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Research Article

2-Pyrrolidinones and 3-Pyrrolin-2-ones: A Study on the Chemical Reactivity of These Structural Moieties

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The chemical reactivity of 2-pyrrolidinones and 3-pyrrolin-2-ones was evaluated in reactions of addition, nucleophilic substitution, elimination, and reduction as well as the protection of the lactamic nitrogen.

1. Introduction

In connection with our studies on the syntheses of potentially bioactive 2-pyrrolidinones and 3-pyrrolin-2-ones [1], we describe in this paper the results of the performed study on the chemical reactivity of these structural moieties in reactions of addition, nucleophilic substitution, elimination, and reduction as well as the protection of the lactamic nitrogen.

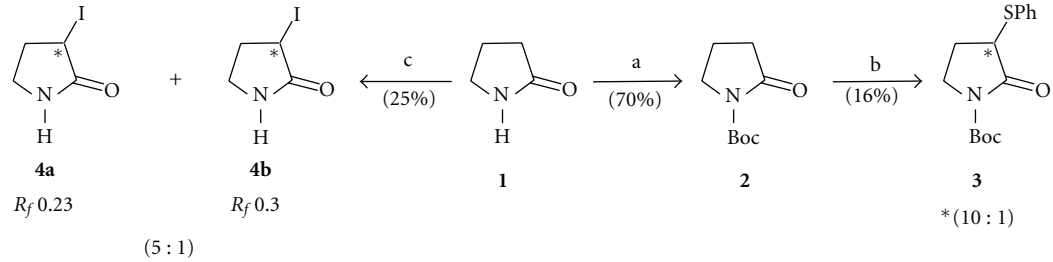
2. Results and Discussion

2.1. Reactions of Enolates Derived from 2-pyrrolidinone and N-tert-butoxycarbonyl-2-pyrrolidinone with Iodine and Diphenyl Disulfide. For execution of the reactions described in Scheme 1, we used as starting material the commercial reagent 2-pyrrolidinone(**1**), and for protection of the lactamic nitrogen of **1**, we planned to use the electron withdrawing group *tert*-butoxycarbonyl (Boc). This choice was due to the facility to be removed and also because this group increases the acidity of the hydrogens *alpha* to the carbamate group [2]. This enhancement of reactivity of the *alpha* hydrogens, in basic conditions, would be useful in posterior reactions. Thus, the treatment of **1** with a suspension of NaH in THF followed by reaction with $(Boc)_2O$ [3] generated a compound characterized by ^{1}H NMR as the pyrrolidinone **2**. The substance **2** was partially converted to a product identified by ^{1}H NMR as the thiophenoxylactam **3**, as result of *alpha* deprotonation of the carbamate of **2** with LDA solution [4], followed by nucleophilic substitution of the generated lithium enolate with diphenyl disulfide [5]. At the ^{1}H NMR spectrum of **3**, signals were detected relative to two isomers in the proportion (10 : 1) measured by integrals relative to methyls of the groups *tert*-butoxycarbonyl at δ 1.52 (major isomer) and δ 1.43 (minor isomer).

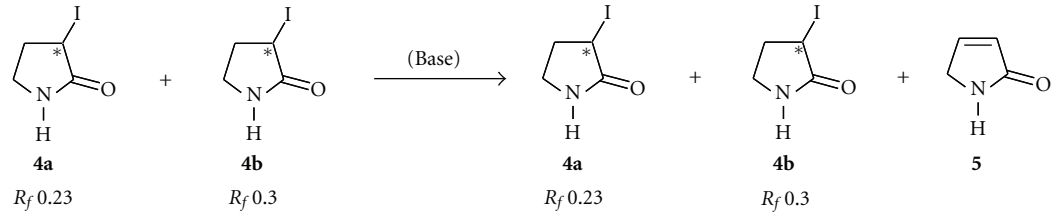
The isomers **4a**-**b**, characterized by ^{1}H NMR (Table 2), were obtained by addition reaction of iodine to silyl enol ether [6] derived from 2-pyrrolidinone(**1**) (Scheme 1). The moderate yield of this reaction (25%), in relation to high yields described for iodination of silyl enol ethers derived from ϵ-caprolactams [7] and δ-valerolactams [6], was attributed to the high tension of the γ-lactamic ring of **1** turning it more reactive and, therefore, susceptible to the formation of byproducts.

2.2. Elimination Reactions of Hydrogen Iodide on 3-iodine-2-pyrrolidinone. The study of elimination of hydrogen iodide on 3-iodine-2-pyrrolidinone was based on a method of dehydrohalogenation reported in the literature [8]. The results from that study, performed with the pyrrolidinones **4a**-**b**, are described in Scheme 2 and Table 1.

After the respective times of reaction described in Table 1, crude products were isolated, filtered over column chromatography of silica gel, and then analysed by ^{1}H NMR. The signals of hydrogens relative to elimination product **5** were not observed at the spectrum of experiment 1. However,



Scheme 1: Reagents and conditions: (a) (i) NaH (1.2 equiv), THF (r.t., 15 min), (ii) $(Boc)_2O$ (1.2 equiv, r.t., 40 min); (b) (i) LDA (1.4 equiv, −78°C, 30 min), (ii) $(PhS)_2$ (1.4 equiv), THF [−78°C (15 min), r.t. (2 h)]; (c) (i) Et_3N (5.0 equiv), TMSCl (3.0 equiv), CH_2Cl_2 (−15°C, 10 min), (ii) I_2 (2.0 equiv, 0°C, 2 h).



Scheme 2: Reagents: Experiment 1: **4** (1.0 equiv), LiCl (5.0 equiv); Experiment 2-3: **4** (1.0 equiv), Et_3N (5.0 equiv).

we verified a larger proportion of the thermodynamic isomer **4b** in relation to the kinetic isomer **4a** previously obtained at low temperature in the experiment described in Scheme 1. In experiments 2 and 3 where there was substitution of LiCl for a stronger base (Et_3N), we observed, in their ^1H NMR spectra, signals relative to olefinic hydrogens C3-H and C4-H of the substance **5** at δ 6.1 and 7.1 ppm, respectively. At the spectrum of product from experiment 3, where the reaction was accomplished with heating, we verified the absence of signal relative to hydrogen C3-H of the isomer **4a** indicating total isomerization of **4a** to **4b**.

2.3. Reactions of Reduction of the Carbamate and Aldol Addition on N-tert-butoxycarbonyl-2-pyrrolidinone. We used as starting material in these reactions the pyrrolidinone **2**, previously obtained in the conditions described in Scheme 1, and the reaction conditions for execution of this study were based on procedures reported in the literature (Scheme 3). Thus, $NaBH_4$ in methanol was used for reduction of the carbamate at lactamic ring of the pyrrolidinone **2** [9]. The product from this reaction was characterized by ^1H NMR as the hemiaminal **6**. The mixture of isomers **7**, characterized by ^1H NMR, was obtained by aldol addition of enolate derived from the pyrrolidinone **2** to benzaldehyde [10].

2.4. Evaluation of the Reactivity of N-benzyl-3-pyrrolin-2-one in Reactions of Reduction and Additions of Carbanion and Benzylamine. For execution of the reactions described in Scheme 4, we used as substrate *N*-benzyl-3-pyrrolin-2-one(**8**), which was previously obtained [1]. Thus, the treatment of **8** with TMSCl followed by reaction with the Grignard reagent PhMgBr and $CuBr{\cdot}SMe_2$ [11–13] generated a product identified by ^1H NMR, IR, and LRMS as the hemiaminal **9**. The compound **10**, identified by ^1H NMR, was obtained by hydrogenation of **8** with hydrogen and the Pearlman catalyst $Pd(OH)_2/C$ [14]. The reaction of **8** with *S*-*α*-methylbenzylamine generated a complex mixture of substances. After a detailed analysis of ^1H NMR, ^{13}C NMR, $^1Hx^1H$-Cosy, HETCOR, IR and GC/MS spectra, we propose the structure of the probable isomers **11–13** as products of that reaction, resulting from the speculative mechanism depicted in Scheme 5. The proposition of the substances **11–13** as the probable products from that reaction was reinforced at the GC/MS spectra by the peaks at m/z 281 (T_R 2.1, 7.4 and 8.4 min), attributed to the protonated $[M + H]^+$ ions of that mixture of isomers.

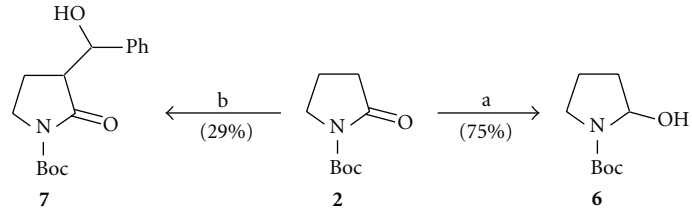
The reactions described in Scheme 4 clearly show the low reactivity of lactam **8** in conjugate addition reactions of carbanion (condition **a**) and amine (condition **c**). In condition **a** the addition of TMSCl, to the reaction medium, generally used to activate the C-4 position to the nucleophilic attack of carbanion, was not able to do this; the substrate **8** was reduced *in situ* yielding compound **9**. In condition **c** lactam **8** was totally inert to the conjugate addition reaction of amine, furnishing probable products of opening of the lactamic ring. There was evidence of condition **b**, the better reactivity of double bond C3-C4 in relation to benzyl group attached to lactamic nitrogen in hydrogenation reaction, using a specific catalyst for hydrogenolysis of benzyl group (the Pearlman catalyst).

2.5. Reinvestigation of the Byproduct Obtained in the Protection Reaction of the Lactamic Nitrogen on 3-pyrrolin-2-one. In previous publication [1] we described the protection of the lactamic nitrogen on 3-pyrrolin-2-one(**5**) with $(Boc)_2O$ in a multigram scale (4.7 g of **5**) and 40% yield. In this paper we describe the results of this reaction performed in milligram scale (0.65 g of **5**) (Scheme 6). We obtained

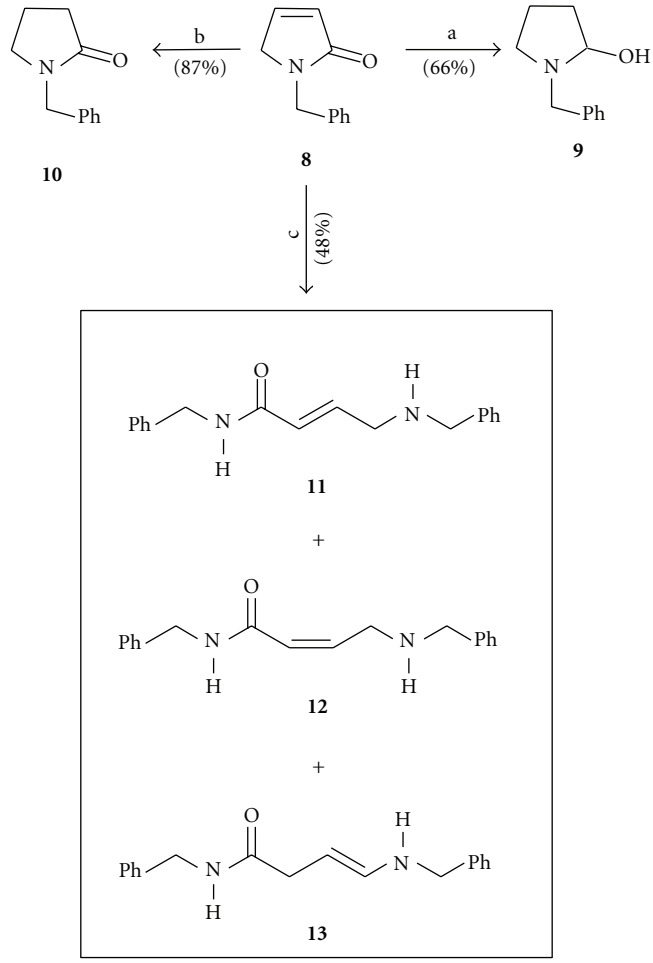
Table 1: Evaluation of the elimination reactions performed with lactam **4**.

Experiment	Substrate (proportion)	Base	Solvent	Temperature (°C)	Time (h)	Products (proportion)[a]	(%)[b]
1	**4a** + **4b** (5 : 1)	LiCl	DMF	100	5	**4a** + **4b** (1 : 10)	40
2	**4a** + **4b** (5 : 1)	Et_3N	CH_3CN	25	72	**4a** + **4b** + **5** (1 : 5 : 1)	41
3	**4a** + **4b** (5 : 1)	Et_3N	CH_3CN	85	3	**4b** + **5** (2 : 1)	40

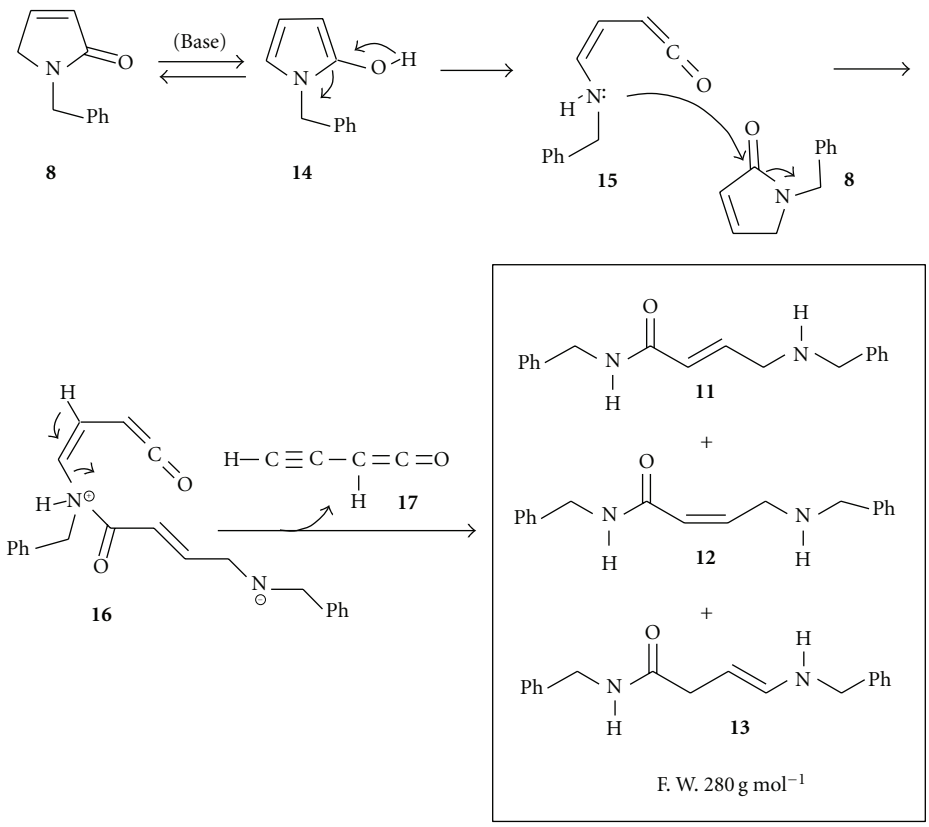
[a]The proportion of products was measured by integrals relative to the signals of hydrogen C3-H (^{1}H NMR). [b]After filtration over column of silica gel.



Scheme 3: Reagents and conditions: (a) $NaBH_4$ (1.1 equiv), MeOH (r.t., 5 h); (b) (i) LDA (1.1 equiv), THF (−78°C, 30 min), (ii) PhCHO [1.1 equiv, −78°C (2.5 h), r.t. (1 h)].



Scheme 4: Reagents and conditions: (a) (i) TMSCl (2.0 equiv), r.t. (10 min), (ii) PhMgBr (1.5 equiv), $CuBr \cdot SMe_2$ (0.2 equiv), THF (−78°C, 3 h); (b) H_2 (balloon), 20% $Pd(OH)_2/C$ (0.1 equiv), MeOH (r.t., 12 h); (c) *S*-*α*-methylbenzylamine (6.5 equiv), r.t. (72 h).



Base = S-α-methylbenzylamine

Scheme 5: Speculative mechanism for reaction of lactam **8** with *S*-α-methylbenzylamine.

compound **18** as the major product, previously described [1], after purification over column chromatography of silica gel. An apolar fraction was also isolated and identified by ^{1}H NMR and ^{13}C NMR as the byproduct **19** (10 : 1) and 61% of general yield. The increase of yield observed in this reaction, accomplished in milligram scale, was attributed to the better homogeneity of the reagents that usually occurs in these conditions. We propose that compound **19** was obtained as result of *in situ* acylation of the enol form derived from lactam **18** with $(Boc)_2O$. That kind of equilibrium between 3-pyrrolin-2-ones and their enol forms, in basic medium, was previously described [15].

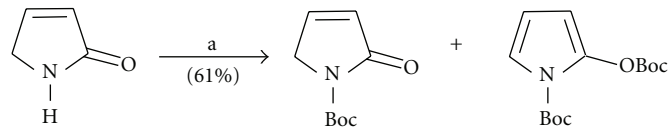
2.6. Conjugate Addition Reactions of Some Nucleophiles to N-tert-butoxycarbonyl-3-pyrrolin-2-one. As we have described in previous publication [1], the conjugate addition reaction of nitromethane to α,β-unsaturated system of *N-tert*-butoxycarbonyl-3-pyrrolin-2-one(**18**) proceeded in smooth conditions. We planned to use compound **18** as substrate for accomplishment of that conjugate addition reaction with other nucleophiles, based on previous experiments reported in the literature. Thus, the addition of amines [15] and malonate anion [16] to α,β-unsaturated system of **18** was evaluated. The results from these addition reactions are displayed in Table 3 with the respective products analysed by NMR.

Table 2: ^{1}H NMR data of the isomers **4a** and **4b**.

Hydrogens	**4a** δ (Multiplicity, *J*/Hz)	**4b** δ (Multiplicity, *J*/Hz)
N-H	6.55 (bs)	6.90 (bs)
C3-H	4.46 (dd, 2.4 and 7.3)	4.32 (dd, 4.9 and 7.5)
C4-H	2.76–2.50 (m)	2.78–2.50 (m)
	2.42–2.24 (m)	2.42–2.24 (m)
C5-H	3.50–3.24 (m)	3.65–3.48 (m)
		3.48–3.25 (m)

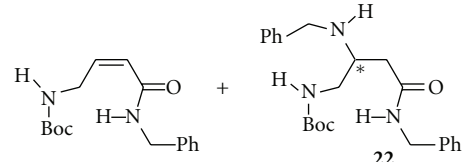
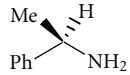
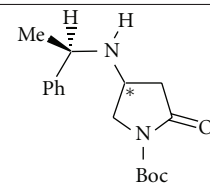
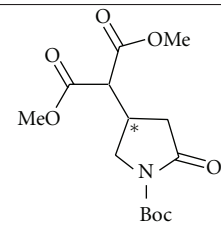
The mixture of compounds obtained in experiment 1 suggests that addition of benzylamine was initially performed on the carbamate at the lactamic ring of **18** to yield a product of opening of the γ-lactam, amide **21**. This compound underwent subsequent *in situ* reaction of conjugate addition with benzylamine to furnish amide **22**. In experiment 2 the reaction was accomplished without H_2O, and a mixture of isomers **24** was obtained. The product from experiment 3 was identified by ^{1}H NMR and ^{13}C NMR as a mixture of isomers **26**.

2.7. Protection of the Lactamic Nitrogen on 4-phenyl-2-pyrrolidinone. The protection of the lactamic nitrogen on



Scheme 6: Reagents and conditions: (a) DMAP (0.05 equiv), $(Boc)_2O$ (1.1 equiv), THF (r.t., 10 min).

Table 3: Reactions of lactam **18** with some nucleophiles.

Experiment[a]	Substrate	Nucleophile	Time (h)	Products (proportion)	(%)[b]
1	 **18**	$PhCH_2NH_2$ **20**	1	 **21**[c] (2 : 3) **22** *(3 : 1)	25
2	**18**	 **23**	120	 **24** *(1 : 1)	33
3	**18**	$CH_2(CO_2Me)_2$ **25**	1.5	 **26** *(7 : 1)	28

Reagents: Experiment 1: $PhCH_2NH_2$ (1.7 equiv), H_2O (5.0 equiv); Experiment 2: *R*-α-methylbenzylamine (1.2 equiv), THF; Experiment 3: $CH_2(CO_2Me)_2$ (1.1 equiv), MeONa (0.4 equiv), MeOH. [a]The experiments were performed at room temperature. [b]After purification over column chromatography of silica gel. [c]Four isomers were detected at the ^{1}H NMR spectrum in the proportion (2 : 1 : 10 : 2), measured by integrals relative to signals of hydrogens of the groups *tert*-butoxycarbonyl [δ 1.52 (minor), δ 1.51 (minor), δ 1.47 (major), δ 1.43 (minor)]. *The proportions of the mixtures of isomers were measured at the ^{1}H NMR spectra by integrals relative to signals of hydrogens of the groups *tert*-butoxycarbonyl: Experiment 1 [δ 1.52 (minor), δ 1.43 (major)]; Experiment 2 [δ 1.52, δ 1.48]; Experiment 3 [δ 1.52 (major), δ 1.45 (minor)].

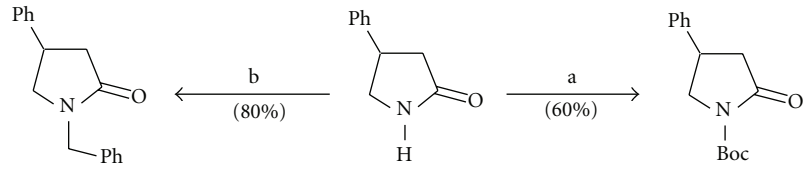
4-phenyl-2-pyrrolidinone(**27**), previously obtained [17], was performed in the conditions described in Scheme 7. In conditions **a** we used as deprotonating agent the base NaH, and the generated amide ion was acylated with $(Boc)_2O$ [3]. In conditions **b** we used the base KH with catalytic amount of the crown ether 18-crown-6 [18] and with benzyl bromide as alkylating agent. Products **28** and **29** were identified by ^{1}H NMR, ^{13}C NMR, IR, and LRMS.

3. Conclusions

In summary, the chemical reactivity of 2-pyrrolidinones and 3-pyrrolin-2-ones was evaluated in different reaction conditions. The reactions presented in this paper led to the preparation of functionalized γ-lactams, and, therefore, they can be useful for future studies with these classes of substances.

4. Experimental

Infrared spectra were recorded on a Perkin Elmer-1600 model 1605 spectrophotometer (KBr). NMR spectra were recorded on a Varian Gemini-200 (^{1}H: 200 MHz and ^{13}C: 50.3 MHz) spectrometer, using $CDCl_3$ as the solvent and TMS as internal standard. Coupling constants (*J*) are reported in Hertz (Hz), and multiplicities are indicated as singlet (s), broad singlet (bs), doublet (d), broad doublet (bd), double doublet (dd), triplet (t), and multiplet (m).



29 **27** **28**

Scheme 7: Reagents and conditions: (a) (i) NaH (1.2 equiv), THF (r.t., 10 min), (ii) $(Boc)_2O$ (1.4 equiv, r.t., 20 min); (b) (i) KH (1.5 equiv), 18-crown-6 (0.5 equiv), THF (r.t., 5 min), (ii) Bn-Br (1.2 equiv, r.t., 10 min).

Low-resolution mass spectra (LRMS) were obtained by electron impact (70 eV) on a Varian GC-MS Saturn 2000 spectrometer. 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. The purifications by column chromatography were performed on silica gel (230–400 mesh). The solvents and reagents were dried and purified by usual procedures [19].

*4.1. 2-Pyrrolidinone(**1**).* It is used as starting material to obtain some compounds. R_f 0.18 (EtOAc). ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.61 (bs, 1H), 3.40 (m, 2H), 2.36–2.22 (m, 2H), 2.22–2.03 (m, 2H).

*4.2. N-(tert-butoxycarbonyl)-2-pyrrolidinone(**2**).* 2-Pyrrolidinone(**1**) (2.000 g, 23.500 mmol) was added to a stirred suspension of NaH (0.677 g, 28.200 mmol) in THF (47 mL), at room temperature and nitrogen atmosphere. After 15 minutes, $(Boc)_2O$ (6.154 g, 28.200 mmol) was added and the mixture was stirred at room temperature and nitrogen atmosphere for 40 minutes. Saturated solution of NH_4Cl (60 mL) was added and then extracted with EtOAc (2 × 200 mL). The organic extracts were dried with Na_2SO_4, filtered, and concentrated in vacuum. The crude product was purified over column chromatography of silica gel eluted with 30% EtOAc/hexane and crescent gradient of EtOAc (50 and 100%). A colourless oil was obtained (3.043 g, 70%), characterized as the pyrrolidinone **2**. R_f 0.33 (50% EtOAc/hexane). ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.75 (m, 2H), 2.51 (m, 2H), 2.00 (m, 2H), 1.53 (s, 9H).

*4.3. N-(tert-butoxycarbonyl)-3-thiophenoxy-2-pyrrolidinone (**3**).* *n*-BuLi 1.85 mol L^{-1} (3.0 mL, 5.520 mmol) was added dropwise to a stirred solution of diisopropylamine (0.55 mL, 3.940 mmol) in THF (26 mL) at 0°C and stirred for 20 minutes under nitrogen atmosphere. The stirred solution was put on a bath at −78°C, and the pyrrolidinone **2** (0.552 g, 2.820 mmol) in THF (2.8 mL) was added. After 30 minutes $(PhS)_2$ (0.860 g, 3.94 mmol) in THF (39 mL) was added and left under magnetic stirring, −78°C and nitrogen atmosphere for 15 minutes, and then at room temperature for 2 h. The mixture was concentrated in vacuum, diluted with EtOAc (50 mL), and then washed with saturated solution of NH_4Cl (1 × 50 mL) and H_2O (1 × 50 mL). The organic layer was separated, and the aqueous phases were extracted with EtOAc (2 × 50 mL). The organic extracts were dried with Na_2SO_4, filtered, and concentrated in vacuum. The crude product was purified over column chromatography of silica gel eluted with 20% EtOAc/hexane. Pyrrolidinone **3** (0.070 g, 16%) was obtained as a colourless oil, and substrate **2** (0.247 g, 47%) was recovered without reacting. *Pyrrolidinone **3***: R_f 0.61 (50% EtOAc/hexane). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.60–7.45 (m, 2H), 7.40–7.30 (m, 3H), 3.90–3.80 (m, 1H), 3.70–3.45 (m, 2H), 2.55–2.25 (m, 1H), 2.15–1.90 (m, 1H), 1.52 (s, 9H). *Minor isomer*: δ 1.43 (s, 9H).

*4.4. 3-iodine-2-pyrrolidinone(**4a**): Kinetic Product.* To a solution of 2-pyrrolidinone(**1**) (0.569 g, 6.686 mmol) in CH_2Cl_2 (15 mL) at −15°C and magnetic stirring, Et_3N (4.7 mL, 33.430 mmol) and then TMSCl (2.5 mL, 20.058 mmol) were added. After 10 minutes, I_2 (3.394 g, 13.372 mmol) in CH_2Cl_2 (20 mL) was added, and the mixture was transferred to a bath at 0°C. After 2 h, the mixture was washed with aqueous solution of 10% Na_2SO_3 (2 × 100 mL) and then saturated solution of NaCl (1 × 100 mL). The organic layer was separated, and the aqueous phases were extracted with CH_2Cl_2 (3 × 100 mL). The organic extracts were dried with Na_2SO_4, filtered, and concentrated in vacuum. The crude product was purified over column chromatography of silica gel eluted with EtOAc. A yellowish crystalline residue was obtained (0.352 g, 25%) characterized as 3-iodine-2-pyrrolidinone (**4a** + **4b**/5 : 1). *Major product (**4a**)*: R_f 0.23 (EtOAc). ^{1}H NMR (200 MHz, $CDCl_3$): Table 2.

*4.5. 3-iodine-2-pyrrolidinone(**4b**): Thermodynamic Product (Experiment 1, Table 1).* A mixture of 3-iodine-2-pyrrolidinone (**4a** + **4b**/5 : 1) (0.060 g, 0.284 mmol), LiCl (0.060 g, 1.415 mmol), and DMF (1.4 mL) was heated at 100°C, under magnetic stirring and nitrogen atmosphere for 5 h. The mixture was concentrated in vacuum, diluted with CH_2Cl_2 (20 mL), and then washed with H_2O (1 × 20 mL). The organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (1 × 30 mL). The organic extracts were dried with Na_2SO_4, filtered, and concentrated in vacuum. The crude product was purified over column chromatography of silica gel eluted with EtOAc. A colourless crystalline residue (0.024 g, 40%) was obtained characterized as 3-iodine-2-pyrrolidinone (**4a** + **4b**/1 : 10). *Major product (**4b**)*: R_f 0.30 (EtOAc). ^{1}H NMR (200 MHz, $CDCl_3$): Table 2.

*4.6. Elimination Reaction Performed with Lactam **4** : (Experiment 2, Table 1).* A mixture of 3-iodine-2-pyrrolidinone (**4a** + **4b**/5 : 1) (0.037 g, 0.175 mmol), Et_3N (0.12 mL, 0.875 mmol), and CH_3CN (0.5 mL) was stirred at 25°C for 72 h. The mixture was concentrated in vacuum, diluted with EtOAc (20 mL), and then washed with saturated solution of NH_4Cl (1 × 30 mL) and H_2O (1 × 30 mL). The organic layer was separated, and the aqueous phases were extracted with EtOAc (1 × 30 mL). The organic extracts were dried with Na_2SO_4, filtered, and concentrated in vacuum. The crude product was purified over column chromatography of silica gel eluted with EtOAc and 10% MeOH/EtOAc. A brownish oil (0.014 g, 41%) was obtained characterized by ^{1}H NMR as a mixture of 3-iodine-2-pyrrolidinone (**4a** + **4b**) and 3-pyrrolin-2-one(**5**), previously described [1], in a respective proportion of (1 : 5 : 1).

*4.7. Elimination Reaction Performed with Lactam **4**: (Experiment 3, Table 1).* A mixture of 3-iodine-2-pyrrolidinone (**4a** + **4b**/5 : 1) (0.046 g, 0.218 mmol), Et_3N (0.15 mL, 1.09 mmol), and CH_3CN (0.6 mL) under magnetic stirring and nitrogen atmosphere was heated at 85°C for 3 h. The mixture was concentrated in vacuum, diluted with EtOAc (20 mL), and then washed with saturated solution of NH_4Cl (1 × 20 mL) and H_2O (1 × 20 mL). The organic layer was separated, and the aqueous phases were extracted with EtOAc (1 × 30 mL). The organic extracts were dried with Na_2SO_4, filtered, and concentrated in vacuum. The crude product was purified over column chromatography of silica gel eluted with 50% EtOAc/hexane and EtOAc. A colourless crystalline residue was obtained (0.012 g, 27%) characterized as 3-iodine-2-pyrrolidinone (**4b**) (R_f 0.30, EtOAc) and a brownish oil (0.003 g, 13%) characterized as 3-pyrrolin-2-one(**5**), previously described [1].

*4.8. N-(tert-butoxycarbonyl)-2-hydroxy-pyrrolidine(**6**).* $NaBH_4$ (0.012 g, 0.317 mmol) was added to a solution of the pyrrolidinone **2** (0.053 g, 0.286 mmol) in MeOH (1.0 mL). The mixture was left under magnetic stirring, room temperature, and nitrogen atmosphere for 5 h. H_2O (30 mL) was added and then extracted with CH_2Cl_2 (2 × 50 mL). The organic extracts were dried with Na_2SO_4, filtered, and concentrated in vacuum. The crude product was purified over column chromatography of silica gel eluted with 50% EtOAc/hexane and EtOAc. A colourless oil (0.040 g, 75%) was obtained characterized as the hemiaminal **6**. R_f 0.22 (60% EtOAc/hexane). ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.66 (bs, 1H), 3.67 (m, 2H), 3.15 (m, 2H), 1.58 (m, 3H), 1.44 (s, 9H).

*4.9. N-(tert-butoxycarbonyl)-3-(α-hydroxy-benzyl)-2-pyrrolidinone(**7**).* *n*-BuLi 1.41 mol L^{-1} (1.15 mL, 1.621 mmol) was added dropwise to a stirred solution of diisopropylamine (0.21 mL, 1.498 mmol) in THF (5.0 mL) at 0°C and stirred for 10 minutes under nitrogen atmosphere. The stirred solution was put in a bath at −78°C, and pyrrolidinone **2** (0.248 g, 1.339 mmol) in THF (6.0 mL) was added. After 30 minutes, benzaldehyde (0.15 mL, 1.475 mmol) was added dropwise, and the mixture was left at −78°C for 2.5 h and then at room temperature for 1 h. Aqueous solution of 10% HCl (v/v) was added until pH 1, and the mixture was transferred to a separatory funnel, diluted with EtOAc (50 mL), and then washed with H_2O (1 × 50 mL). The organic layer was separated, and the aqueous phase was extracted with EtOAc (1 × 50 mL). The organic extracts were dried with Na_2SO_4, filtered, and concentrated in vacuum. The crude product was purified over column chromatography of silica gel eluted with hexane and crescent gradient of EtOAc (70 and 100%). A colourless crystalline residue was obtained (0.114 g, 29%) characterized as a mixture of isomers **7**. R_f 0.27 (EtOAc). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.55–7.28 (m, 5H), 7.23 (bs, 1H, D_2O exchange), 3.57 (t, *J* 6.5 Hz, 2H), 3.28 (m, 1H), 3.22-3.10 (m, 2H), 1.80 (m, 1H), 1.41 (s, 9H). *Minor isomers*: δ 7.25–7.20 (m, 1H, D_2O exchange), 6.80 (bs, 1H, D_2O exchange), 6.60 (bs, 1H, D_2O exchange), 4.83 (bd, *J* 7.5 Hz, 1H), 4.72 (d, *J* 9.6 Hz, 1H), 3.32–3.23 (m, 1H), 2.86 (m, 1H), 2.71 (m, 1H), 1.44 (s, 9H).

*4.10. N-benzyl-2-hydroxy-pyrrolidine(**9**)*

4.10.1. Preparation of the Grignard Reagent. A mixture of magnesium (0.027 g, 1.111 mmol), bromobenzene (0.11 mL, 1.044 mmol), and THF (5.0 mL) was heated at reflux, under magnetic stirring and argon atmosphere for 3 h. It was then allowed to cool at room temperature, and the recently prepared solution of the Grignard reagent was used in the following reaction.

*4.10.2. Reaction of PhMgBr-CuBr·SMe_2 with N-benzyl-3-pirrolin-2-one(**8**), TMSCl/THF.* The recently prepared solution of the Grignard reagent (5.0 mL) was added to a stirred suspension of CuBr·SMe_2 (0.031 g, 0.151 mmol) in THF (0.5 mL) at room temperature and stirred for 10 minutes under argon atmosphere. The stirred mixture was put in a bath at −78°C, and then a solution of lactam **8** (0.116 g, 0.669 mmol) and TMSCl (0.17 mL, 1.339 mmol) in THF (2.0 mL) was added. The mixture was left at −78°C for 3 h and then allowed to reach the room temperature. The mixture was transferred to a separatory funnel, and EtOAc (40 mL) was added and then washed with saturated solution of NH_4Cl (1 × 20 mL). The organic layer was separated, and the aqueous phase was extracted with EtOAc (1 × 40 mL). The organic extracts were dried with Na_2SO_4, filtered, and concentrated in vacuum. The crude product was purified over column chromatography of silica gel eluted with EtOAc. A brownish crystalline residue was obtained characterized as compound **9** (0.078 g, 66%). R_f 0.24 (EtOAc). IR (KBr) ν_{max}/cm^{-1}: 3172, 2927, 1643, 1448, 1331, 1259, 1076, 996, 946, 700. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.38–7.24 (m, 5H), 5.08 (m, 1H), 4.83 (d, *J* 14.7 Hz, 1H), 4.20 (d, *J* 14.7 Hz, 1H), 3.21 (bd, *J* 7.2 Hz, 1H, D_2O exchange), 2.72–2.50 (m, 2H), 2.46–2.16 (m, 3H), 2.06–1.80 (m, 1H). m/z (%): 177 ($M^{+\cdot}$, 1%), 173 (100), 91 (100), 65 (30).

*4.11. N-benzyl-2-pyrrolidinone(**10**).* A mixture of lactam **8** (0.100 g, 0.577 mmol), 20% $Pd(OH)_2$/C (0.041 g, 0.0577 mmol), and MeOH (6.0 mL), inside a round-bottom flask,

was submitted to hydrogen atmosphere (balloon) under magnetic stirring and room temperature for 12 h. The mixture was filtered, concentrated in vacuum, and then purified over column chromatography of silica gel eluted with EtOAc. A brownish oil was obtained characterized as the lactam **10** (0.088 g, 87%). R_f 0.47 (EtOAc). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.39–7.20 (m, 5H), 4.45 (s, 2H), 3.26 (m, 2H), 2.45 (m, 2H), 1.99 (m, 2H).

*4.12. Mixture of the Probable Isomers **11–13**.* A solution of lactam **8** (0.102 g, 0.589 mmol) in *S*-α-methylbenzylamine (0.5 mL, 3.878 mmol) was left under magnetic stirring, room temperature, and nitrogen atmosphere for 72 h. The mixture was transferred to a separatory funnel, diluted with EtOAc (30 mL), and then washed with aqueous 10% HCl (v/v) (1 × 20 mL) and H_2O (1 × 20 mL). The organic layer was separated, and the aqueous phases were extracted with EtOAc (1 × 30 mL). The organic extracts were dried with Na_2SO_4, filtered, and concentrated in vacuum. The crude product was purified over column chromatography of silica gel eluted with hexane and 50% EtOAc/hexane. A colourless oil was obtained characterized as a mixture of the probable isomers **11–13** (0.079 g, 48%). R_f 0.30 (50% EtOAc/hexane). IR (KBr) ν_{max}/cm^{-1}: 3418, 2924, 1743, 1689, 1613, 1496, 1429, 1396, 1339, 1292, 1254, 1188, 1129, 1061, 1014, 930, 871, 823, 696, 626, 522, 458, 433, 408. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.44–7.20 (m), 7.10–7.00 (m), 4.93 (s), 4.63 (s), 3.50 (dd, *J* 1.7 and 3.5 Hz), 3.46 (m), 3.45 (dd, *J* 1.7 and 3.5 Hz), 3.43 (t, *J* 1.7 Hz), 3.26 (t, *J* 1.7 Hz), 3.24 (d, *J* 7.7 Hz), 2.80–2.60 (m). ^{13}C NMR (50 MHz, $CDCl_3$): δ 177.67 (C=O), 173.38 (C=O), 170.56 (C=O), 152.27 (C), 135.97 (C), 135.73 (C), 129.19 (CH), 128.69 (CH), 128.45 (CH), 127.75 (CH), 127.69 (CH), 125.05 (CH), 96.12 (C), 44.36 (CH_2), 41.94 (CH_2), 32.93 (CH_2), 27.45 (CH_2), 25.40 (CH_2). m/z (%) (T_R 2.1 min, GC): 281 (M + 1, 15%), 264 (5), 247 (3), 225 (3), 209 (18), 191 (5), 179 (5), 167 (8), 147 (35), 132 (100), 105 (85), 91 (22), 77 (90), 55 (63). m/z (%) (T_R 7.4 min, GC): 281 (M + 1, 8%), 267 (3), 243 (1), 209 (5), 189 (100), 173 (10), 160 (45), 149 (10), 132 (35), 119 (25), 104 (38), 91 (28), 77 (20), 65 (15), 51 (18). m/z (%) (T_R 8.4 min, GC): 281 (M + 1, 13%), 264 (3), 249 (1), 225 (2), 209 (10), 189 (15), 173 (85), 160 (8), 146 (20), 132 (5), 118 (8), 104 (28), 91 (100), 77 (15), 65 (28), 55 (15), 44 (18).

*4.13. N-(tert-butoxycarbonyl)-3-pyrrolin-2-one(**18**) and N,2-O-[bis(tert-butoxycarbonyl)]-pyrrole(**19**).* This reaction was performed by previously described procedure [1], starting from 3-pyrrolin-2-one(**5**) (0.654 g, 7.876 mmol). After purification of crude product over column chromatography of silica gel eluted with 30% EtOAc/hexane and crescent gradient of EtOAc (50 and 100%), lactam **18** (0.802 g, 55.5%), previously described [1] [R_f 0.29 (50% EtOAc/hexane)], was obtained. A colourless oil was also isolated and characterized as compound **19** (0.124 g, 5.5%). *Compound **19**:* R_f 0.66 (50% EtOAc/hexane). ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.94 (dd, *J* 2.0 and 3.7 Hz, 1H), 6.04 (dd, *J* 3.6 and 3.7 Hz, 1H), 5.84 (dd, *J* 2.0 and 3.6 Hz, 1H), 1.57 (s, 9H), 1.55 (s, 9H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 150.88 (C=O), 147.43 (C=O), 136.88 (C), 116.33 (CH), 107.95 (CH), 100.23 (CH), 84.03 (C), 83.74 (C), 27.68 (3 CH_3), 27.34 (3 CH_3).

*4.14. N-benzyl-4-amino(tert-butoxycarbonyl)-2-butenamide (**21**) and N-benzyl-3-aminobenzyl-4-amino(tert-butoxy-carbonyl)-butanamide(**22**) (Experiment 1, Table 3).* H_2O (0.03 mL, 1.665 mmol) was added to a solution of lactam **18** (0.059 g, 0.322 mmol) in benzylamine (0.06 mL, 0.549 mmol), under magnetic stirring, at room temperature and nitrogen atmosphere. After 1 h the mixture was concentrated in vacuum, diluted with CH_2Cl_2 (1.0 mL), transferred with a pipette to the top of a column chromatography of silica gel, and then eluted with hexane and crescent gradient of EtOAc (10, 50, and 100%). *Butenamide **21*** (0.009 g, 10%) was obtained as a colourless oil. R_f 0.46 (70% EtOAc/hexane). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.54–7.40 (m, 1H), 7.40–7.14 (m, 5H), 6.66 (m, 1H), 6.02 (m, 1H), 4.66 (m, 1H), 4.43 (d, *J* 5.7 Hz, 2H), 2.93 (m, 2H), 1.47 (s, 9H). *Minor isomers*: δ 1.52 (s, 9H), 1.51 (s, 9H), 1.43 (s, 9H). *Butanamide **22*** (0.019 g, 15%) was obtained as a colourless oil. R_f 0.23 (70% EtOAc/hexane). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.83 (m, 1H), 7.40–7.12 (m, 10H), 4.92 (m, 1H), 4.41 (m, 2H), 3.85 (m, 1H), 3.79 (m, 2H), 3.26 (m, 2H), 3.06 (m, 1H), 2.34 (m, 2H), 1.43 (s, 9H). *Minor isomer*: δ 1.52 (s, 9H).

*4.15. N-(tert-butoxycarbonyl), 4[N(R)-α-methylbenzylamine]-2-pyrrolidinone(**24**) (Experiment 2, Table 3).* *R*-α-methylbenzylamine (0.05 mL, 0.388 mmol) was added to a solution of lactam **18** (0.056 g, 0.306 mmol) in THF (0.5 mL), under magnetic stirring, at room temperature and nitrogen atmosphere. After 120 h, the mixture was concentrated in vacuum, diluted with CH_2Cl_2 (1.5 mL), transferred with a pipette to the top of a column chromatography of silica gel, and then eluted with hexane and crescent gradient of EtOAc (50 and 100%). A colourless oil was obtained characterized as a mixture (1 : 1) of isomers **24** (0.031 g, 33%). R_f 0.36 (70% EtOAc/hexane). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.40–7.20 (m, 10H), 3.90–3.50 (m, 6H), 3.42–3.15 (m, 4H), 2.74–2.14 (m, 4H), 1.52 (s, 9H), 1.48 (s, 9H), 1.36 (d, *J* 6.6 Hz, 6H).

*4.16. N-(tert-butoxycarbonyl)-4-(dimethyl malonyl)-2-pyrrolidinone(**26**) (Experiment 3, Table 3).* Dimethyl malonate (0.04 mL, 0.35 mmol) was added to a stirred solution of MeONa [Na (0.003 g, 0.130 mmol), MeOH (0.2 mL)] at room temperature and nitrogen atmosphere. After 10 minutes, lactam **18** (0.053 g, 0.289 mmol) in MeOH (0.5 mL) was added and the mixture was left under magnetic stirring, at room temperature and nitrogen atmosphere for 1.5 h. The mixture was concentrated in vacuum, diluted with EtOAc (20 mL), and then washed with saturated solution of NH_4Cl (1 × 30 mL). The organic layer was separated, and the aqueous phase was extracted with EtOAc (1 × 30 mL). The organic extracts were dried with Na_2SO_4, filtered, and concentrated in vacuum. The crude product was purified over column chromatography of silica gel eluted with hexane and crescent gradient of EtOAc (20 and 30%). A colourless oil was obtained characterized as a mixture of isomers **26** (0.026 g, 28%). R_f 0.35 (50% EtOAc/hexane). ^{1}H NMR

(200 MHz, $CDCl_3$): δ 4.07 (d, J 8.0 Hz, 1H), 3.80 (s, 3H), 3.70 (s, 3H), 3.38 (m, 2H), 3.11 (m, 1H), 2.54 (m, 2H), 1.52 (s, 9H). *Minor isomers*: δ 4.12 (d, J 8.0 Hz, 1H), 3.76 (d, J 3.9 Hz, 1H), 3.68 (d, J 4.4 Hz, 1H), 1.45 (s, 9H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.93 (C=O), 168.17 (C=O), 167.38 (C=O), 149.45 (C=O), 83.59 (C), 55.42 (CH), 52.80 (CH_3), 51.84 (CH_3), 49.51 (CH_2), 36.52 (CH_2), 31.10 (CH), 27.82 (3 CH_3).

*4.17. N-(tert-butoxycarbonyl)-4-phenyl-2-pyrrolidinone(**28**).* 4-Phenyl-2-pyrrolidinone(**27**) (0.213 g, 1.321 mmol) in THF (9.5 mL) was added to a stirred suspension of NaH (0.038 g, 1.583 mmol) in THF (1.5 mL), at room temperature and nitrogen atmosphere. After 10 minutes, $(Boc)_2O$ (0.407 g, 1.865 mmol) was added and the mixture was left under magnetic stirring, at room temperature and nitrogen atmosphere for 20 minutes. Saturated solution of NH_4Cl (50 mL) was added, and then extracted with EtOAc (2 × 50 mL). The organic extracts were dried with Na_2SO_4, filtered, and concentrated in vacuum. The crude product was purified over column chromatography of silica gel eluted with 20% EtOAc/hexane. A yellowish crystalline residue was obtained characterized as pyrrolidinone **28** (0.207 g, 60%). R_f 0.50 (50% EtOAc/hexane). IR (KBr) ν_{max}/cm^{-1}: 2978, 1774, 1694, 1493, 1457, 1366, 1296, 1255, 1155, 1092, 1019, 839, 766, 701. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.43–7.21 (m, 5H), 4.24–4.10 (m, 1H), 3.76–3.44 (m, 2H), 3.00–2.62 (m, 2H), 1.53 (s, 9H). *Minor isomer*: δ 1.41 (s, 9H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 172.69 (C=O), 149.53 (C=O), 140.26 (C), 128.63 (2 CH), 127.07 (CH), 126.42 (2 CH), 82.64 (C), 52.80 (CH_2), 39.95 (CH_2), 36.05 (CH), 27.69 (3 CH_3). m/z (%): 263 (M + 2, 1%), 206 (13), 162 (48), 132 (20), 104 (100), 78 (33).

*4.18. N-benzyl-4-phenyl-2-pyrrolidinone(**29**).* 18-Crown-6 (0.066 g, 0.250 mmol) in THF (0.2 mL) and 4-phenyl-2-pyrrolidinone(**27**) (0.080 g, 0.496 mmol) in THF (0.7 mL) were added to a stirred suspension of KH (0.030 g, 0.748 mmol) in THF (0.1 mL) at room temperature and nitrogen atmosphere. After 5 minutes, benzyl bromide (0.104 g, 0.608 mmol) was added and the mixture was left under magnetic stirring, at room temperature and nitrogen atmosphere for 10 minutes. Saturated solution of NH_4Cl (15 mL) was added, and the mixture was extracted with EtOAc (2 × 20 mL). The organic extracts were dried with Na_2SO_4, filtered, and concentrated in vacuum. The crude product was purified over column chromatography of silica gel eluted with 30% EtOAc/hexane. A colourless crystalline residue was obtained characterized as pyrrolidinone **29** (0.100 g, 80%). R_f 0.45 (EtOAc). IR (KBr) ν_{max}/cm^{-1}: 3027, 2929, 2848, 1691, 1668, 1492, 1425, 1248, 850, 746, 698, 664, 609, 524. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.40–7.10 (m, 10H), 4.56 (d, J 14.6 Hz, 1H), 4.44 (d, J 14.6 Hz, 1H), 3.68–3.42 (m, 2H), 3.38–3.16 (m, 1H), 2.95–2.78 (m, 1H), 2.68–2.52 (m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 173.40 (C=O), 142.00 (C), 136.07 (C), 128.54 (2 CH), 128.47 (2 CH), 127.96 (2 CH), 127.41 (CH), 126.75 (CH), 126.43 (2 CH), 53.49 (CH_2), 46.34 (CH_2), 38.65 (CH_2), 36.90 (CH). m/z (%): 251 ($M^{+\cdot}$, 100%), 160 (35), 146 (20), 120 (13), 104 (48), 91 (45), 78 (15), 65 (15), 51 (10).

See the supplementary material displaying the speculative mechanisms for the reactions presented in the text of the paper. The supplementary material is available online at doi: 10.1155/2011/803120.

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