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Article

Preliminary Studies towards the Preparation of Reactive 3-Pyrrolin-2-ones in Conjugate Addition Reactions for the Syntheses of Potentially Bioactive 2-Pyrrolidinones and Pyrrolidines

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Pirrolin-2-onas e 2-pirrolidinonas são subunidades geralmente encontradas na estrutura de vários produtos naturais bioativos e 3-pirrolin-2-onas são valiosos materiais de partida em síntese orgânica devido à habilidade de reagirem como aceptores em reações de adição conjugada. Neste artigo relatamos os resultados iniciais do estudo realizado objetivando as sínteses de 3-pirrolin-2-onas reativas em reações de adição conjugada e a preparação de um precursor potencial para a síntese do nootrópico (+/-)-nebracetam.

Pyrrolin-2-ones and 2-pyrrolidinones are moieties often found in the structure of several biologically active natural products and 3-pyrrolin-2-ones are valuable starting materials in organic synthesis due to their ability to react as acceptors in conjugate addition reactions. In this article we report the initial results about the performed study aiming at the syntheses of reactive 3-pyrrolin-2-ones in conjugate addition reactions and the preparation of a potential precursor for the synthesis of the nootropic (+/-)-nebracetam.

Keywords: 2-pyrrolidinones, 3-pyrrolin-2-ones, conjugate addition reaction, 2,5-dimethoxydihydrofuran, nebracetam

Introduction

Pyrrolin-2-ones and 2-pyrrolidinones are moieties often found in the structure of several biologically active natural products and 3-pyrrolin-2-ones are valuable starting materials in organic synthesis due to their ability to react as acceptors in conjugate addition reactions of organocuprates, enolates and nitrogen nucleophiles, beyond suffering hydroxylation, epoxidation, cyclopropanation and cycloaddition reactions.[1] Moreover, 2-pyrrolidinones are important key intermediates for the synthesis of pyrrolidines[2] such as the excitatory amino acids, in which are included kainic acid (KA) and its analogous.[3] These substances are also important in the field of Medicinal Chemistry, being described in recent literature the syntheses of pyrrolinones and 2-pyrrolidinones as inhibitors of prostate cancer cell growth,[4] reverse transcriptase[5] and HIV-1 protease.[6]

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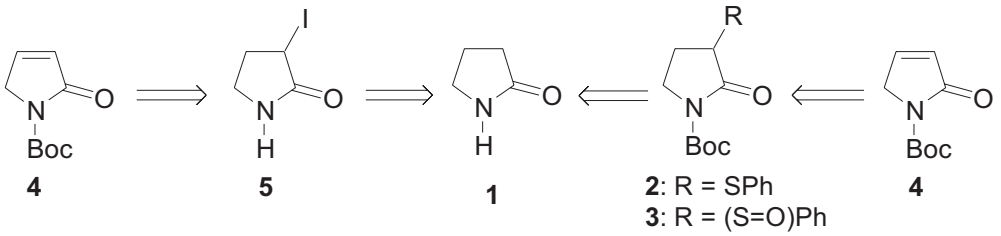
In this article we report a study aiming at the preparation of reactive 3-pyrrolin-2-ones in conjugate addition reactions, for the syntheses of potentially bioactive 2-pyrrolidinones and pyrrolidines.

Results and Discussion

Initially, we planned to synthesize the α,β-unsaturated γ-lactam **4** starting from 2-pyrrolidinone (**1**) by the two sequences depicted in Scheme 1.

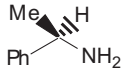
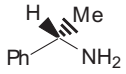
Our initial attempts to get the target molecule **4** by elimination of sulfoxide at compound **3** or iodide at the lactam **5**, followed by protection of nitrogen with the group *tert*-butoxycarbonyl (Boc), were unsuccessful due to the low yields obtained in the introduction step of the leaving groups at the α-position of the respective carbamates. With these unsatisfactory results, we focused our attention to the syntheses of 3-pyrrolin-2-ones with different substitution patterns at the nitrogen atom, using an attractive and convenient procedure in one step from



Scheme 1.

2,5-dimethoxydihydrofuran (**6**) and primary amines (**7**) (Scheme 2). It was previously proposed that the α,β-unsaturated γ-lactams such as **8** would be generated from an intramolecular oxido-reduction similar to a Cannizzaro reaction.[7] Our primary interest was the performance of the condensation of substrate **6** with the amines benzylamine (**7a**), *R*-α-methylbenzylamine (**7b**) and *S*-α-methylbenzylamine (**7c**) (Exp. 1-3, Table). After optimization of the reaction conditions, the lactams **8a-c** were obtained in 55-56% yield after purification of crude products by column chromatography of silica gel.

Table. Preparation of 3-pyrrolin-2-ones (**8a-c**)

Exp.	Amine	time/h	Product	(%)[a]
1	$PhCH_2NH_2$	3	8a	55
2		6	8b	56
3		6	8c	56

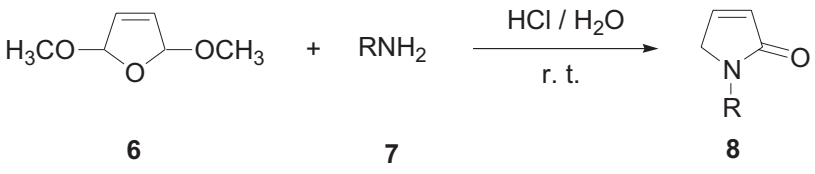
[a]After flash chromatography on silica gel.

Initial attempts to add the nucleophiles nitromethane, benzylamine, *R*-α- and *S*-α-methylbenzylamine to the lactams **8a-c**, in a conjugate fashion, were unsuccessful due to the generation of complex mixtures of substances that did not correspond to the expected addition products, as revealed in their NMR spectra. However, previous studies[8] have demonstrated that the addition of some nucleophilic species to the α,β-unsaturated system of γ-lactams requires an electron-withdrawing group attached to the amide nitrogen. Thus, we planned to obtain 3-pyrrolin-2-one (**9**), followed by the introduction of electron-withdrawing Boc as a protective group for the amide nitrogen, aiming at the preparation of N-(*tert*-butoxycarbonyl)-3-pyrrolin-2-one (**4**).

The generation of γ-lactams **8a-c** in mild conditions from 2,5-dimethoxydihydrofuran (**6**), inspired us to investigate this reaction in order to obtain the α,β-unsaturated γ-lactam **9** using aqueous ammonium chloride. Indeed, when the condensation reaction of the substrate **6** was performed at conditions depicted in Scheme 3, we obtained a mixture of two substances that were isolated, separated by column chromatography and then identified by spectroscopy methods as the regioisomers 3-pyrrolin-2-one (**9**) and 4-pyrrolin-2-one (**10**),[9] with 40% yield in a respective proportion of 7:1.

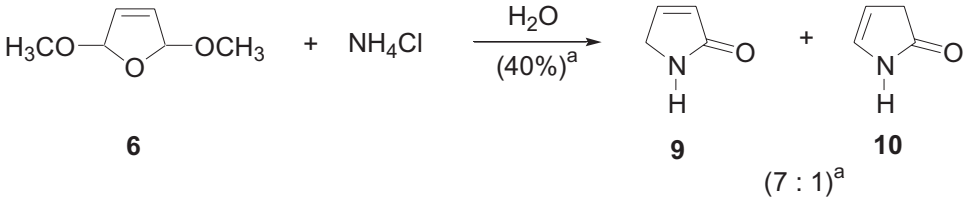
The transformation of compound **9** into *N*-protected γ-lactam **4** was carried out in a sequence constituted of deprotonation of the nitrogen with DMAP, followed by reaction of the generated amide ion with $(Boc)_2O$ (Scheme 4 - step *i*).[10] The crude product of this reaction was purified by column chromatography of silica gel to furnish the γ-lactam **4** in 40% yield.

With the α,β-unsaturated γ-lactam **4** in hand, we passed to the following stage of the reactivity evaluation of this compound as acceptor in conjugate addition reaction. Indeed, the strength of the α,β-unsaturated system of this compound, with the Boc protection group, was demonstrated by smooth conditions employed at the Nef's reaction to afford the nitro compound **11** (Scheme 4 - step *ii*).[11] The γ-lactam **11** was idealized as a precursor for the synthesis of the nootropic (+/-)-nebracetam (**12**).[12]

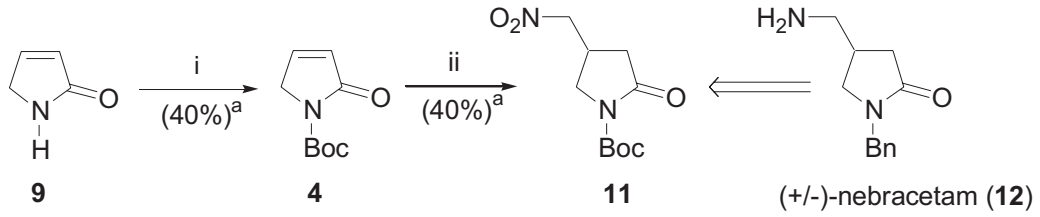


a: R = CH_2Ph **b**: R = *R*-α-$(CH_3)CHPh$ **c**: R = *S*-α-$(CH_3)CHPh$

Scheme 2. Reagents: **6** (1.0 equiv.), RNH_2 (1.1 equiv.), conc. HCl (0.3 equiv.).



Scheme 3. Reagents and conditions: **6** (1.0 equiv.), NH_4Cl (5.0 equiv.), H_2O (r. t. - 1 h); [a]After flash chromatography on silica gel.



Scheme 4. Reagents and conditions: *i*) DMAP (0.05 equiv.), $(Boc)_2O$ (1.1 equiv.), THF (r. t. - 10 min.); *ii*) $MeNO_2$ (5.0 equiv.), DBU (1.0 eq.), CH_3CN (r. t. - 1 h); [a]After flash chromatography on silica gel.

Conclusions

In summary, we prepared the new 3-pyrrolin-2-ones **8a-c**, in one pot procedure, starting from the inexpensive reagent 2,5-dimethoxydihydrofuran (**6**) and primary amines (**7a-c**). Although the lactams **8a-c** were shown unreactive in conjugate addition reactions, they are ideally adequate as templates for the construction of highly functionalized 2-pyrrolidinones and pyrrolidines, by exploiting functionalization of double bond in some other reactions, such as epoxidation, hydroxylation and cycloadditions besides reduction of the amide group. Using the same methodology for the preparation of compounds **8a-c**, we developed a new procedure, in one step, for the synthesis of 3-pyrrolin-2-one (**9**) from 2,5-dimethoxydihydrofuran (**6**) and aqueous ammonium chloride. The α,β-unsaturated γ-lactam **9** was transformed, in two steps, into N-(*tert*-butoxycarbonyl)-4-nitromethylene-2-pyrrolidinone (**11**), that can be used as intermediate for further studies towards the synthesis of the nootropic (+/-)-nebracetam (**12**). Furthermore, the inexpensive one pot procedure used with the substrate **6** and aqueous ammonium chloride is appropriate to synthesize in a multigram scale the γ-lactam **4**, considered a building block for the syntheses of other potentially bioactive 4-substituted 2-pyrrolidinones as well as the pyrrolidines analogous to kainic acid (KA).

Experimental

Infrared spectra were recorded on a Nicolet model Magna-IR 760 or Perkin Elmer-1600 model 1605 spectrophotometer (film or KBr). ^1H NMR and ^{13}C NMR spectra were recorded on a Varian Gemini-200 (200 MHz) or on a Bruker Spectrospin-400 (400 MHz) spectrometer, using $CDCl_3$ or CD_3OD as the solvent and TMS as internal standard. Coupling constants (*J*) are reported in Hertz (Hz) and multiplicities are indicated as s (singlet), bs (broad singlet), d (doublet), dd (double doublet), dt (double triplet), q (quartet), m (multiplet). Low Resolution Mass Spectra (LRMS) were obtained by electron-impact (70 eV) on a Varian GC-MS Saturn 2000 spectrometer and optical rotations were measured at 25 °C on a Perkin-Elmer 243-B polarimeter. Thin layer chromatography was performed on aluminium sheets coated with 60 F_{254} silica and visualization by UV light and/or for contact of the plates with 7% ethanolic solution of phosphomolybdic acid and posterior heating. Flash column chromatography was performed on silica gel (230-400 mesh). The solvents and reagents were dried and purified by usual procedures.[13]

*General procedure for the preparation of lactams **8a-c** (Exp. 1-3, Table)*

The appropriate amine **7a/7b/7c** (4.225 mmol) was allowed to react with a mixture of 2,5-dimethoxydihydrofuran (**6**) (0.500 g, 3.841 mmol) and conc. HCl (0.10 mL, 1.207 mmol) as a solution in H_2O (3.0 mL) during the respective times indicated at the Table. After the end of reaction, saturated solution of $NaHCO_3$ was added until pH 6 and the mixture was extracted with EtOAc (3 × 50 mL). The organic layers were dried with Na_2SO_4, filtered, concentrated in vacuum and crude product was then purified by column chromatography eluted with EtOAc.

*N-Benzyl-3-pyrrolin-2-one (**8a**)*

(0.365 g, 55%) as a brownish oil. R_f 0.29 (EtOAc). IR (film) ν_{max} / cm^{-1}: 3030, 2922, 1704, 1678, 1605, 1495,

1451, 1406, 1343, 1244, 805, 700. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.40-7.20 (m, 5H), 7.05 (m, 1H), 6.22 (m, 1H), 4.64 (s, 2H), 3.87 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 171.08 (C=O), 142.78 (CH), 136.88 (C), 128.41 (2 CH), 127.54 (2 CH), 127.43 (CH), 127.24 (CH), 51.98 (CH_2), 45.57 (CH_2). *m/z* (%): 173 (M^+, 97%), 149 (12), 131 (5), 115 (5), 106 (17), 91 (100), 77 (15), 65 (30), 55 (15), 44 (15).

*N-[(R)-α-Methylbenzyl]-3-pyrrolin-2-one (**8b**)*

(0.402 g, 56%) as a brownish oil. R_f 0.37 (EtOAc). $[\alpha]_D^{25}$ + 114 (c 1.20, CH_3OH). IR (film) ν_{max} / cm^{-1}: 3030, 2977, 1687, 1666, 1586, 1495, 1447, 1400, 1240, 802, 701. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.40-7.21 (m, 5H), 7.03 (m, 1H), 6.18 (m, 1H), 5.58 (q, *J* 7.1 Hz, 1H), 3.94 (dt, *J* 1.8 and 20.4 Hz, 1H), 3.62 (dt, *J* 1.8 and 20.4 Hz, 1H), 1.61 (d, *J* 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.76 (C=O), 142.65 (CH), 140.66 (C), 128.29 (2 CH), 127.45 (CH), 127.14 (CH), 126.54 (2 CH), 48.72 (CH), 48.41 (CH_2), 17.43 (CH_3). *m/z* (%): 187 (M^+, 80%), 172 (100), 160 (40), 149 (15), 132 (10), 117 (15), 105 (97), 96 (17), 77 (60), 69 (17), 51 (35), 44 (17).

*N-[(S)-α-Methylbenzyl]-3-pyrrolin-2-one (**8c**)*

(0.402 g, 56%) as a brownish oil. R_f 0.37 (EtOAc). $[\alpha]_D^{25}$ –107 (c 1.12, CH_3OH).

*3-Pyrrolin-2-one (**9**) and 4-pyrrolin-2-one (**10**)*

To a solution of NH_4Cl (6.162 g, 115.225 mmol) in H_2O (18 mL) it was added 2,5-dimethoxydihydrofuran (**6**) (3.000 g, 23.051 mmol). The mixture was left under magnetic stirring at room temperature for 1 h. It was added solid $NaHCO_3$ until pH 7 and then it was vigorously extracted with EtOAc (2 × 200 mL). The organic layers were dried with Na_2SO_4, filtered, concentrated in vacuum and crude product was then purified by column chromatography eluted with EtOAc.

*3-Pyrrolin-2-one (**9**)*

(0.681 g, 35%) as a brownish oil. R_f 0.10 (EtOAc). IR (film) ν_{max} / cm^{-1}: 3286, 2920, 1681, 1448, 1370, 1244, 1054, 807, 691. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.00 (bs, 1H), 7.18 (m, 1H), 6.17 (m, 1H), 4.08 (m, 2H). ^{13}C NMR (50 MHz, CD_3OD): δ 177.17 (C=O), 148.93 (CH), 127.55 (CH), 50.33 (CH_2). *m/z* (%): 83 (M^+, 72%), 55 (100). Literature:[14,15] IR (film) ν_{max} / cm^{-1}: 3250, 1680. ^{1}H NMR (100 MHz, acetone-d6): δ 8.00 (bs, 1H), 7.30 (m, 1H), 6.10 (m, 1H), 4.07 (m, 2H). ^{13}C NMR: δ 175.5 (C=O), 147.6 (CH), 127.6 (CH), 49.5 (CH_2).

*4-Pyrrolin-2-one (**10**)*

(0.097 g, 5%) as a brownish oil. R_f 0.25 (EtOAc). IR (film) ν_{max} / cm^{-1}: 3352, 3098, 2927, 1694, 1448, 1352, 1276, 1241, 1196, 1129, 1021, 806, 736. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.39 (bs, 1H), 6.45 (m, 1H), 5.26 (m, 1H), 3.02 (m, 2H). Literature:[14] ^{1}H NMR (100 MHz, acetone-d6): δ 8.00 (bs, 1H), 6.59 (m, 1H), 5.19 (m, 1H), 2.91 (m, 2H).

*N-(tert-butoxycarbonyl)-3-pyrrolin-2-one (**4**)*

To a solution of 3-pyrrolin-2-one (**9**) (4.698 g, 56.541 mmol) in THF (70 mL), under magnetic stirring and room temperature, it was added DMAP (0.345 g, 2.827 mmol) dissolved in THF (10 mL) and then $(Boc)_2O$ (13.574 g, 62.195 mmol). After 10 minutes, the mixture was concentrated in vacuum, diluted with EtOAc (100 mL) and then washed with saturated solution of NH_4Cl (1 × 100 mL) and H_2O (1 × 100 mL). The organic layer was separated and the aqueous phases were extracted with EtOAc (2 × 100 mL). The combined organic layers were dried with Na_2SO_4, filtered, concentrated in vacuum and crude product was then purified by column chromatography eluted with 30% EtOAc/hexane and crescent gradient of EtOAc (50 and 100%). (4.187 g, 40%) as a brown oil. R_f 0.29 (50% EtOAc/hexane). IR (film) ν_{max} / cm^{-1}: 3097, 2979, 1768, 1691, 1455, 1360, 1301, 1256, 1163, 1102, 1050, 971, 844, 817, 782, 701. ^{1}H NMR (200 MHz , $CDCl_3$): δ 7.18 (dt, *J* 2.1 and 6.1 Hz, 1H), 6.16 (dt, *J* 2.0 and 6.1 Hz, 1H), 4.35 (t, *J* 2.0 Hz, 2H), 1.56 (s, 9H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 168.89 (C=O), 149.22 (C=O), 145.02 (CH), 127.53 (CH), 82.61 (C), 51.39 (CH_2), 27.79 (3 CH_3). *m/z* (%): 183 (M^+, 1%), 128 (65), 110 (48), 84 (20), 56 (100), 44 (68).

*N-(tert-butoxycarbonyl)-4-nitromethylene-2-pyrrolidinone (**11**)*

To a mixture of $MeNO_2$ (0.44 mL, 8.185 mmol), DBU (0.24 mL, 1.637 mmol) and MeCN (2.0 mL), under magnetic stirring and room temperature, it was added N-(*tert*-butoxycarbonyl)-3-pyrrolin-2-one (**4**) (0.300 g, 1.637 mmol) dissolved in MeCN (3.5 mL). After 1 h, the mixture was diluted with EtOAc (50 mL) and washed with saturated solution of NH_4Cl (1 × 30 mL). The organic layer was separated and the aqueous phase was extracted with EtOAc (2 × 50 mL). The combined organic layers were dried with Na_2SO_4, filtered, concentrated in vacuum and crude product was then purified by column chromatography eluted with 50% EtOAc/hexane. (0.160 g, 40%) as a yellowish crystalline residue. R_f 0.47 (60% EtOAc/hexane). IR (KBr) ν_{max} / cm^{-1}: 2983, 1779, 1552, 1373, 1311, 1258, 1156, 1023, 946, 778, 749, 643. ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.48 (d,

J 7.4 Hz, 2H), 4.03 (dd, *J* 7.8 and 11.4 Hz, 1H), 3.55 (dd, *J* 6.4 and 11.4 Hz, 1H), 3.13 (m, 1H), 2.80 (dd, *J* 8.7 and 17.5 Hz, 1H), 2.36 (dd, *J* 7.6 and 17.5 Hz, 1H), 1.53 (s, 9H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 171.13 (C=O), 149.14 (C=O), 83.20 (C), 76.71 (CH_2), 48.80 (CH_2), 35.82 (CH_2), 28.49 (CH), 27.63 (3 CH_3).

Supplementary Information

NMR spectra for the compounds **4**, **8a**-**b** and **9**-**11** are available free of charge as PDF file at http://jbcs.sbq.org.br.

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Preliminary Studies towards the Preparation of Reactive 3-Pyrrolin-2-ones in Conjugate Addition Reactions for the Syntheses of Potentially Bioactive 2-Pyrrolidinones and Pyrrolidines

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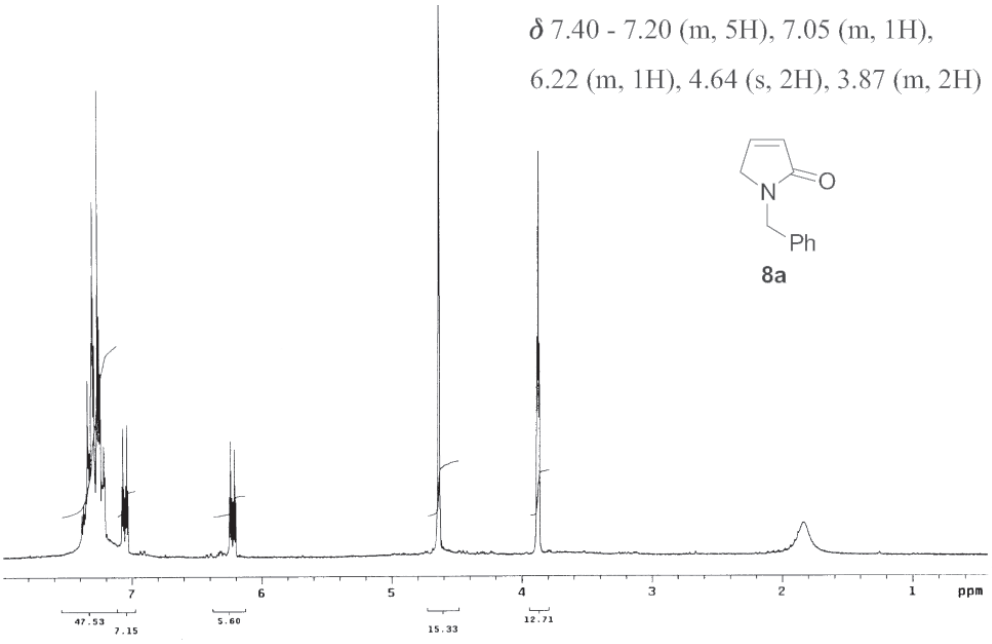

Figure S1. ^{1}H NMR spectrum of compound **8a** (200 MHz, $CDCl_3$).

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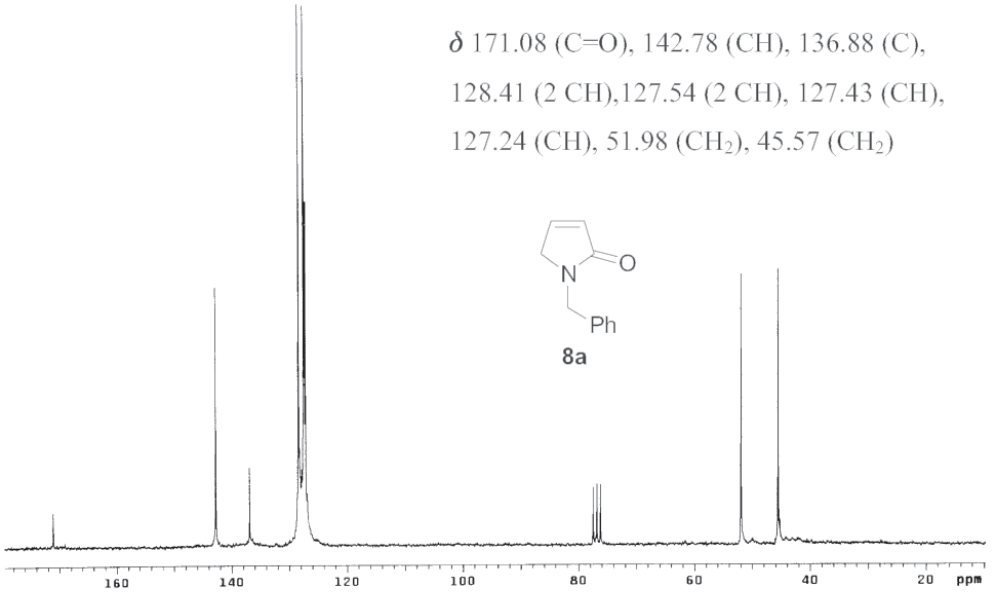

Figure S2. ^{13}C NMR spectrum of compound **8a** (50 MHz, $CDCl_3$).

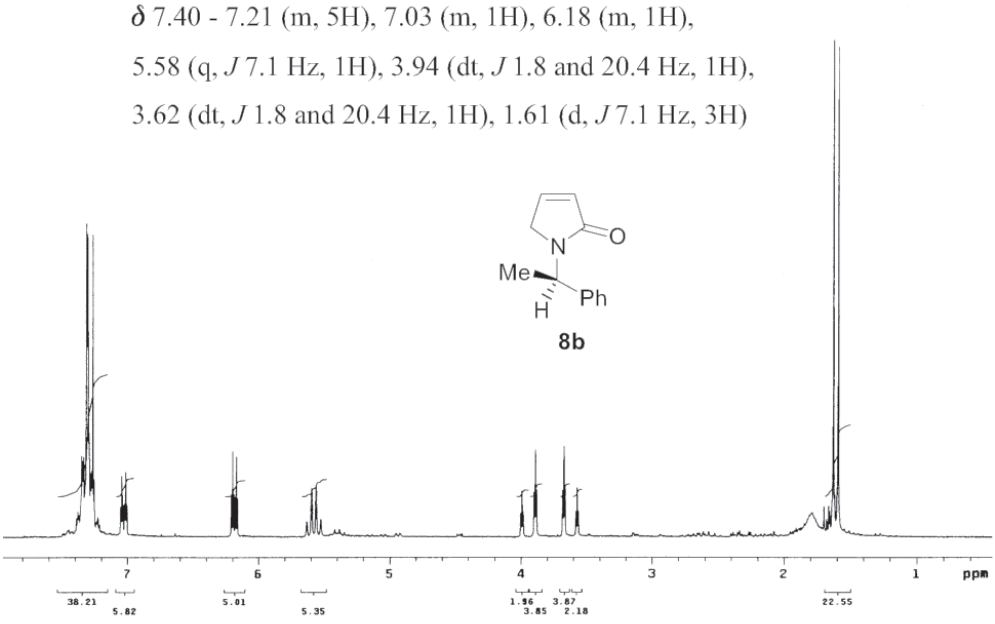

Figure S3. ^{1}H NMR spectrum of compound **8b** (200 MHz, $CDCl_3$).

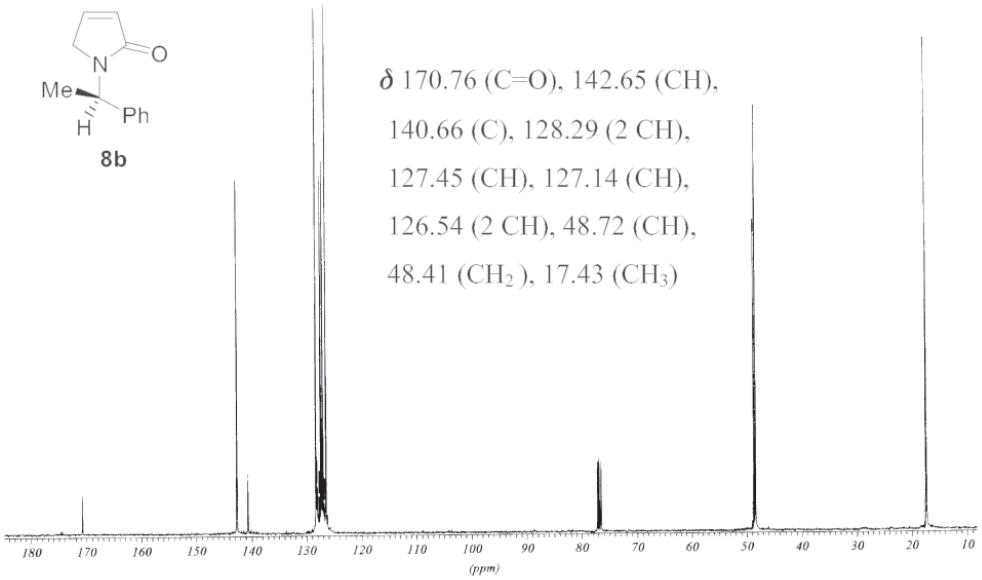

Figure S4. ^{13}C NMR spectrum of compound **8b** (100 MHz, $CDCl_3$).

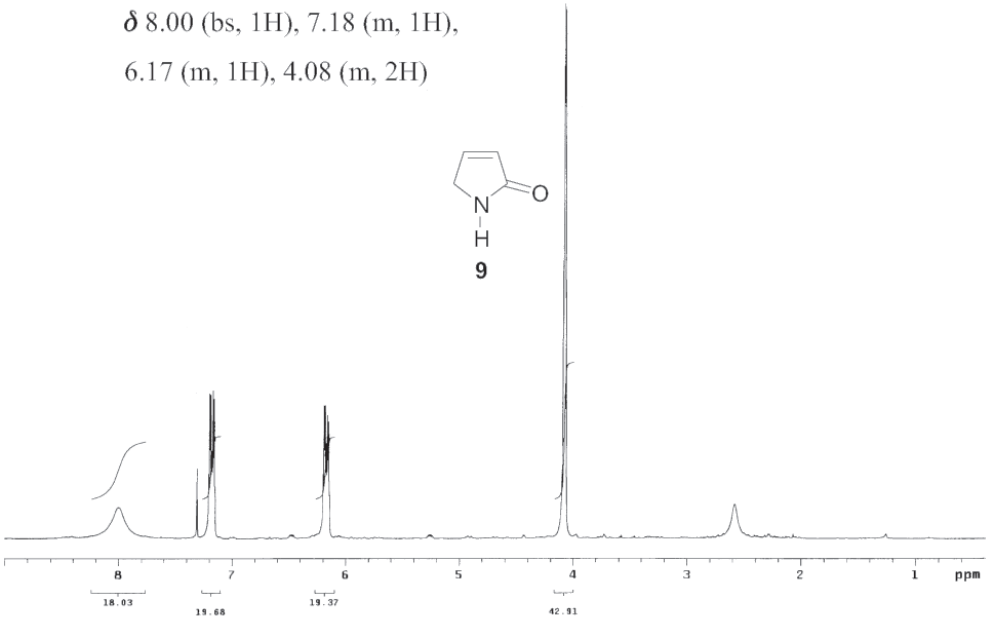

Figure S5. ^{1}H NMR spectrum of compound **9** (200 MHz, $CDCl_3$).

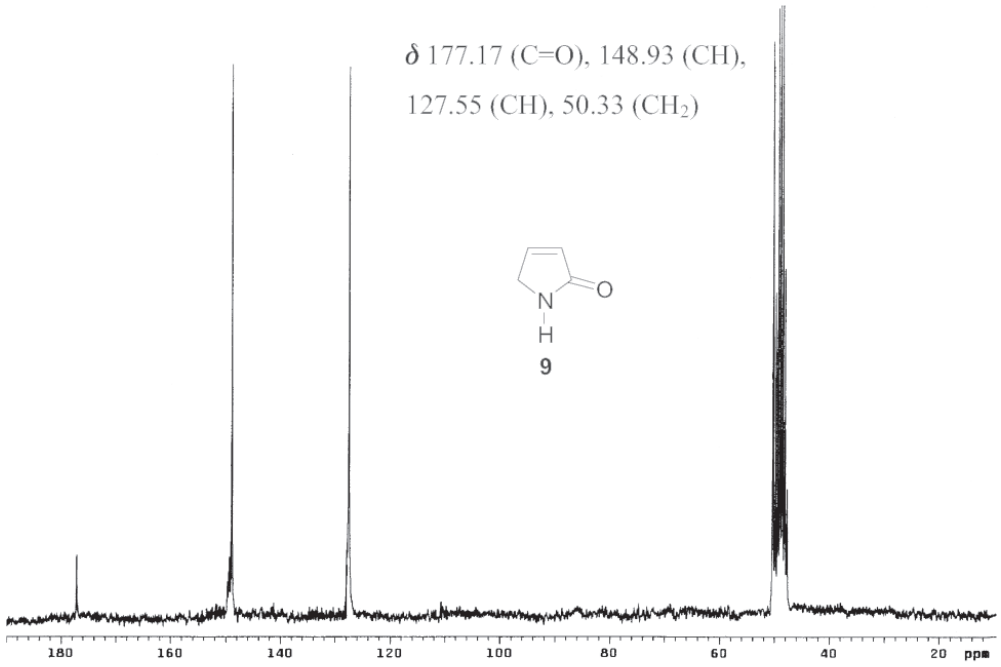

Figure S6. ^{13}C NMR spectrum of compound **9** (50 MHz, CD_3OD).

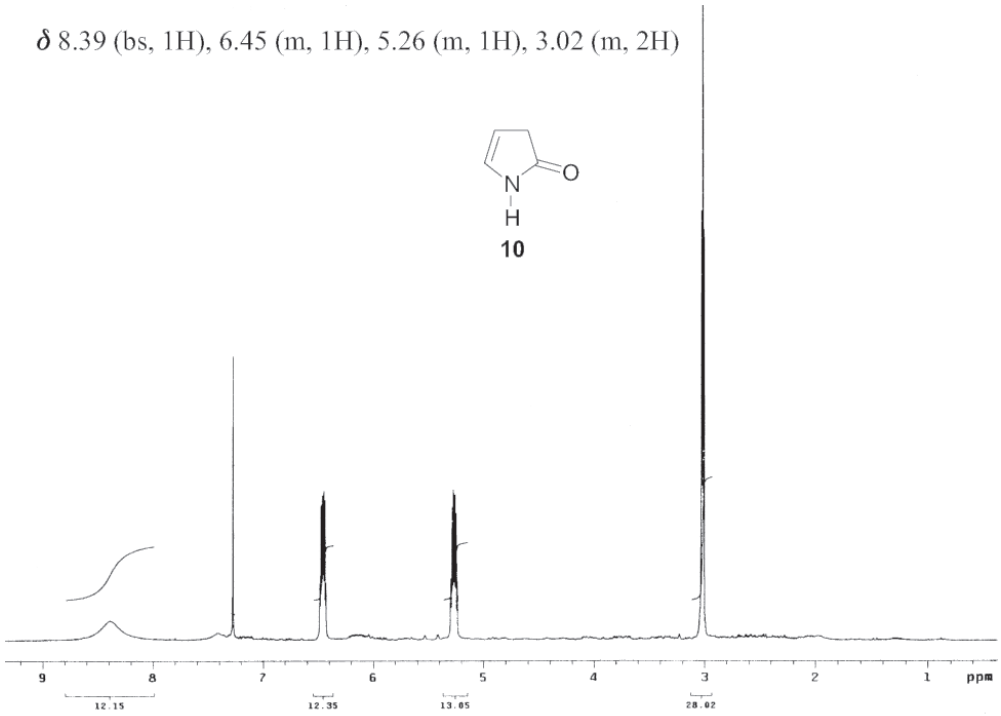

Figure S7. ^{1}H NMR spectrum of compound **10** (200 MHz, $CDCl_3$).

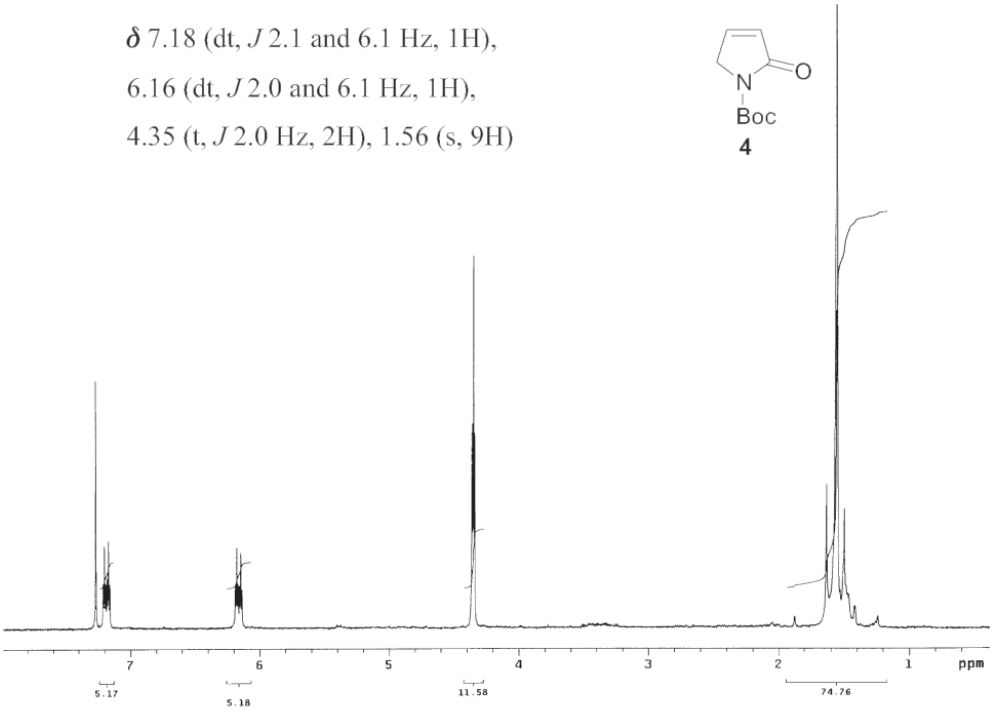

Figure S8. ^{1}H NMR spectrum of compound **4** (200 MHz, $CDCl_3$).

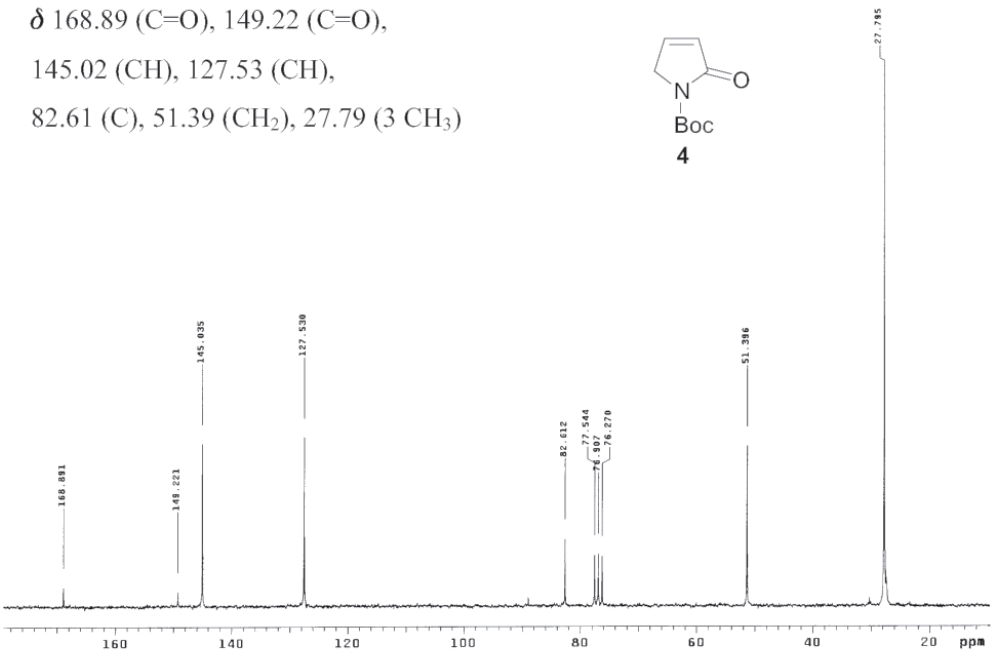

Figure S9. ^{13}C NMR spectrum of compound **4** (50 MHz, $CDCl_3$).

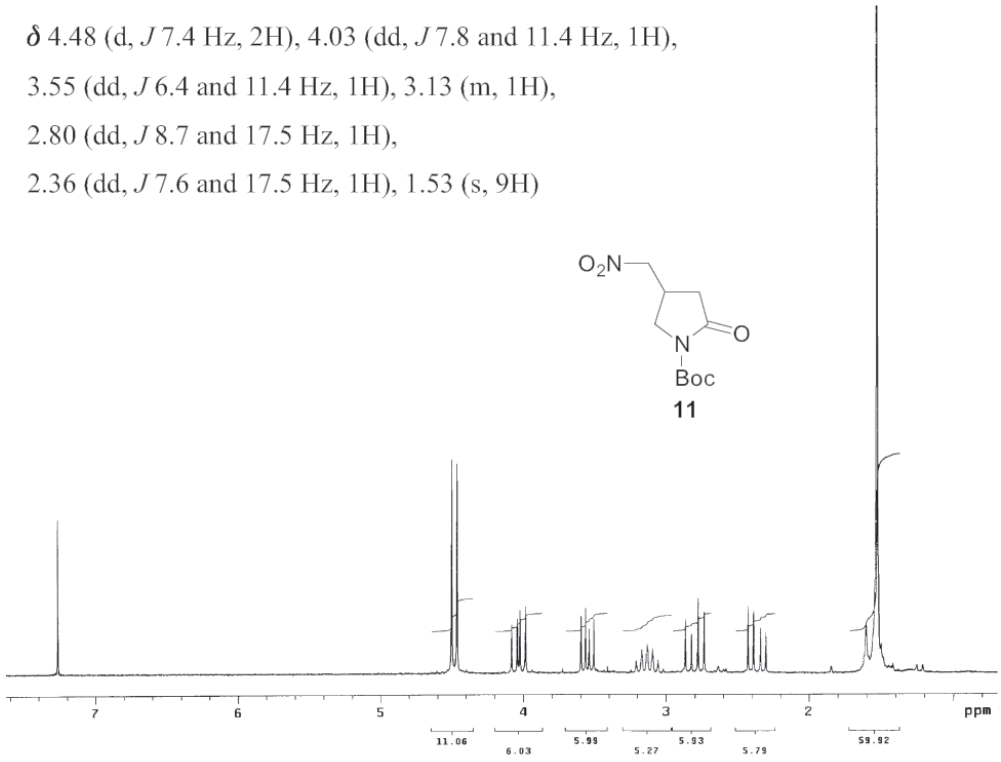

Figure S10. ^{1}H NMR spectrum of compound **11** (200 MHz, $CDCl_3$).

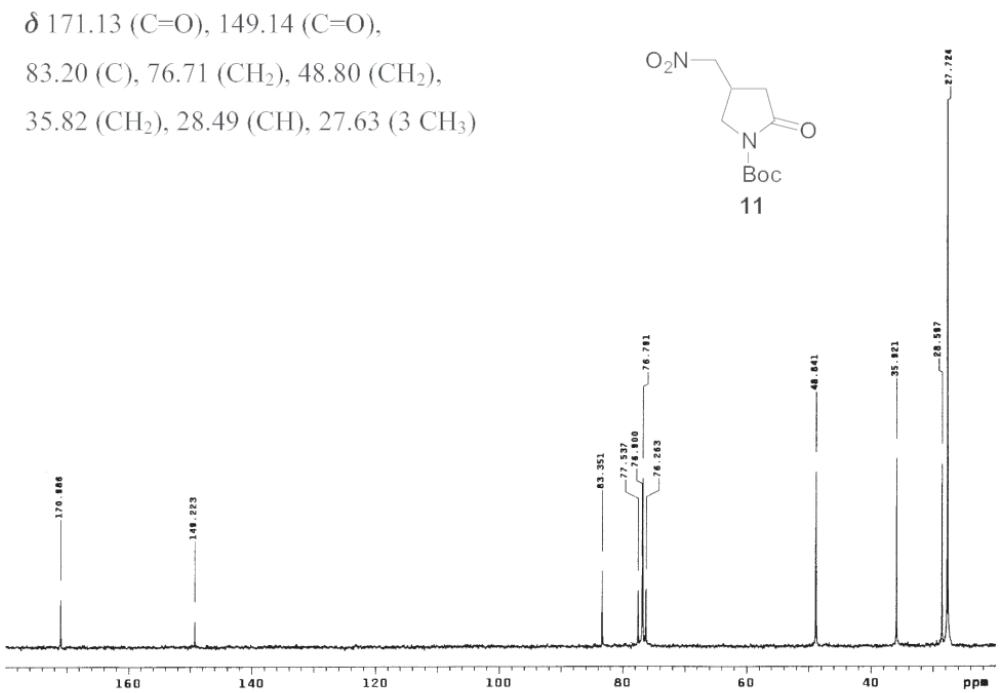

Figure S11. ^{13}C NMR spectrum of compound **11** (50 MHz, $CDCl_3$).