_2Cl_2, 0 °C–rt–Δ, 51 h	 **2e** (31%)	 **3e** (54%)
9	**1a**	Toluene, 80 °C, 1 h 15 min	**2e** (74%)	—
10	**1a**	$Cl_2CHCOCl$ (2.0 equiv), NEt_3 (4.0 equiv) toluene, rt, 1 h	 **2f** (4%)	 **3f** (75%)
11	**1a**	$Cl_2CHCOCl$ (1.72 equiv), NEt_3 (4.8 equiv) toluene, 80 °C, 4 h	—	 **3f'** (80%)
12	**1b**	$PhthNCH_2COCl$ (1.72 equiv), NEt_3 (4.8 equiv) toluene, 80 °C, 19 h	 **2g** (71%)	—
13	**1b**	$AcOCH_2COCl$ (1.72 equiv), NEt_3 (4.8 equiv) CH_2Cl_2, 0 °C–rt, 20 h 30 min	 **2h** (73%)	—
14	**1b**	2,5-$(CH_3O)_2$-$C_6H_3CH_2COCl$ (3.40 equiv), NEt_3 (9.60 equiv) toluene, 80 °C, 18 h	 **2i** (71%)	—

β-lactams were unsuccessful under thermodynamic and kinetic conditions. When *i*-butyryl chloride, *n*-butyryl chloride and 3-methylbut-2-enoyl chloride were used as ketene precursors, complex mixtures of N-acylated compounds were isolated. In contrast, the reaction of **1a** with dichloroacetyl chloride in toluene at room temperature led to N-acylated derivative **3f** (75%), along with a trace amount of β-lactam **2f** (4%). Increasing the temperature led to the isolation of **3f′** (80%) with loss of the silyl protecting group (entries 10 and 11).[12]

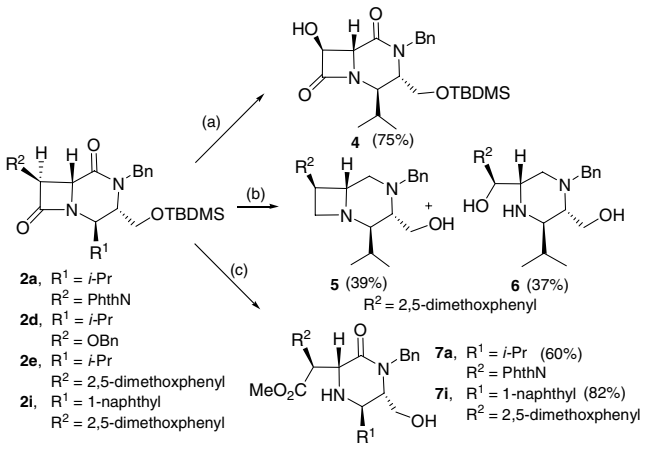
The structural assignment of the bicyclic β-lactams **2a**–**i** was based on spectroscopic data (Scheme 3). The trans relative stereochemistry was easily determined by the small coupling constant between H-3 and H-6 ranging from 1.9 to 2.6 Hz. The absolute configuration was established by 2D-NOESY experiments which showed cross points between H-6 and protons of R^1.[13] The trans stereochemical outcome could be rationalized in terms of an *exo* approach, which places the electrodonating



Scheme 3.

ketene substituent (R^2) outward without further isomerization of the imine. With respect to the diastereofacial selectivity, the pseudo axial arrangement of R^1 probably blocks the β-face of the iminium intermediate and therefore cyclization takes place by the less hindered convex face.[14]

In addition, we examined the reactivity of oxopiperazino-β-lactams **2** (Scheme 4). Thus, **2d** underwent smooth hydrogenation when EtOAc was used as a solvent ren-



Scheme 4. Reagents and conditions: (a) Pd–C (10%), H_2, 45 psi, EtOAc, rt, (b) $BH_3{\cdot}SMe_2$, THF, Δ; then 0.2 N HCl, Δ, (c) TMSCl, MeOH, rt.

dering α-hydroxy-β-lactam **4** in 75% yield. The use of nucleophilic solvents as methanol should be avoided due to the lability of these bicyclic β-lactams. We have also explored the behavior of these β-lactams under reductive conditions. The treatment of **2e** with $BH_3{\cdot}SMe_2$ in THF under reflux gave rise to a mixture of the bicyclic azetidine **5** (39%) and piperazinyl ethanol **6** (37%). Finally, treatment of **2a** and **2i** with trimethylchlorosilane in methanol smoothly produced the cleavage of the β-lactam ring with simultaneous deprotection of the hydroxymethyl group to give 2-oxopiperazine-3-acetic acid methyl esters **7a** and **7i** in good yields.[15]

In conclusion, we have developed a general method to prepare fused oxopiperazino-β-lactams **2** by reaction between functionalized ketenes and 5,6-dihydropyrazin-2(1*H*)-ones **1** in excellent yields and with complete stereocontrol induced by the piperazine system. Subsequent methanolysis of the four-membered ring produces enantiopure 2-oxopiperazine-3-acetic acid methyl esters **7** in good yields.

Acknowledgments

This research was supported by DGI MEC (Grants BQU2003-02921 and CTQ2005-04632/BQU). We thank JANSSEN-CILAG for generous additional support and CAM for a doctoral fellowship to A.F.

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9. Compound **2a**: A mixture of **1a** (0.045 mmol), Et_3N (0.218 mmol) and phthalimidoacetyl chloride (0.078 mmol) in CH_2Cl_2 (10 mL/mmol) at room temperature, was stirred until disappearance of **1a** (TLC) and then diluted with CH_2Cl_2 (10 mL/mmol). The mixture was quenched with brine (7 mL/mmol). The aqueous phase was extracted with CH_2Cl_2 (2×10 mL/mmol) and the combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure to give a crude product. Compound **2a** (25 mg, 99%) was obtained after purification by column chromatography (10–30% EtOAc–hexane) as a white foam. Data for **2a**: $R_f = 0.17$ (30% EtOAc–hexane). $[\alpha]_D^{20}$ +9.9 (*c* 1.01, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz) δ 0.12 (s, 3H, TBDMS), 0.14 (s, 3H, TBDMS), 0.47 (d, 3H, $J = 6.4$ Hz, *i*-Pr), 0.91 (s, 9H, TBDMS), 1.06 (d, 3H, $J = 6.8$ Hz, *i*-Pr), 1.57–1.65 (m, 1H, *i*-Pr), 3.40 (dd, 1H, $J = 7.0$, 3.7 Hz, H-3), 3.53 (d, 1H, $J = 10.6$ Hz, H-2), 3.68 (dd, 1H, $J = 10.4$, 7.0 Hz, CH_2O), 3.73 (d, 1H, $J = 14.3$ Hz, CH_2Ph), 3.73 (dd, 1H, $J = 10.4$, 3.7 Hz, CH_2O), 4.49 (d, 1H, $J = 2.6$ Hz, H-6), 5.47 (d, 1H, $J = 2.7$ Hz, H-7), 5.62 (d, 1H, $J = 14.5$ Hz, CH_2Ph), 7.24–7.26 (m, 2H, Ar-H), 7.29–7.36 (m, 3H, Ar-H), 7.74 (dd, 2H, $J = 5.5$, 3.1 Hz, Ar-H), 7.86 (dd, 2H, $J = 5.5$, 3.1 Hz, Ar-H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ −5.5, −5.4, 18.5,

19.0, 19.6, 25.9, 27.4, 48.2, 53.2, 56.1, 58.5, 58.6, 63.4, 123.7 (2C), 128.2, 128.8 (2C), 128.9 (3C), 131.7, 134.5 (2C), 136.3, 164.8 (2C, CO-Phth), 166.2 (CO), 166.6 (CO). IR (film): 2955, 2925, 2854, 1773, 1724, 1657, 1450, 1389, 1254, 1105, 1044, 834, 716 cm^{-1}. MS (ES): 1145 $[2M+Na]^+$, 584 $[M+Na]^+$, 562 $[M+1]^+$ (100%).

10. The absolute configuration of C-3 was established by 2D-NOESY of **3f′**.
11. Under basic conditions and long reaction times, **1b** undergoes isomerization of the C=N bond to conjugation with the naphthyl group. However, this isomerization is not observed under Staudinger conditions.
12. Raising the reaction temperature could either prevent formation of the β-lactam or facilitate its cleavage or decomposition.
13. Compound **2g**: 2D-NOESY showed cross points between H-6/H-7, H-6/Ar-H (H-2, H-3 Naph, 7.31 ppm), H-2/CH_2O, H-2/Ar-H (H-8 Naph, 7.94 ppm).
14. For a recent reference dealing with the stereochemistry of the Staudinger reaction, see: Jiao, L.; Liang, Y.; Xu, J. *J. Am. Chem. Soc.* **2006**, *128*, 6060–6069.
15. Compound **7a**: From a solution of **2a** (32 mg, 0.056 mmol) and TMSCl (0.570 mmol) in MeOH (67 h), **7a** (16 mg, 60%) was isolated as a colorless oil after purification through SCX resin and column chromatography (10–20% EtOAc–CH_2Cl_2). $R_f = 0.33$ (40% EtOAc–CH_2Cl_2). $[\alpha]_D^{20}$ +53.2 (*c* 0.38, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz) δ 0.41 (d, 3H, $J = 6.4$ Hz, *i*-Pr), 0.87 (d, 3H, $J = 6.6$ Hz, *i*-Pr), 1.54 (br s, 1H, NH), 1.62–1.69 (m, 1H, *i*-Pr), 2.59 (d, 1H, $J = 10.7$ Hz, H-6′), 3.28 (ap t, 1H, $J = 3.3$ Hz, H-5′), 3.74 (s, 1H, OCH_3), 3.74 (dd, 1H, $J = 11.4$, 3.2 Hz, CH_2O), 3.96 (d, 1H, $J = 14.6$ Hz, CH_2Ph), 3.99 (d, 1H, $J = 3.9$ Hz, H-2′), 4.02 (dd, 1H, $J = 11.1$, 4.7 Hz, CH_2O), 5.42 (d, 1H, $J = 14.6$ Hz, CH_2Ph), 5.91 (d, 1H, $J = 3.9$ Hz, H-2), 7.27 (m, 5H, Ar–H), 7.73 (dd, 2H, $J = 5.5$, 2.9 Hz, Ar–H), 7.88 (dd, 2H, $J = 5.5$, 2.9 Hz, Ar–H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.8, 19.6, 25.8, 48.6, 52.7, 54.7, 55.5, 55.6, 59.8, 63.8, 123.8 (2C), 127.8, 128.6 (3C), 128.7 (2C), 131.8, 134.3 (2C), 136.9, 166.9, 167.9, 168.4 (3C, CO–Phth, CO–N). IR (film): 3356, 2925, 1748, 1719, 1645, 1449, 1436, 1387, 1247, 1109, 1069, 1047 cm^{-1}. MS (ES): 981 $[2M+Na]^+$, 512 $[M+MeOH+1]^+$, 480 $[M+1]^+$ (100%).