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Cyclisation at very high temperature. Thermal transformations of *N*-alkyl and *N*,*N*-dialkyl cinnamic amides into pyrrolidin-2-ones under FVT conditions

Stanisław Leśniak* and Beata Pasternak

Department of Organic and Applied Chemistry, University of Łódź, Narutowicza 68, 90-136 Łódź, Poland

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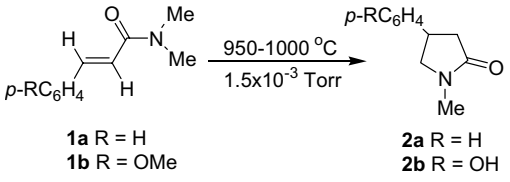
Abstract—Novel cyclisations of *N*-alkyl and *N*,*N*-dialkyl cinnamic amides to the corresponding pyrrolidin-2-ones under the conditions of flash vacuum thermolysis, are described. It was found that this reaction proceeds at 950–1000 °C affording a mixture of isomeric pyrrolidin-2-ones in various yields. Two possible mechanisms are proposed for the process.

Flash vacuum thermolysis (FVT) has been widely applied in retro-ene reactions.[1] It appears from the numerous relevant contributions, that there is no common mechanism for all the reactions of this kind. In any individual case, the pathway can be purely concerted or radical, however, the former is in most cases preferred. It is also well known that retro-ene reactions under FVT conditions are methods for accessing unsaturated (and often very reactive) species. Indeed, simultaneous formation of vinylketenes and imines in the retro-ene reactions of allenic *N*,*N*-dialkylamides was observed by Wentrup and co-workers,[2] however, related lactams, as expected products of the Staudinger reaction between these reactive systems, were not detected.

We report here that cinnamic amides bearing one or two alkyl groups at the nitrogen atom undergo cyclisation under FVT conditions. According to Wentrup's results, flash vacuum thermolysis of a *N*,*N*-dimethyl cinnamic amide should theoretically afford a benzylketene together with methyl-methylene-amine. However, we found that thermolysis[3] of *N*,*N*-dimethyl 3-phenylacrylamide **1a**, at 950–1000 °C and under a pressure of 1.5×10^{-3} Torr, gave an unexpected result. 1-Methyl-4-phenyl-pyrrolidin-2-one[4] **2a** was found as the exclusive product in 88% yield (Scheme 1). The temperature range was the lowest possible at which the starting material



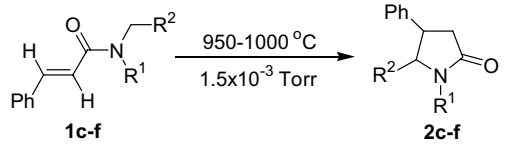
1a R = H
1b R = OMe

2a R = H
2b R = OH

Scheme 1.

was not present in the post-reaction mixture. Similarly, *N*,*N*-dimethyl 3-(4-methoxyphenyl)-acrylamide **1b** underwent cyclisation to afford 1-methyl-4-(4-hydroxyphenyl)-pyrrolidin-2-one[5] **2b** (43%) (Scheme 1). The reaction proceeded with simultaneous dealkylation of the methoxy group.

To determine the limitations of such an approach, various *N*-mono- and *N*,*N*-disubstituted cinnamic amides were investigated. Thus, when amides **1c**–**f** were subjected to FVT in a conventional flow system (950–1000 °C, 1.5×10^{-3} Torr) the expected pyrrolidin-2-ones (γ-lactams) **2c**–**f** were produced in variable yields as diastereoisomeric mixtures. Our results are summarised in Scheme 2 and in the Table 1.



1c-f **2c-f**

Scheme 2.

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* Corresponding author. Tel.: +48 42 635 57 65; fax: +48 42 678 16 09; e-mail: slesniak@chemul.uni.lodz.pl

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Table 1.

Starting amide	Product[a]	Yield[b] (%)	*trans*/*cis* ratio[c]	Ref.
1c: R^1 = Et, R^2 = Me	**2c**: R^1 = Et, R^2 = Me	38	2/1	6
	2e: R^1 = H, R^2 = Me	12	2/1	7
1d: R^1 = Ph, R^2 = Me	**2d**: R^1 = Ph, R^2 = Me	63	2/1	8
1e: R^1 = H, R^2 = Me	**2e**: R^1 = H, R^2 = Me	62	2/1	7
1f: R^1 = H, R^2 = Ph	**2f**: R^1 = H, R^2 = Ph	50	2/1	9

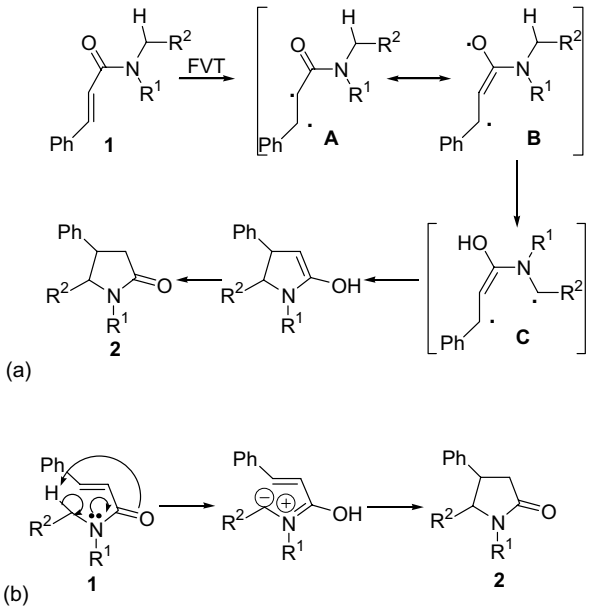
[a] In all cases in crude thermolysis mixtures small amounts of styrene were detected, additionally in the case of **1f**, traces of bibenzyl were observed (^{1}H NMR).
[b] Yields are for pure products isolated by flash chromatography.
[c] Stereochemical assignments of the *trans* and *cis* isomers are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

The formation of the dealkylated product **2e** starting from substrate **1c** can be explained as a result of a secondary retro-ene reaction of **2c**, that is, by the β-elimination reaction of amides. Indeed, when **2c** was re-pyrolysed at about 1050 °C, lactam **2e** was obtained in a pure state.

The *trans* and *cis* isomers of pyrrolidin-2-ones **2** can be easily distinguished[9a] from each other on the basis of the characteristic chemical shifts of protons in the methyl group at C-5 (for **2c**–**e**) or the methine proton at C-5 for **2f**. For *trans* isomers, the protons of the methyl groups at C-5 appear at $\delta \approx 1.1$ ppm, whereas related protons in *cis* isomers resonate at $\delta \approx 0.8$ ppm. Similarly, for the *trans* isomer of **2f** the C-5 proton appears at $\delta = 4.68$ ppm, (d, $J = 6.6$ Hz), whereas that in the *cis* isomer is at $\delta = 5.00$ ppm (d, $J = 7.6$ Hz). Thus, the *trans*/*cis* ratios were determined by integration of the aforementioned signals in the ^{1}H NMR spectra of crude diastereoisomeric mixtures.

Next we examined the reactivity of *N*,*N*-dialkylamides without an aryl substituent at the 3-position of acrylic moiety. Thus, *N*,*N*-dimethyl acrylamide and *trans*-but-2-enoic acid *N*,*N*-dimethyl amide were found to be stable in the whole accessible range of temperatures (up to 1200 °C). On the contrary, 3-methylbut-2-enoic acid *N*,*N*-dimethylamide underwent the retro-ene reaction easily at 1000 °C, with the quantitative formation of 3-methylbut-3-enoic acid *N*,*N*-dimethylamide. These results showed clearly that a phenyl group incorporated into α,β-unsaturated *N*-alkylamides is essential for effecting cyclisation to pyrrolidin-2-ones **2**.

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 step of the reaction (Scheme 3a). In our opinion, the cyclisation can proceed via a biradical process. The biradical **A** is stabilised by an adjacent phenyl group, and by resonance between the canonical forms **A** and **B**, in which an unpaired electron is localised on an oxygen atom. Subsequent intramolecular [1,4]-hydrogen atom transfer via a five-membered transition state, from the *N*-alkyl substituent to an oxyl group (form **B**) results in the formation of a new biradical **C** which cyclises to an unobserved enol, after a low-energy rotation around the C–N bond. Alternatively, an enol biradical **C** could tautomerise to its keto form before closure to give directly the γ-lactam **2** (path not shown in Scheme 3). An analogous hydrogen atom transfer under



Scheme 3.

FVT conditions from the alkylamide group to phenoxyl or thiophenoxyl radicals via a six- or seven-membered transition state has been described by McNab.[10]

Another possible mechanism can be postulated as a process in which the key intermediate is a dipolar species formed via [1,4]-hydrogen atom transfer, and stabilised by the phenyl group in an analogous fashion to a diradical (Scheme 3b).

It was in principle possible that amide **1** could also undergo a retro-ene reaction in line with Wentrup's results, with the formation of a corresponding benzylketene and an imine. An interaction between such highly reactive species would be expected to lead to zwitterionic intermediates which subsequently cyclise to β- or δ-lactams, as has been found in many related reactions.[11] However, none of these products was detected in our experiments.

In order to exclude the formation of γ-lactams as a result of interaction between the species mentioned above, we examined the reaction of benzylketene with benzylidene aniline using an 'acid chloride–imine approach'.[12] This procedure afforded *trans* -3-benzyl-1,4-diphenylazetidin-2-one[13] in moderate yield, but 4,5-diphenylpyrrolidin-2-one was not detected in the post-reaction

mixture. Therefore, the alternative mechanism involving a retro-ene reaction of amide **1** was disproved.

Support for a biradical mechanism came from the thermolysis of 2,*N*,*N*-trimethyl-3-phenylacrylamide **1g**. FVT performed under the aforementioned conditions afforded *trans* and *cis* 1,3-dimethyl-4-phenyl-pyrrolidin-2-one[14] (2:1) in 32% yield, together with a 68% recovery of the starting amide, which was found as an equimolar mixture of *trans*- and *cis*-isomers. The lower yield of γ-lactam and formation of *E*- and *Z*-isomers of the substrate **1g** can be explained by a different stabilisation of the initial biradical. This reversible process produces a benzylic and tertiary carbon-centred biradical, which reacts far less rapidly than the structurally related system with a secondary carbon-centred radical. As a consequence of the greater significance of resonance structure **A** (compared with **B**) easier isomerisation of the starting amide and, at the same time, a lower yield of the cyclisation would be expected, as found.

In summary, a thermal transformation of cinnamic amides into pyrrolidin-2-ones, followed by intramolecular cyclisation, has been demonstrated. Although the products obtained are fairly simple and can be prepared by other methods, it should be noted that this type of cyclisation is reported here for the first time and further applications of this reaction are now being examined. Our results show that flash vacuum thermolysis can provide unexpected results.

Acknowledgements

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3. Flash vacuum thermolysis was carried out in a $30 \times 2.5\ cm^2$ electrically heated horizontal quartz tube packed with quartz rings at 1.5×10^{-3} Torr. The compounds **1** (2 mmol) were slowly sublimed from a flask held at 80 °C into the thermolysis tube preheated to 950–1000 °C. The products were collected in a CO_2–acetone trap. After thermolysis, the system was brought to atmospheric pressure allowing a slow warming up to room temperature and the products were dissolved in $CHCl_3$. The solvent was removed under reduced pressure and the products were purified chromatographically on silica gel and by recrystallisation.
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5. Selected data for compound **2b**: Purified by chromatography (silica gel, hexane:AcOEt 1:1). Mp 112–114 °C (hexane). IR (KBr, cm^{-1}): ν_{OH} 3385, $\nu_{C=O}$ 1675. ^1H NMR (200 MHz, $CDCl_3$, TMS): $\delta = 2.47–2.80$ (m, 2H), 2.90 (s, 3H), 3.25–3.75 (m, 3H), 6.70–7.10 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$, TMS): $\delta = 29.82$ (NCH_3), 36.57 (CH), 39.13 (CH_2), 57.37 (CH_2), 116.23, 127.93 ($2 \times C_{ar}$), 133.52, 156.36 ($2 \times C_{q\ ar}$), 175.42 (C=O). Anal. Calcd for $C_{11}H_{13}NO_2$ (191.23): C, 69.09; H, 6.85; N, 7.32. Found: C, 69.22; H, 6.84; N, 7.11.
6. Selected data for compounds **2c**. The isomers were separated chromatographically (silica gel, hexane:AcOEt): *cis*-1-ethyl-5-methyl-4-phenyl-pyrrolidin-2-one. Mp 106–108 °C (hexane/dichloromethane). IR (KBr) $\nu_{C=O}$ 1680 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz, TMS) $\delta = 0.78$ (d, $J = 7.6$ Hz, 3H), 1.11 (t, $J = 7$ Hz, 3H), 2.50–3.25 (m, 3H), 3.45–4.15 (m, 3H), 7.10–7.50 (m, 5H). ^{13}C NMR ($CDCl_3$, 50 MHz, TMS) $\delta = 13.04$ (CH_3), 14.90 (CH_3), 35.48 ($2 \times CH_2$), 42.72 (CH), 57.19 (CH), 127.48, 128.39, 128.91 (C_{ar}), 139.33 (C_q), 174.17 (C=O). MS (70 eV); *m*/*z* (%): 203 (4), 175 (45, $M^+ - C_2H_4$), 117 (7), 105 (10), 104 (100), 103 (23), 77 (11). HRMS *m*/*z* calcd for $C_{13}H_{17}NO$ 203.13101, found 203.13093. Anal. Calcd for $C_{13}H_{17}NO$ (203.29): C, 76.81; H, 8.43; N, 6.89. Found: C, 76.88; H, 8.56; N, 6.76. *trans*-1-Ethyl-5-methyl-4-phenyl-pyrrolidin-2-one. Mp 115–117 °C (hexane/dichloromethane). IR (KBr) $\nu_{C=O}$ 1680 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz, TMS) $\delta = 1.11$ (d, $J = 6.6$ Hz, 3H), 1.24 (t, $J = 7$ Hz, 3H), 2.40–3.90 (m, 6H), 7.10–7.50 (m, 5H). ^{13}C NMR ($CDCl_3$, 50 MHz, TMS) $\delta = 17.66$ (CH_3), 20.55 (CH_3), 35.51 (CH_2), 39.46 (CH_2), 49.86 (CH), 57.83 (CH), 127.48, 127.57, 129.21 (C_{ar}), 141.40 (C_q), 176.97 (C=O). MS (70 eV); *m*/*z* (%): 203 (4), 175 (49, $M^+ - C_2H_4$), 117 (9), 105 (12), 104 (100), 103 (23), 77 (11). HRMS *m*/*z* calcd for $C_{13}H_{17}NO$ 203.13101, found 203.13089. Anal. Calcd for $C_{13}H_{17}NO$ (203.29): C, 76.81; H, 8.43; N, 6.89. Found: C, 76.84; H, 8.31; N, 6.72.
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8. Selected data for compound **2d**. Purified by chromatography (silica gel, hexane:AcOEt 1:1). As a diastereoisomeric mixture. IR (neat): $\nu_{C=O}$ 1693 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz, TMS) $\delta = 0.84$ (d, $J = 7.6$ Hz, 3H, *cis*), 1.21 (d, $J = 6.5$ Hz, 3H, *trans*), 2.65–3.30 (m, 2H), 3.70–4.05 (m, 1H,), 4.07–4.30 (m, 1H, *trans*) 4.35–4.72 (m, 1H, *cis*) 7.15–7.60 (m, 10H). ^{13}C NMR ($CDCl_3$, 50 MHz, TMS) $\delta = 14.11$(CH_3, *cis*), 19.09 (CH_3, *trans*), 36.03 (CH_2, *cis*), 39.64 (CH_2, *trans*) 42.32 (CH, *cis*), 46.76 (CH, *trans*), 59.89 (CH, *cis*), 63.21 (CH, *trans*), 126.19, 126.48, 127.57, 127.69 128.30, 129.00, 129.33 (C_{ar}), 137.81, 138.30, 138.76, 141.95 ($4 \times C_q$), 173.23 (C=O, *trans*), 173.60 (C=O, *cis*). Anal. Calcd for $C_{17}H_{17}NO$ (251.33): C, 81.24; H, 6.82; N, 5.57. Found: C, 81.01; H, 7.06; N, 5.29.
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