Tetrahedron 65 (2009) 6364–6369

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Cyclisation at very high temperature. Thermal transformations of *N*-alkyl and *N*, *N*-dialkyl amides of α,β-unsaturated acids into mono- and bicyclic heterocycles under FVT conditions

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ARTICLE INFO

Article history:
Received 18 February 2009
Received in revised form 21 May 2009
Accepted 4 June 2009
Available online 10 June 2009

ABSTRACT

Cyclisations of *N*-alkyl and *N*,*N*-dialkyl cinnamic amides to the corresponding pyrrolidin-2-ones under the conditions of flash vacuum thermolysis (FVT), are described. It was found that these reactions proceed at 950–1000 °C affording in various yields the mixtures of isomeric mono and bicyclic γ-lactams, which were separated chromatographically and analysed by means of NMR spectroscopy. Two alternative mechanisms for the title process are proposed.

1. Introduction

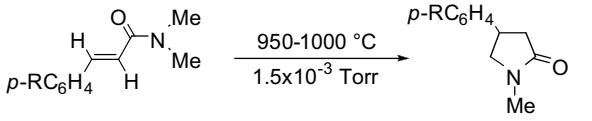
The FVT-technique (flash vacuum thermolysis) has been broadly applied in retro-ene reactions.[1] It seems from numerous relevant contributions, that no common mechanism governs all reactions of this kind. Indeed, accordingly to each case, they can follow the reaction pathway included between that purely concerted and radical. The former mechanism is in most cases preferred, however. On the other hand, it is well known that retro-ene reactions realised under the foregoing conditions are synthetic methods for the preparation of unsaturated, and therefore, often very reactive species.

Thus, simultaneous formation of vinylketenes and imines in the retro-ene reaction of allenic *N*,*N*-dialkylamides was postulated by Wentrup and co-workers,[2] but related lactams (as expected products of the Staudinger reaction) were not detected. According to Wentrup's results, the FVT of *N*,*N*-dimethyl cinnamic amide should afford methyl-methylene-amine together with benzylketene. However, as a matter of fact, we shown in our preliminary communication[3] that cinnamic amides bearing one or two alkyl groups at the nitrogen atom undergo cyclisation to the pyrrolidin-2-one ring under such reaction conditions.

In this paper we report the full details of our studies on such thermal transformations orientated towards to the synthesis of various bicyclic systems of the pyrrolizidinone or indolizidinone type.

2. Results and discussion

Our initial FVT experiments with *N*,*N*-dimethyl cinnamic amide (**1a**) at 950–1000 °C under a pressure 1.5×10^{-3} Torr led, unexpectedly, to 1-methyl-4-phenyl-pyrrolidin-2-one (**2a**) as an exclusive product in 88% yield (Scheme 1). Also, (*E*)-3-(4-methoxyphenyl)-*N*,*N*-dimethyl-acrylamide (**1b**) underwent cyclisation under such conditions to afford 1-methyl-4-(4-hydroxy-phenyl)-pyrrolidin-2-one (**2b**) in 43% yield. A simultaneous dealkylation of the aryl-ring methoxy group occurred in this process.



1a R = H
1b R = OMe

2a R = H
2b R = OH

Scheme 1.

In the next steps of this work, several *N*-mono and *N*,*N*-disubstituted cinnamic amides were investigated. When amides **1c–f** were subjected to FVT in a conventional flow system (950–1000 °C, 1.5×10^{-3} Torr) the expected γ-lactams **2c–f** were obtained in variable yields as diastereoisomeric mixtures (Scheme 2, Table 1). Such a stereochemical problem obviously did not exist for the above amides **1a** and **1b** in which two Me groups in the *N*-alkyl unit prompted the formation of 5-unsubstituted products.

The formation of *N*-dealkylated compound **2e** from the substrate **1c** can be easily explained as a result of the secondary retro-

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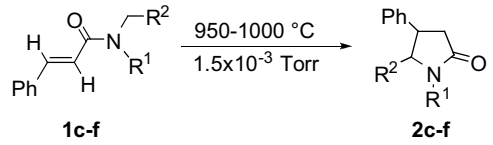
doi:10.1016/j.tet.2009.06.011



Scheme 2.

Table 1
Synthesis of pyrrolidin-2-ones **2**

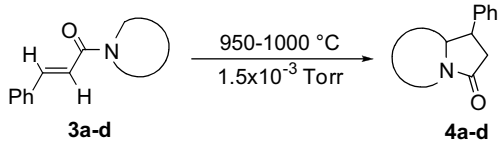
Entry	Substrate	Product[a]	Yield[b] (%)	trans/cis ratio[c]
1	**1c**: R^1=Et, R^2=Me	**2c**: R^1=Et, R^2=Me	38	2:1
		2e: R^1=H, R^2=Me	12	2:1
2	**1d**: R^1=Ph, R^2=Me	**2d**: R^1=Ph, R^2=Me	63	2:1
3	**1e**: R^1=H, R^2=Me	**2e**: R^1=H, R^2=Me	62	2:1
4	**1f**: R^1=H, R^2=Ph	**2f**: R^1=H, R^2=Ph	50	2:1

[a] In all of the cases small amounts of styrene were detected in crude thermolysis mixtures.
[b] Yields for pure products isolated by chromatography.
[c] Stereochemical assignments of the isomers trans and cis are based on the ^{1}H NMR spectra (see text).

ene reaction of an initial product **2c**, that is, by the well-know β-elimination reaction of amides. Indeed, when **2c** was re-pyrolysed at about 1050 °C, lactam **2e** was obtained almost quantitatively.

The trans and cis stereoisomers of pyrrolidin-2-ones **2** can be easily distinguished[4] from each other by ^{1}H NMR, on the basis of characteristic chemical shifts of the protons of the Me group at C-5 (for **2c**–**e**) or of the methine proton at C-5, for **2f**. For trans isomers, the Me group protons at C-5 generally appear at δ 1.10–1.25 ppm, whereas related protons in the cis species resonate at $\delta \approx 0.8$ ppm. Similarly, for the trans isomer of pyrrolidin-2-one **2f**, C-5 proton appears at δ=4.69 ppm, (d, J=7.3 Hz), whereas that in the cis isomer is observed at δ=5.00 ppm (d, J=7.8 Hz). Thus, trans/cis ratios were easily determined by integration of the aforementioned signals in ^{1}H NMR spectra of the crude diastereoisomeric mixtures.

The successful FVT cyclisation reaction of the cinnamic amides prompted us to an extension of this method to the synthesis of some bicyclic lactams containing inter alia the pyrrolizidine or indolizidine skeleton. Taking into account that the aforementioned reaction took place on an α-atom of the *N*-alkyl substituent, we assumed that its use for corresponding amides obtained from the cyclic amines would allow access to analogous bicyclic structures. Indeed, the FVT of the cinnamic amides **3a**–**d**[5–8] (easily accessible from pyrrolidine, piperidine, morpholine and thiomorpholine) afforded corresponding bicyclic systems (Scheme 3) in good yields (Table 2).



Scheme 3.

The relative configurations of ring-fused bicyclic systems **4a**–**d** accessed in this manner has been unambiguously established on the basis of ^{1}H and, especially, ^{13}C NMR spectra of single isomers separated chromatographically (except for lactams **4a** examined in a mixture enriched in one of the components), which were analysed in the light of chemical shift values predicted for low-energy conformers of these molecules, by applying the GIAO DFT method[9] (Experimental). It was found that a trans-configuration is characteristic of the major (less polar, simultaneously) stereoisomers

Table 2
Synthesis of bicyclic lactams **4** from related amides **3**[5–8]

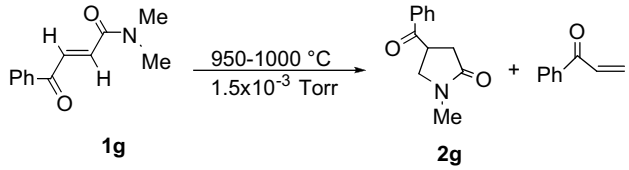
Entry	Substrate	Product	Yield[a] (%)	trans/cis ratio[b]
1	**3a**[5]	**4a**	71	2:1
2	**3b**[6]	**4b**	73	2:1
3	**3c**[7]	**4c**	69	2:1
4	**3d**[8]	**4d**	64	2:1

[a] Yields are for pure products isolated by flash chromatography.
[b] Stereochemical assignments of isomers trans and cis (i.e., with the phenyl group occupying the *exo* and *endo* position, respectively) are based mainly on the ^{13}C NMR spectra (see text).

obtained. Two series of the ^{13}C NMR signals found for two coexisting (~1:1) conformers of the minor product *cis*-**4d** are particularly worthy of mention. A full stereochemical and conformational analysis of the bicyclic lactams **4** in solution will be published independently.[10]

Next, we examined the scope and limitations of an applied method and, especially, a role of the aryl group at the 3-position of an acrylic moiety. Thus, *N*,*N*-dimethyl acrylamide and (*E*)-but-2-enoic acid *N*,*N*-dimethyl amide were found to be stable in the whole accessible range of temperatures, i.e., up to 1200 °C. However, 3-methylbut-2-enoic acid *N*,*N*-dimethylamide easily underwent the retro-ene reaction at 1000 °C, with the quantitative formation of 3-methylbut-3-enoic acid *N*,*N*-dimethylamide.

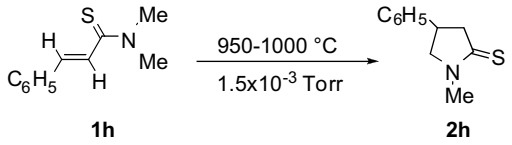
On the contrary, FVT of amide **1g**[11] possessing the benzoyl group at the 3-position resulted in the formation of a suitable cyclisation target **2g** as a new compound, but only in 11% isolated yield (Scheme 4). Unfortunately, the major product of this reaction was phenyl vinyl ketone (64%).



Scheme 4.

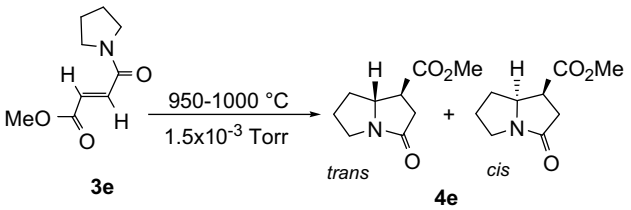
In agreement with our expectation, (*E*)-*N*,*N*-dimethyl-3-phenyl-thioacrylamide **1h**[12] underwent easily a cyclisation reaction that afforded related 1-methyl-4-phenyl-pyrrolidin-2-thion in 50% yield (Scheme 5).

Finally, an interesting result has been obtained with (*E*)-4-oxo-4-pyrrolidin-1-yl-but-2-enoic acid methyl ester (**3e**), derived from (*E*)-3-chlorocarbonyl-acrylic acid methyl ester[13] and pyrrolidine.



Scheme 5.

This conjugated monoamide **3e** (with $^3J_{HH}$ of 15.2 Hz for olefinic protons, indicating a trans-configuration of the C=C double bond)[12] under FVT conditions led to a mixture of trans and cis (2:1) isomers of the known 3-oxo-hexahydro-pyrrolizine-1-carboxylic acid methyl ester (**4e**)[14–17] in 62% yield (Scheme 6, only one pair of these diastereomers is shown).



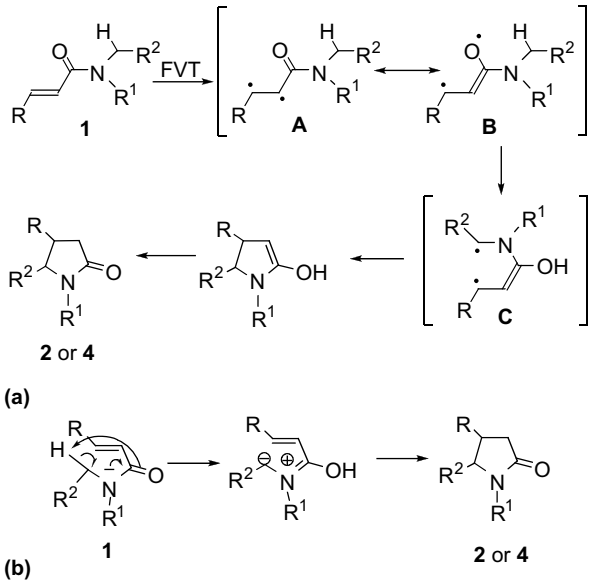
Scheme 6.

This interesting finding shows that our method provides a very simple and efficient access to the *Senecio* alkaloids containing the pyrrolizidine ring system. Indeed, stereoselective reduction of both the lactam carbonyl group and ester moieties of trans and cis isomers of the product **4e** could cleanly give the two diastereomeric pairs of 1-hydroxymethylpyrrolizidine, i.e., (+)-*laburnine* or (−)-*trachelanthamidine* and (±)-*isoretronecanol*, respectively, as the two simplest necine bases.[14–17]

On the whole, the results presented above clearly showed that the phenyl or another activating group incorporated into an α,β-unsaturated *N*-alkylamide skeleton is essential for effecting the FVT cyclisations to lactams **2** or **4**.

The mechanistic explanation for a formation of the lactam systems **2** and **4** under the used FVT conditions is presented in Scheme 7. In our opinion two alternative mechanisms could be proposed. First—in which the cyclisation reaction proceeds as a biradical process. This can be explained in terms of a significant stabilisation of the biradical **A** formed by a reversible cleavage of the C=C double bond, in the first reaction step (Scheme 7a). The species **A** is stabilised by an adjacent phenyl, benzoyl or ester group, and by the resonance between the canonical forms **A** and **B** (in which an unpaired electron is localised on an oxygen atom). A subsequent intramolecular [1,4]-H atom transfer occurring afterwards via a five-membered transition state, from an α *N*-alkyl substituent to an oxyl group (in the form **B**), results in the formation of a new biradical species **C** cyclising next to the intermediate enol, after initial low-energy rotation around the C–N bond. Alternatively, the enol biradical **C** could tautomerise into its keto form before a ring closure to give directly γ-lactam **2** (path not shown in Scheme 7). An analogous H-atom transfer under FVT conditions, from the alkylamide group to phenoxyl or thiophenoxyl radicals, proceeding via the six- or seven-membered ring transition states has been described by McNab and co-workers.[18]

The second possible mechanism can be postulated as a process in which the key intermediate is a dipolar species formed by [1,4]-H atom transfer, and being stabilised by the phenyl group in an analogous fashion to that for a biradical (Scheme 7b). Presently, it is not possible to judge which of two proposed mechanisms governs the reaction course, and, a competition of both cannot be excluded.



Scheme 7.

It was possible, in principle, that amide **1** could also undergo a retro-ene reaction in line with Wentrup's results, giving rise to the formation of corresponding benzyl ketene and the imine. An interaction between such highly reactive species would be expected to give related zwitterionic intermediates subsequently cyclise to corresponding β- or δ-lactams, as has been found in many related reactions.[19] However, no such products were detected in our experiments.

In order to exclude the γ-lactams formation as a result of interactions between the species mentioned above, we examined the reaction of benzyl ketene with benzylidene aniline using the 'acid chloride–imine approach'.[20] This procedure afforded *trans*-3-benzyl-1,4-diphenylazetidin-2-one[21] in moderate yield, but 4,5-diphenyl-pyrrolidin-2-one was not detected in the post-reaction mixture. Therefore, the alternative mechanism involving a retro-ene reaction of amide **1** was disproved, at this stage.

Some support for the biradical mechanism came from the results of the thermolysis of 2,*N*,*N*-trimethyl-3-phenylacrylamide. The FVT performed under the foregoing conditions afforded *trans* and *cis* 1,3-dimethyl-4-phenyl-pyrrolidin-2-one[22] (2:1) in 32% yield, together with 68% recovery of the starting amide. The latter compound was found as an equimolar mixture of its *E* and *Z* isomers (for biradical isomerization of other cinnamic derivatives under FVP conditions, see Ref. 23). A lower yield of γ-lactam and the formation of *E* and *Z* isomers of the amide substrate can be explained by different stabilisation of an initially formed biradical **A**⇔**B**. This reversible process produces the benzylic and tertiary carbon-centred biradical. The latter species reacts far less rapidly than the structurally related system with a secondary carbon-centred radical. As a consequence of the greater significance of the resonance structure **A** (compared with **B**), an easier substrate isomerization and, simultaneously, the lowered yield of the cyclisation product would be expected, as found experimentally.

3. Conclusion

In summary, a thermal transformation of variously *N*-alkyl substituted cinnamic amides into pyrrolidin-2-one systems under the FVT conditions has been demonstrated. Although the majority of products obtained are fairly simple and they can be prepared by other methods, it should be noted that the cyclisation of this type is reported here for the first time and its further applications are now

being intensively examined. Our findings show that the FVT approach is really a particular synthetic tool and it can provide quite unexpected results.

4. Experimental

4.1. General

The ^{1}H and ^{1}H-decoupled ^{13}C NMR spectra were recorded at ca. 21 °C in $CDCl_3$ solutions with a *Varian Gemini 200 BB* instrument operating at 200.11 and 50.33 MHz for the ^{1}H and ^{13}C nuclei, respectively. Chemical shifts, δ_Xs, are reported in ppm (vs an internal TMS), while coupling constants *J* are given in Hz (first-order analysis). Signals are reported as p (pseudo), s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad). A vast majority of the NMR spectra were assigned with selective decoupling, experiments COSY, ATP, DEPT or HECTOR and/or using the values of δ_Xs (X=H and, especially, C) predicted by a gauge independent atomic orbital (GIAO) method[9] at the DFT B3LYP/6-31G*//B3LYP/6-31G* level of theory. IR spectra were recorded on a *Thermo-Nicolet Nexus FT-IR* spectrometer as neat samples (liquid films on NaCl plates) or in KBr discs. All MS-EI mass spectra were taken on a *Finnigan MAT 95* spectrometer at 70 eV using a direct inlet; the peaks ≥10% rel intensities are usually given only. Melting points (uncorrected) were determined on a *Boëtius* hot-stage apparatus. Column chromatography was carried out with silica gel (*Merck type 60*, 63–200 microns). Analytical thin-layer chromatography (TLC) was performed on *Merck 5554* aluminium-backed SiO_2 plates. Preparative TLC was performed using Merck silica gel 60 (PF_{254}) and a mixture of hexane and ethyl acetate as an eluent. Products were visualised by UV light (254 nm).

4.2. Starting materials

Starting compounds **1a**–**g** and **3a**–**d**[5–8] were freshly prepared by the treatment of the appropriate amines with acid chlorides.

4.2.1. (*E*)-3-Phenyl-1-thiomorpholin-4-yl-propenone (**3d**)[8]

The previously unreported spectral data are as follows. IR (KBr, cm^{-1}): 1644 ($\nu_{C=O}$), 1597, 1498, 1454, 1438, 1428, 1280, 1187, 977, 956, 761, 758. ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ=2.60–2.69 (m, 4H, 2×C*H*$_2$S), 3.92 (br s, 4H, 2×C*H*$_2$N), 6.85 (d, *J*=15.4 Hz, 1H, C2–*H*), 7.30–7.42 (m, 3H, C*H*$_{ar}$), 7.54–7.62 (m, 2H, C*H*$_{ar}$), 7.66 (d, *J*=15.4 Hz, 1H, C1–*H*). ^{13}C NMR (50 MHz, $CDCl_3$, TMS) δ=27.39 [*C*H$_2$S (*CO*$_{syn}$)], 28.08 [*C*H$_2$S (*CO*$_{anti}$)], 44.93 [*C*H$_2$N (*CO*$_{syn}$)], 48.62 [*C*H$_2$N (*CO*$_{anti}$)], 117.10 (=*C*-2), 127.82 and 128.87 (2×2*C*H), 129.77 (*C*H), 135.17 (*C*), 143.11 (=*C*-1), 165.67 (*C*=O$_{amide}$).

4.2.2. (*E*)-4-Oxo-4-pyrrolidin-1-yl-but-2-enoic acid methyl ester (**3e**)

A solution of (*E*)-3-chlorocarbonyl-acrylic acid methyl ester,[13] (2.23 g, 15 mmol), pyrrolidine (1.06 g, 15 mmol), and triethylamine (1.52 g, 15 mmol) in 20 mL of CH_2Cl_2 was stirred for 1 h at rt, washed with saturated aqueous sodium bicarbonate and then with brine. The organic phase was dried, concentrated in vacuo and the crude product obtained was purified by preparative TLC (hexane/AcOEt, 6:1). Yield: 907 mg (33%). Colourless crystals. Mp 56–57 °C (petrol ether/CH_2Cl_2). IR (KBr, cm^{-1}): 2976, 2953, 1720 ($\nu_{C=O\ ester}$), 1655 ($\nu_{C=O\ amide}$), 1616 ($\nu_{C=C}$), 1444, 1437, 1306, 1297, 1277, 1197, 1170, 992, 976, 766, 551. ^{1}H NMR (200 MHz, $CDCl_3$) δ=1.85–2.10 (m, 4H, C*H*$_{2\beta\text{-pyrr}}$), 3.55 (t, *J*=6.5 Hz, 2H, C*H*$_{2\alpha'\text{-pyrr}}$ (*CO*$_{anti}$)), 3.63 (t, *J*=6.4 Hz, 2H, C*H*$_{2\alpha\text{-pyrr}}$ (*CO*$_{syn}$)), 3.80 (s, 3H, OC*H*$_3$), 6.84 (d, *J*=15.25 Hz, 1H, C2–*H*), 7.27 (d, *J*=15.25 Hz, 1H, C3–*H*). ^{13}C NMR (50 MHz, $CDCl_3$, TMS) δ=24.27 (*C*H$_{2\beta\text{-pyrr}}$), 26.11 (*CH*$_{2\beta'\text{-pyrr}}$), 46.24 (*CH*$_{2\alpha'\text{-pyrr}}$), 46.89 (*CH*$_{2\alpha\text{-pyrr}}$), 52.13 (O*CH*$_3$), 130.35 (=*C*-2), 134.96 (=*C*-3), 162.53 (*C*=O$_{amide}$), 166.33 (*C*=O$_{ester}$). MS (70 eV) *m*/*z* (%): 183 (9, M^+), 152 (11), 114 (11), 113 (21), 70 (100). Anal. Calcd for $C_9H_{13}NO_3$ (183.21): C, 59.00; H, 7.15; N, 7.65%. Found: C, 58.59; H, 7.11; N, 7.73%.

4.3. Preparative flash vacuum thermolysis

General procedure. The FVT reactions were carried out in a 30×2.5 cm electrically heated horizontally oriented quartz tube packed with quartz rings, at 1.5×10^{-3} Torr. All of the synthetic precursors (2 mmol) were slowly sublimed at 80–100 °C from a flask held into a thermolysis tube preheated to 950–1000 °C. The products thereby obtained were collected in a CO_2–aceton trap. After thermolysis, the whole system was brought to atmospheric pressure, allowing slow warming up to rt and the products were dissolved in $CHCl_3$. The solvent was removed under reduced pressure and products were purified chromatographically on SiO_2 column and/or by recrystallization.

4.3.1. 1-Methyl-4-phenyl-pyrrolidin-2-one (**2a**)

Purified by chromatography (hexane/AcOEt, 1:1). Yield: 308 mg (88%) of colourless solids. Mp 135–137 °C (lit.[22] mp 128–135 °C). This product shows identical ^{1}H NMR spectral data with those described in the literature.[24]

4.3.2. 1-Methyl-4-(4-hydroxyphenyl)-pyrrolidin-2-one (**2b**)

Purified by chromatography (hexane/AcOEt, 1:1) and recrystallization from hexane. Yield: 164 mg (43%) of colourless solids. Mp 112–114 °C (lit.[3] mp 112–114 °C). For spectroscopic and analytical data see Ref. 3.

4.3.3. 1-Ethyl-5-methyl-4-phenyl-pyrrolidin-2-one (**2c**)

Purified by chromatography (hexane/AcOEt, 1:1) to give 154 mg (38%) of trans and cis isomers mixture (2:1 from integrals of C*H*$_3$ doublets, δ 1.11 and 0.78, respectively). The isomers were separated chromatographically (hexane/AcOEt, 1:1) as colourless solids. First (major) eluate: *cis*-**2c**. Mp 106–108 °C (hexane/CH_2Cl_2) (lit.[3] mp 106–108 °C). Second (minor) eluate: *trans*-**2c**. Mp 115–117 °C (hexane/CH_2Cl_2) (lit.[3] mp 115–117 °C). For spectroscopic and analytical data see Ref. 3.

4.3.4. 5-Methyl-4-phenyl-pyrrolidin-2-one (**2e**)

Obtained as a minor product by FVT of **1c**. Purified by chromatography (hexane/AcOEt, 1:1). Yield: 42 mg (12%) of an oily colourless trans and cis isomer mixture (2:1 from integrals of C*H*$_3$ doublets at 1.25 and 0.80 ppm, respectively). These isomers provided ^{1}H NMR data identical with those partially reported by Langlois and co-workers.[25]

4.3.5. 5-Methyl-1,4-diphenyl-pyrrolidin-2-one (**2d**)

Purified by chromatography (hexane/AcOEt, 1:1). Yield 317 mg (63%) of trans and cis isomer mixture (2:1 from integrals of C*H*$_3$ doublets, δ 1.21 and 0.84, respectively). Colourless oil. For spectroscopic and analytical data see Ref. 3.

4.3.6. 5-Methyl-4-phenyl-pyrrolidin-2-one (**2e**)

Obtained by FVT of **1e**. Purified by chromatography (hexane/AcOEt, 1:1). Yield: 217 mg (62%) of trans and cis isomer mixture (2:1 from integrals of C*H*$_3$ doublets at 1.25 and 0.80 ppm, respectively). Colourless oil. Product identical with **2e** described above.

4.3.7. 4,5-Diphenyl-pyrrolidin-2-one (**2f**)

Purified by chromatography (hexane/AcOEt, 1:1). Yield: 237 mg (50%) of an oily colourless trans/cis mixture (2:1; from C-5 proton integrals in $CDCl_3$, δ 4.69 for trans and 5.00 for cis isomer, respectively) in full agreement with spectral data for the compounds of this class.[4]

*4.3.8. 4-Benzoyl-1-methyl-pyrrolidin-2-one (**2g**)*

Separated from the major product by standard column chromatography (hexane/AcOEt, 1:1) and purified with preparative TLC (SiO_2, hexane/AcOEt, 3:7). Yield: 45 mg (11%). Light yellow very viscous oil. IR (KBr, cm^{-1}): 2926, 1683 ($\nu_{C=O\ ketone/amide}$), 1595, 1507, 1451, 1408, 1397, 1303, 1263, 1227, 692. ^1H NMR (200 MHz, $CDCl_3$, TMS) δ=2.77 (d, ^3J=8.7 Hz, 2H, C3–H_2), 2.89 (s, 3H, NCH_3), 3.63 (dd, ^2J=9.9 Hz, ^3J=8.9 Hz, 1H, C5–*H*), 3.78 (dd, ^2J=9.9 Hz, ^3J=5.9 Hz, 1H, C5–*H*), 4.08–4.24 (m, 1H, C4–*H*), 7.46–7.64 (m, 3H, CH_{ar}), 7.91–7.98 (m, 2H, CH_{ar}). ^{13}C NMR (50 MHz, $CDCl_3$, TMS) δ=29.60, 34.19, 38.12, 50.70, 128.65 and 129.11 (2×2*C*H), 133.92 (*C*H), 135.42 (*C*), 172.43 (*C*=O$_{amide}$), 198.07 (*C*=O$_{ketone}$). MS (70 eV) *m*/*z* (%): 204 [8, $(M+1)^+$], 203 (62, M^+), 186 (11), 175 (23), 160 (33), 145 (10), 105 (100), 98 (18), 77 (53), 70 (26), 51 (13), 42 (12). HRMS *m*/*z* calcd for $C_{12}H_{13}NO_2$ 203.09463, found 203.09443.

*4.3.9. 1-Methyl-4-phenyl-pyrrolidin-2-thione (**2h**)*

Obtained by FVT of **1h**.[12] Purified by chromatography on SiO_2 (hexane/AcOEt, 1:1). Yield: 191 mg (50%). Light brown oil. IR (neat, cm^{-1}): 2930, 1603, 1526, 1495, 1463, 1399, 1312, 1135, 759, 700. ^1H NMR (200 MHz, $CDCl_3$, TMS) δ=3.08–3.24 (1H, m, one of C3–H_2), 3.31 (s, 3H, NCH_3), 3.36–3.82 (m, 3H), 4.10 (1H, dd, *J*=11.0 and 8.1 Hz, one of C5–H_2), 7.16–7.39 (m, 5H, CH_{ar}). ^{13}C NMR (50 MHz, $CDCl_3$, TMS) δ=35.43 (NCH_3), 38.85 (*C*H), 52.17 (*C*H_2), 63.85 (*C*H_2), 126.68 (2*C*H), 127.27 (*C*H), 128.99 (2*C*H), 141.57 (*C*), 200.30 (*C*=S). MS (70 eV) *m*/*z* (%): 192 [14, $(M+1)^+$], 191 (100, M^+), 147 (13), 115 (20), 104 (31), 87 (12). HRMS *m*/*z* calcd for $C_{11}H_{13}NS$ 191.07687, found 191.07674.

*4.3.10. 1-Phenyl-hexahydro-pyrrolizin-3-one (**4a**)*

Purified by SiO_2 chromatography (AcOEt) as a partially separable diastereomeric mixture (ratio trans/cis ~2:1, from the integrals of 1H multiplets at 3.95 and 4.27 ppm, respectively). Yield: 285 mg (71%). Light yellow oil. IR (neat, cm^{-1}): 2971, 2879, 1697 ($\nu_{C=O}$), 1497, 1454, 1416, 1333, 755, 702. MS (70 eV) *m*/*z* (%): 201 (47, M^+), 105 (10), 104 (100), 103 (14), 78 (10), 70 (57). HRMS *m*/*z* calcd for $C_{13}H_{15}NO$ 201.11536, found 201.11552. ^1H NMR (200 MHz, $CDCl_3$, TMS) for ~1:1 mixture δ=0.81–1.02 (m, 0.5H, cis), 1.41–1.68 (m, 1H), 1.72–1.98 (m, 1H), 1.98–2.22 (m, 1.5H), 2.66 (dd, ^2J=16.7 Hz, ^3J=2.3 Hz, 0.5H, one of C2–H_2, cis), 2.81 (dd, ^2J=16.0 Hz, ^3J=8.7 Hz, 0.5H, one of C2–H_2, trans), 2.92–3.38 (m, 2.5H), 3.44–3.75 (m, 1.5H), 3.88–4.02 (m, 0.5H, C7a–*H*, trans), 4.20–4.34 (m, 0.5H, C7a–*H*, cis), 7.07–7.14 (m, 1H, CH_{ar}), 7.22–7.42 (m, 4H, CH_{ar}). First (less polar) eluate: *trans*-**4b**. ^{13}C NMR (50 MHz, $CDCl_3$, TMS) δ=27.04, 31.41, 41.39, 43.18, 48.62, 68.67, 127.06 (2*C*H), 127.16 (*C*H), 128.84 (2*C*H), 140.58 (*C*), 173.17 (*C*=O). Second (more polar) eluate: *cis*-**4b**. ^{13}C NMR ($CDCl_3$, 50 MHz, TMS) δ=26.37, 26.79, 41.47, 41.63, 41.79, 66.00, 127.06 (*C*H), 127.69 (2*C*H), 128.65 (2*C*H), 140.62 (*C*), 174.27 (*C*=O).

*4.3.11. 1-Phenyl-hexahydro-indolizin-3-one (**4b**)*

Purified by SiO_2 chromatography (AcOEt) as an isomeric mixture [trans/cis ~2:1, from integrals of the multiplet signals at 3.30 ppm (1H) and 3.66 ppm (2H), respectively]. Yield: 314 mg (73%). Both products were separated chromatographically on SiO_2 (AcOEt). First (major) eluate: trans-**4b**. Light yellow oil. IR (film, cm^{-1}): 1686 ($\nu_{C=O}$), 1444, 1421, 1289, 1260, 1145, 762, 701. ^1H NMR (200 MHz, $CDCl_3$, TMS) δ=1.10–1.50 (m, 3H), 1.60–2.04 (m, 3H), 2.46–2.90 (m, 3H), 2.98–3.13 (m, 1H), 3.28–3.41 (m, 1H), 4.13–4.25 (m, 1H), 7.21–7.39 (m, 5H, CH_{ar}). ^{13}C NMR (50 MHz, $CDCl_3$, TMS) δ=23.52, 24.26, 32.09, 39.11, 40.29, 46.27, 64.56, 127.23 (*C*H), 127.45 and 128.92 (2×2*C*H), 141.47 (*C*), 172.46 (*C*=O). MS (70 eV) *m*/*z* (%): 216 (16), 215 (100, M^+), 214 (63), 104 (87), 103 (12), 84 (76), 83 (35). HRMS *m*/*z* calcd for $C_{14}H_{17}NO$ 215.13101, found 215.13092. Second (minor) eluate: *cis*-**4b**. Colourless semi-solid. IR (KBr, cm^{-1}): 1694 ($\nu_{C=O}$), 1454, 1424, 1353, 1285, 1097, 769, 703, 625, 613. ^1H NMR ($CDCl_3$, 200 MHz, TMS) δ=0.64–0.86 (m, 1H), 1.10–1.46 (m, 3H), 1.54–1.68 (m, 1H), 1.72–1.86 (m, 1H), 2.56–2.86 (m, 3H), 3.58–3.76 (m, 2H), 4.12–4.25 (m, 1H), 7.12–7.37 (m, 5H, CH_{ar}). ^{13}C NMR (50 MHz, $CDCl_3$, TMS) δ=23.81, 24.33, 28.10, 36.61, 40.70, 40.86, 61.28, 127.00 (*C*H), 128.04 and 128.46 (2×2*C*H), 139.58 (*C*), 173.45 (*C*=O). MS (70 eV) *m*/*z* (%): 216 (16), 215 (84.6, M^+), 214 (53), 131 (11), 105 (24), 104 (95), 103 (17), 84 (100), 83 (43), 78 (13), 77 (16), 55 (18). HRMS *m*/*z* calcd for $C_{14}H_{17}NO$ 215.13101, found 215.13107.

*4.3.12. 8-Phenyl-hexahydro-pyrrolo[2,1-c][1,4]oxazin-6-one (**4c**)*

Purified by chromatography (AcOEt) as isomeric mixture [trans/cis ~2:1, from the integral of two 0.5H triplets of the minor product (at 3.79 and 3.86 ppm) and a high-field part of the 1H pseudo triplet of doublets of the major product (at 3.32 ppm)]. Yield: 299 mg (69%). Both isomers were separated chromatographically (SiO_2/AcOEt) and recrystallized from the hexane/CH_2Cl_2 mixture. First (major) eluate: *trans*-**4c**. Colourless crystals. Mp 97–99 °C. IR (KBr, cm^{-1}): 1690 ($\nu_{C=O}$), 1453, 1423, 1285, 1097, 1049, 1026, 769, 702. ^1H NMR (200 MHz, $CDCl_3$, TMS) δ=2.52–2.69 (m, 1H), 2.72–2.91 (m, 1H), 2.94–3.12 (m, 2H), 3.13–3.27 (m, 1H), 3.30–3.48 (m, 1H), 3.62–3.75 (m, 1H), 3.90–4.18 (m, 3H), 7.20–7.44 (m, 5H, CH_{ar}). ^{13}C NMR (50 MHz, $CDCl_3$, TMS) δ=38.93, 40.20, 41.90, 61.60, 65.94, 71.97, 127.20 (2*C*H), 127.50 (*C*H), 129.07 (2*C*H), 140.34 (*C*), 172.01 (*C*=O). MS (70 eV) *m*/*z* (%): 218 [10, $(M+1)^+$], 217 (69, M^+), 187 (13), 104 (100), 103 (11), 86 (20). HRMS *m*/*z* calcd for $C_{13}H_{15}NO_2$ 217.11028, found 217.11022. Second (minor) eluate: *cis*-**4d**. Colourless solids. Mp 84–87 °C. IR (KBr, cm^{-1}): 2902, 1686 ($\nu_{C=O}$), 1452, 1424, 1386, 1352, 1292, 1261, 1094, 769, 702, 626. ^1H NMR (200 MHz, $CDCl_3$, TMS) δ=2.63–2.98 (m, 3H), 2.99–3.12 (m, 1H), 3.13–3.29 (m, 1H), 3.36–3.50 (m, 1H), 3.62–4.10 (m, 4H), 7.13–7.42 (m, 5H, CH_{ar}). ^{13}C NMR (50 MHz, $CDCl_3$, TMS) δ=36.95, 38.62, 40.80, 58.26, 65.68, 69.44, 127.52 (*C*H), 127.65 and 128.82 (2×2*C*H), 138.43 (*C*), 173.55 (*C*=O). MS (70 eV) *m*/*z* (%): 218 [9, $(M+1)^+$], 217 (62, M^+), 187 (11), 104 (100), 103 (11), 86 (20). HRMS *m*/*z* calcd for $C_{13}H_{15}NO_2$ 217.11028, found 217.11025.

*4.3.13. 8-Phenyl-hexahydro-pyrrolo[2,1-c][1,4]thiazin-6-one (**4d**)*

Purified by chromatography (AcOEt) to give an isomeric mixture [trans/cis ~2:1, from integrals of the 1H multiplet signals at 3.61 and two 0.5H signals at 4.05 and 4.37 ppm, respectively]. Yield 298 mg (64%). Both isomers were separated and purified as for **4c**. First (major) eluate: *trans*-**4d**. Almost colourless solids. Mp 99–102 °C. IR (KBr, cm^{-1}): 1686 ($\nu_{C=O}$), 1419, 1365, 1361, 1266, 1252, 773, 707. ^1H NMR (200 MHz, $CDCl_3$, TMS) δ=0.82–0.96 (m, 1H), 1.10–1.60 (m, 2H), 2.45–3.25 (m, 5H), 3.40–3.80 (m, 1H), 4.40–4.50 (m, 1H), 7.10–7.45 (m, 5H, CH_{ar}). ^{13}C NMR (50 MHz, $CDCl_3$, TMS) δ=26.90, 33.00, 38.48, 42.33, 45.76, 65.02, 127.31 (2*C*H), 127.46 (*C*H), 128.98 (2*C*H), 140.43 (*C*), 173.00 (*C*=O). MS (70 eV) *m*/*z* (%): 234 (15), 233 (92, M^+), 187 (16), 186 (11), 172 (13), 159 (10), 104 (100), 103 (15), 102 (17), 77 (10). HRMS *m*/*z* calcd for $C_{13}H_{15}NOS$ 233.08744, found 233.08747. Second (minor) eluate: *cis*-**4d**. Light yellow solids. Mp 101–103 °C. IR (KBr, cm^{-1}): 1686 ($\nu_{C=O}$), 1452, 1424, 1291, 1094, 769, 702, 626. ^1H NMR (200 MHz, $CDCl_3$, TMS) δ=2.44–3.44 (m, 7.5H), 3.84–3.99 (m, 0.5H), 4.00–4.12 (m, 0.5H), 4.32–4.44 (m, 0.5H), 4.52–4.64 (m, 0.5H), 4.66–4.70 (m, 0.5H), 7.10–7.45 (m, 5H, CH_{ar}). ^{13}C NMR (50 MHz, $CDCl_3$, TMS) δ=34.32, 37.39, 37.51, 38.01, 39.65, 44.44, 49.82, 50.16, 53.46, 55.93, 58.75, 62.47, 127.24 and 127.75 (2×2*C*H), 128.30 and 128.42 (2×CH), 128.47 (2×2*C*H), 136.06 and 139.02 (2×*C*), 172.74 and 173.33 (2×*C*=O). MS (70 eV) *m*/*z* (%): 234 (16), 233 (100, M^+), 187 (17), 186 (13), 172 (16), 159 (13), 104 (97), 103 (15), 102 (20), 101 (10), 77 (10). HRMS *m*/*z* calcd for $C_{13}H_{15}NOS$ 233.08744, found 233.08784.

*4.3.14. 3-Oxo-hexahydro-pyrrolizine-1-carboxylic acid methyl ester (**4e**)*

Purified by chromatography on SiO_2 (hexane/AcOEt, 1:3). Yield: 227 mg (62%) of a diastereomeric mixture of the isomers trans and cis [2:1, from integrals of the C(O)OCH_3 singlets at 3.75 and 3.72 ppm,

respectively]. IR (neat, cm^{-1}): 2956, 1736 ($\nu_{C=O\ ester}$), 1683 ($\nu_{C=O\ amide}$), 1438, 1201, 753. This mixture had the ^{13}C NMR spectroscopic data identical with those reported for authentic samples of the single isomers.[14–17] MS (70 eV) *m*/*z* (%): 183 (9, M^+), 152 (11), 114 (11), 113 (21), 70 (100).

Acknowledgements

The authors thank the Rector of the University of Łódź for financial support (Grant 505/740).

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