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Spiro-*β*-lactams Synthesized from Imines Derived from 8-Azabicyclo[3.2.1]octan-3-ones

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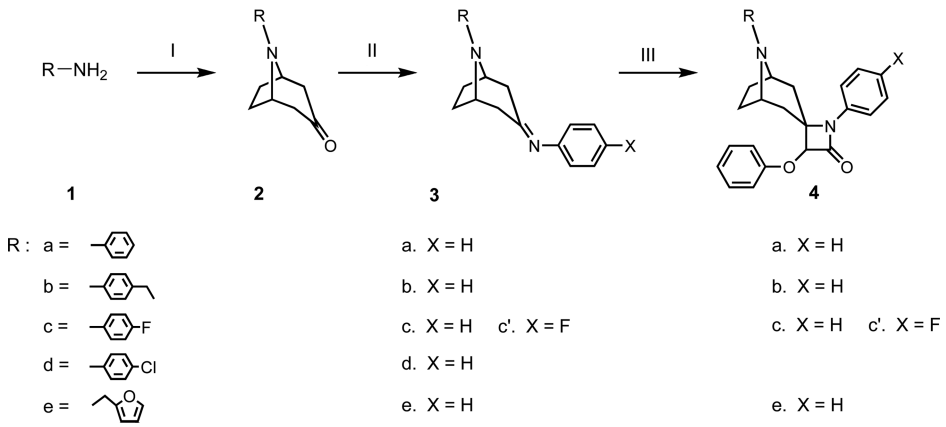
Tropane alkaloids have attracted considerable attention because of their remarkable pharmaceutical significance.[1-4] In particular, a series of tropanes exhibited anticonvulsant activity against pentylenetetrazol-induced convulsions in mice and antiarrhythmic activity in rabbits previously treated with ouabain.[5-8] Therefore, a variety of synthetic approaches to prepare tropane alkaloids have been investigated. In addition, the importance of *β*-lactams for the treatment of bacterial infections has been well established.[9-10] Considerable efforts have been made for the synthesis and structural modification of the *β*-lactam nucleus to increase its antimicrobial activity. Apart from their therapeutic utility, *β*-lactams are versatile synthons that are used for the preparation of *α*- and *β*-amino acids.[10] Although many functionalized monocyclic *β*-lactams have been reported thus far, there have been relatively few efforts toward the synthesis of spiro-*β*-lactams.[11] Among the different strategies employed for the construction of *β*-lactams,[12] the reaction of acid chlorides with imines (Staudinger synthesis)[13] is one of the most popular procedures. As a part of our study on the improvement of anticonvulsants and the development of new drugs, here, we report the synthesis of a new class of spiro-*β*-lactams having an 8-azabicyclo[3.2.1]octan-3-one ring. We have already published a few reports on the synthetic study of pharmacologically interesting 8-azabicyclo[3.2.1]octan-3-one compounds derived from the reaction of corresponding amines **1** with 2,5-dimethoxytetrahydrofuran and 1,3-acetonedicarboxylic acid in the presence of HCl and H_2O.[14-18] Imines **3** derived from 8-azabicyclo[3.2.1]octan-3-one (Scheme 1) may serve as an interesting starting material for the synthesis of a new class of spiro-*β*-lactams such as **4**. Furthermore, in these structures, the inherent reactivity of the 8-azabicyclo[3.2.1]octan-3-one framework can be combined with the synthetic versatility of the *β*-lactam moiety in a single compound. To the best of our knowledge, the Staudinger synthesis of compounds **3** has not been reported previously; therefore, our paper might be the first to report results in this field. Phenyl-(8-phenyl-8-azabicyclo[3.2.1]oct-3-ylidene)-amine **3a** was synthesized by the reaction of 8-phenyl-8-azabicyclo[3.2.1]octan-3-one **2a** (1.0 g, 5 mmol) in benzene with aniline (0.5 g, 5 mmol) and montmorillonite (5 g) by using the Dean-Stark apparatus. The reaction mixture was refluxed for a further 24 h and then cooled to room temperature. After filtering the montmorillonite, the organic layer was concentrated. The residue was chromatographed on a silica gel (*n*-hexane:dichloromethane = 1:10, v/v) to yield **3a** (0.84 g, 61%) as a brown sticky oil. The structures and yields of the synthesized imines (**3a-3e**) are summarized in Scheme 1 and Table 1.



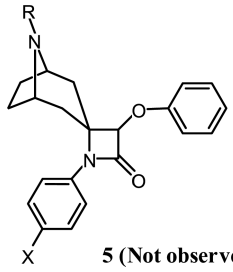
Scheme 1. Synthesis of spiro-*β*-lactams **4** from amines **1**. Reagent and reaction conditions: (I) 2,5-dimethoxytetrahydrofuran, 1,3-acetonedicarboxylic acid, HCl, H_2O, rt; (II) 4-substituted-aniline, montmorillonite, benzene, reflux; (III) phenoxyacetyl chloride, triethylamine, toluene.

Table 1. Physical data from 8-substituted-8-azabicyclo[3.2.1]octan-3-ones **2** to spiro-*β*-lactams **4**

Entry	Reactant	Product	Yield (%)[a]	mp (°C)
1	**1a**	**2a**	51	99–100
2	**1b**	**2b**	85	51–52
3	**1c**	**2c**	85	88–89
4	**1d**	**2d**	85	155–156
5	**1e**	**2e**	78	Liq.
6	**2a**	**3a**	61	Liq.
7	**2b**	**3b**	31	Liq
8	**2c**	**3c**	82	157–158
9	**2c'**	**3c'**	34	148–149
10	**2d**	**3d**	55	Liq.
11	**2e**	**3e**	15	Liq.
12	**3a**	**4a**	91	127–128
13	**3b**	**4b**	69	96–97
14	**3c**	**4c**	30	164–165
15	**3c'**	**4c'**	82	120–121
16	**3e**	**4e**	73	136–137

[a]Yields are isolated yields.

The Staudinger synthesis of compounds **3** with the phenoxyacetyl chloride afforded spiro-*β*-lactams **4** (Scheme 1). 3-Phenoxy-1,8'-diphenyl-8'-azaspiro[azetidine-2,3'-bicyclo-[3.2.1]octan]-4-one **4a** was synthesized by the reaction of phenyl-(8-phenyl-8-azabicyclo[3.2.1]oct-3-ylidene)-amine **3a** (25 mg, 9×10^{-2} mmol) in toluene (50 mL) with triethylamine and phenoxyacetyl chloride (16 mg, 9.5×10^{-2} mmol). The reaction mixture was stirred at room temperature for a further 5 h. After stirring for 5 h, the organic layer was filtered and concentrated. The residue was chromatographed on a silica gel (*n*-hexane:EtOAc = 4:1, v/v) to yield **4a** (34 mg, 91%) as a light-yellow solid. The structures and yields of the synthesized spiro-*β*-lactams (**4a-4c'**) are summarized in Scheme 1 and Table 1. These were obtained as single diastereomers, and no traces of the corresponding isomeric exo-*β*-lactam **5** were observed.



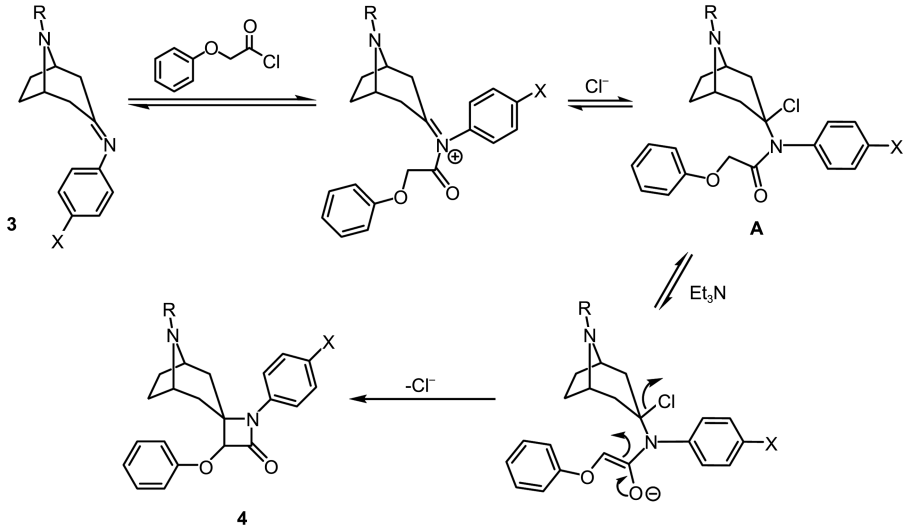
5 (Not observed)

It is noteworthy that this stereochemical outcome of *β*-lactam formation with phenoxyacetyl chloride under Staudinger synthesis conditions was opposite to that expected from a simple [2+2]-cycloaddition reaction,[19,20] which should have occurred from the exo face of compound **2** to afford compounds **4**.[21] A plausible mechanism for the formation of spiro-*β*-lactams **4** is shown in Scheme 2.

The initial acylation of imines **3** followed by the addition of a chloride ion[21] from the exo-face of the iminium ion should afford intermediate **A**. Enolization followed by intramolecular endo-displacement of the chloride should afford spiro-*β*-lactams **4**. This is the reaction pathway observed for the highly reactive oxygen-substituted enolate as a phenoxyacetyl chloride.[22] In conclusion, the Staudinger synthesis of imines derived from 8-azabicyclo[3.2.1]octan-3-one with phenoxyacetyl chloride affords the corresponding spiro-*β*-lactams, but with an unexpected exo stereochemistry. Studies aimed at gaining a greater understanding of this Staudinger synthesis of imines with new structures as well as those aimed at the synthetic application of these findings are underway and these will be reported in due course.

Experimental Section

Melting points were determined using an electrothermal capillary melting point apparatus and uncorrected. Thin layer chromatography (TLC) was performed on glass plates coated with silicon oxide (silica gel $60F_{254}$), and compounds were visualized using a UV lamp. ^{1}H and ^{13}C NMR spectra were



Scheme 2. Plausible mechanism for the formation of *β*-lactams **4** from imines **3**.

obtained with Bruker AC 2000 (200 MHz) and Varian Gemini (200 or 300 MHz) spectrometers. Mass spectra were measured with HP 5890 GC/Mass (70 eV, EI). The organic solvents and chemicals were obtained from commercial products and purified by the appropriate methods before use. Except where explicitly stated, all the starting materials were purchased from Aldrich, Fluka, Fisher, Lancaster, or TCI chemical companies and used as received.

3-Phenoxy-1,8'-diphenyl-8'-azaspiro[azetidine-2,3'-bicyclo[3.2.1]octan]-4-one (4a). Yield: 91%; mp 127–128 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (m, 7H), 7.04 (s, 1H), 6.95 (m, 2H), 6.81 (t, 1H), 6.77 (s, 2H), 6.74 (d, *J* = 7.9 Hz, 2H), 4.60 (s, 1H), 4.37 (m, 2H), 4.29 (s, 2H), 2.63 (dd, , *J* = 3.2, 17.1 Hz, 1H), 2.34 (m, 1H), 2.16 (s, 1H), 2.14 (m, 1H), 1.78 (s, 1H), 1.61 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.10, 157.99, 146.50, 133.72, 129.52, 129.38, 128.84, 126.44, 125.16, 121.42, 121.41, 116.42, 114.70, 66.74, 53.47, 34.15, 33.02, 29.80; GC/MS *m/z* 410 (M+); Anal. Calcd. for $C_{27}H_{26}N_2O_2$: C, 79.00; H, 6.38; N, 6.82; O, 7.79. Found: C, 78.70; H, 6.46; N, 6.77; O, 7.83.

3-Phenoxy-1-phenyl-8'-*p*-ethylphenyl-8'-azaspiro[azetidine-2,3'-bicyclo[3.2.1]octan]-4-one (4b). Yield: 69%; mp 96–97 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (m, 7H), 7.01 (s, 1H), 6.89 (m, 2H), 6.75 (s, 2H), 6.71 (d, , *J* = 7.9 Hz, 2H), 4.59 (s, 1H), 4.34 (m, 2H), 4.28 (s, 2H), 2.61 (dd, , *J* = 3.0, 17.1 Hz, 1H), 2.59 (q, *J* = 7.6 Hz, 2H), 2.32 (m, 1H), 2.15 (s, 1H), 2.11 (m, 1H), 1.77 (s, 1H), 1.59 (s, 1H), 1.21 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.13, 157.98, 146.45, 133.52, 129.87, 129.35, 129.28, 128.84, 126.40, 125.15, 121.42, 121.40, 114.72, 66.69, 53.61, 34.27, 33.15, 29.89, 27.80, 15.54; GC/MS *m/z* 438 (M+); Anal. Calcd. for $C_{29}H_{30}N_2O_2$: C, 79.42; H, 6.89; N, 6.39; O, 7.30. Found: C, 79.40; H, 6.93; N, 6.38; O, 7.31.

3-Phenoxy-1-phenyl-8'-*p*-fluorophenyl-8'-azaspiro[azetidine-2,3'-bicyclo[3.2.1]octan]-4-one (4c). Yield: 30%; mp 164–165 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (m, 5H), 6.93 (m, 5H), 6.76 (m, 4H), 4.56 (s, 1H), 4.33 (s, 2H), 4.26 (d, *J* = 8.2 Hz, 2H), 2.55 (dd, *J* = 3.3, 17.2 Hz, 1H), 2.31 (m, 1H), 2.10 (m, 2H), 1.76 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.10, 158.32, 155.17, 143.74, 129.88, 129.51, 127.02, 125.65, 121.95, 117.87, 116.28, 115.14, 67.27, 54.33, 34.68, 33.25, 30.27; GC/MS *m/z* 428 (M+); Anal. Calcd. for $C_{27}H_{25}FN_2O_2C$, 75.68; H, 5.88; F, 4.43; N, 6.54; O, 7.47. Found: C, 75.57; H, 5.92; F, 4.49; N, 6.53; O, 7.49.

3-Phenoxy-1-*p*-fluorophenyl-8'-*p*-fluorophenyl-8'-azaspiro[azetidine-2,3'-bicyclo[3.2.1]octan]-4-one (4c'). Yield: 82%; mp 120–121 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.02 (m, 4H), 6.80 (m, 5H), 6.69 (m, 4H), 4.58 (s, 1H), 4.42 (s, 2H), 4.28 (d, *J* = 8.2 Hz, 2H), 2.65 (dd, *J* = 3.3, 17.2 Hz, 1H), 2.35 (m, 1H), 2.13 (m, 2H), 1.79 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.16, 158.22, 155.20, 153.52, 143.51, 130.40, 129.55, 123.13, 120.90, 117.97, 116.51, 115.93, 115.47, 67.47, 54.38, 34.95, 33.46, 30.33; GC/MS *m/z* 446 (M+); Anal. Calcd. for $C_{27}H_{24}F_2N_2O_2$: C, 72.63; H, 5.42; F, 8.51; N, 6.27; O, 7.17. Found: C, 72.58; H, 5.45; F, 8.53; N, 6.20; O, 7.19.

3-Phenoxy-1-phenyl-8'-furfuryl-8'-azaspiro[azetidine-2,3'-bicyclo[3.2.1]octan]-4-one (4e). Yield: 73%; mp 136–137 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (m, 7H), 7.06 (d, *J* = 2.17 Hz, 1H), 6.99 (s, 1H), 6.87 (m, 2H), 6.80 (t, 1H), 6.77 (s, 2H), 6.45 (d, *J* = 7.8 Hz, 2H), 6.32 (m, 1H), 6.23 (d, *J* = 3.56 Hz, 1H), 4.59 (s, 1H), 4.37 (m, 2H), 4.25 (s, 2H), 3.68 (s, 2H), 2.68 (dd, *J* = 3.1, 17.1 Hz, 1H), 2.30 (m, 1H), 2.12 (s, 1H), 2.07 (m, 1H), 1.71 (s, 1H), 1.48 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.05, 157.59, 145.34, 134.33, 129.79, 129.12, 128.86, 127.96, 126.10, 125.03, 121.42, 113.88, 66.21, 52.42, 33.97, 33.15, 28.37; GC/MS *m/z* 414 (M+); Anal. Calcd. for $C_{26}H_{26}N_2O_3$: C, 75.34; H, 6.32; N, 6.76; O, 11.58. Found: C, 75.32; H, 6.33; N, 6.79; O, 7.81.

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