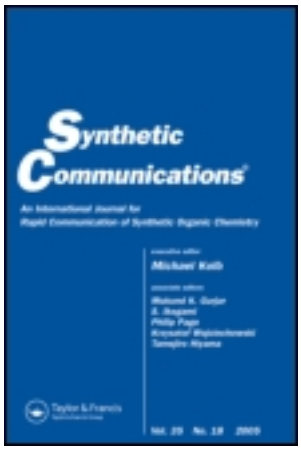

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SUCCESSFUL THERMAL REARRANGEMENTS OF ACRYLENAMIDES TO GIVE TETRAHYDRO-2-PYRIDONES UNDER FVT CONDITIONS

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SUCCESSFUL THERMAL REARRANGEMENTS OF ACRYLENAMIDES TO GIVE TETRAHYDRO-2-PYRIDONES UNDER FVT CONDITIONS

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ABSTRACT

Enamides of α,β-unsaturated acids are theoretically capable of electrocyclisation to give tetrahydro-2-pyridones. The only successful method reported for this conversion involved photochemical activation. We would like to present new and effective method for this transformation using flash vacuum thermolysis.

Nitrogen-containing six-membered ring systems, such as the piperidines and decahydroquinolines have been popular synthetic targets due to the array of potent biological activities of these compounds. From a number of methods of synthesis our attention has been attracted to the reaction of imines with activated acrylate derivatives. It was found

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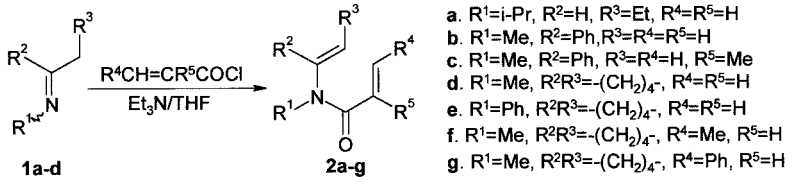
by Stille[1a] and earlier by Hicmott[1b] that 1,2,3,4-tetrahydro-2-pyridones or 3,4,5,6,7,8-hexahydro-2(1*H*)-quinolinones can be prepared by the aza-annulation of imines with acrylate derivatives. Generally, the reaction of acryloyl chloride with imines in the presence of the base (Et_3N) resulted in the formation of acrylenamides, whereas in the absence of triethylamine δ-lactams were formed. However, the chemical cyclisation failed when it was applied to synthesis of natural products.[2] Although the transformation of acrylenamides to tetrahydro-2-pyridones or hexahydro-2(1*H*)-quinolinones has been attempted using a number of thermal, protic and Lewis acidic conditions, the only successful method involved photolysis.[3]

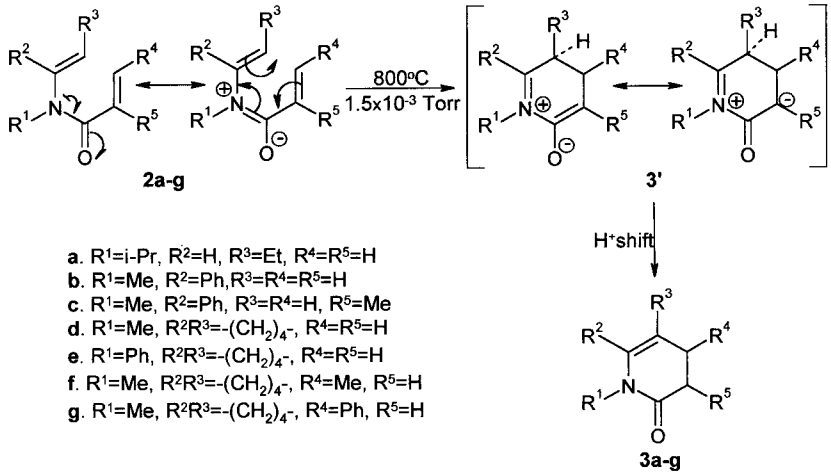
In our work we wish to present a simple and efficient method for this conversion, which seems to be general and revises existing opinion regarding the exceptional thermal stability of acrylenamides. In our laboratory we have investigated the behaviour of enamides of α,β-unsaturated acids under FVT conditions, particularly their possibility to undergo, electrocyclisation.

The required compounds were prepared by *N*-acylation of imines. The reaction of imines **1a–d** with α,β-unsaturated acid chlorides in the presence of triethylamine under standard conditions[1a] afforded corresponding enamides **2a–g** (Scheme 1).



Scheme 1.

All prepared compounds represents the wide range of starting materials which could define the scope and limitations of the method, particularly the influence of substituents in acryloyl and vinyl moiety. The enamides **2a–g** were thermolysed in FVT conditions at 800°C under pressure 1.5×10^{-3} Torr. The temperature 800°C was chosen as the lowest possible at which the starting material was not present in the reaction mixture after thermolysis. We found that thermolyses of **2a–g** resulted in the formation of 1,2,3,4-tetrahydro-2-pyridones **3a–c** or 3,4,5,6,7,8-hexahydro-2(1*H*)-quinolinones **3d–g**, respectively, as the exclusive products of the reaction in high yield (Scheme 2).



Scheme 2.

None of products **3** contain two asymmetric carbon atoms, therefore the formation of diastereoisomers is not possible.

The formation of **3** can be rationalised in terms of an initial formation of 1,4-dipole **3′** by electrocyclic rearrangement of **2**. The resulting betaines undergo a subsequent proton shift (probably as [1,5] shift[4a]) to generate **3**. The last reaction is well known[4a,4b,3] for a variety cyclic betaines.

Compounds **3a–g** were purified by flash chromatography on neutral Al_2O_3 and identified by spectral methods. The yields of crude products were excellent, but purification on Al_2O_3 caused their decomposition and final yields were around 50% (use of silica gel resulted in a much higher loss of the products). The rearrangement occurred easily and the substituents in acryloyl and vinyl moiety were of insignificant consequence. This makes our method more general in comparison with aza-annulation, which is considerably affected by the substituents. Although, our results can be rationalized by an electrocyclisation or the formation of the diradical, the last is unlikely considering of the selectivity of the reaction and literature data which showed that the photolytic reaction of *N*-(α,β-unsaturated carbonyl)thioamides proceeded as a diradical process and led to different products.[5]

In conclusion, we have found that enamides of α,β-unsaturated acids can undergo electrocyclic cyclisations under FVT conditions at 800°C. In contrast to the aza-annulation pathway no effects of the substituents in the starting enamides were observed.

EXPERIMENTAL

General

Infrared (IR) absorption spectra were performed on a Specord-75 spectrophotometer. The band frequencies are reported in cm^{-1}. ^1H NMR and ^{13}C NMR spectra ($CDCl_3$) were recorded on a Tesla 487 (80 MHz) or a Varian Gemini 200 (200, 50.4 MHz for ^{13}C) apparatus using TMS as an internal standard.

Starting Materials

All starting materials were prepared according to described procedures: butylidene-isopropylamine (**1a**),[1a] methyl-(1-phenyl-ethylidene)-amine (**1b**),[6a] cyclohexylidene-methyl-amine (**1c**),[6b] *N*-cyclohexylidene-aniline (**1d**)[6c] and *N*-isopropyl-*N*-vinyl-acrylamide (**2a**).[1a]

General Procedure for the Preparation of Enamides 2b–g[1a]

To 40 ml of dry THF were added the imine (8 mmol) and Et_3N (1.21 g, 12.0 mmol) at 0°C. The appropriate α,β-unsaturated acid chloride (9.0 mmol) was added slowly to this solution at 0°C. After the addition was complete, the resulting mixture was stirred at rt. for 4 h. Solids were removed from the mixture by filtration and were then washed thoroughly with Et_2O. The combined filtrate was concentrated, and the corresponding enamide was isolated by column chromatography on neutral Al_2O_3 (hexane/AcOEt 9 : 1). Reported yields refer to isolated products.

2b: (90%) IR (film): 1665, 1605. ^1H NMR: 3.08 (s, 3H), 5.16 (bs, 1H), 5.40–5.65 (m, 1H), 5.67 (bs, 1H), 6.35–6.57 (m, 2H), 7.37 (bs, 5H).

2c: (87%) IR (film): 1670, 1610. ^1H NMR: 1.73–1.83 (m, 3H), 3.12 (s, 3H), 4.95–5.05 (m, 1H), 5.08 (bs, 1H), 5.18–5.30 (m, 1H), 5.45 (bs, 1H), 7.30–7.50 (m, 5H).

2d: (93%) IR (film): 1665, 1605. ^1H NMR: 1.45–1.76 (m, 4H), 1.76–2.33 (m, 4H), 3.02 (s, 3H), 5.43–5.73 (m, 2H), 6.33–6.50 (m, 2H).

2e: (95%) IR (film): 1640, 1620. ^1H NMR: 1.58–1.83 (m, 4H), 1.90–2.33 (m, 4H), 5.47–5.83 (m, 2H), 6.29–6.50 (m, 2H), 7.18–7.29 (m, 5H).

2f: (52%) IR (film): 1650, 1620. ^1H NMR: 1.50–1.93 (m, 4H), 1.82 (dd, $J = 1.5$ and 7 Hz, 3H), 1.94–2.45 (m, 4H), 3.02 (s, 3H), 5.54–5.71 (m, 1H), 6.14 (dq, $J = 1.5$ and 15 Hz, 1H), 6.98 (dq, $J = 7$ and 15 Hz, 1H).

2g: (91%) IR (film): 1670, 1625. ^{1}H NMR: 1.50–1.83 (m, 4H), 2.00–2.27 (m, 4H), 3.07 (s, 3H), 5.58–5.75 (m, 1H), 6.76 (d, $J = 16$ Hz, 1H), 7.17–7.52 (m, 5H), 7.66 (d, $J = 16$ Hz, 1H).

General Procedure for Flash Vacuum Thermolysis

The Flash vacuum thermolyses were carried out in a 30×2 cm horizontal quartz tube packed with quartz rings, electrically heated to 800°C at 1.5×10^{-3} Torr. Compounds **2a–g** were slowly distilled from a flask held at 60°C into the thermolysis tube. The products were collected in a CO_2/acetone trap. After thermolysis, the system was brought to atmospheric pressure, allowing a slow warm up to room temperature and the products were dissolved in CH_2Cl_2. The solvent was removed under reduced pressure and the crude products, obtained in practically quantitative yield, were purified by flash chromatography on neutral Al_2O_3 with hexane: AcOEt (75 : 25) mixture.

Syntheses of compounds **3a**,[1a] **3b**,[7a] **3d**,[7b] and **3e**[7c] by other methods were described earlier but no spectral data for **3b** and **3d**. Spectroscopic details for **3a** and **3e** were identical to those reported.[1a,7c] For **3b** and **3e** the authors didn't submit the spectral data of these products, that's why they are presented below.

5-Ethyl-1-isopropyl-3,4-dihydro-1*H*-pyridin-2-one (3a).[1a] Yield: 55%.

1-Methyl-6-phenyl-3,4-dihydro-1*H*-pyridin-2-one (3b).[7a] Yield: 51%. IR (film): 1680, 1610. ^{1}H NMR: 2.10–2.75 (m, 4H). 2.90 (s, 3H), 5.29 (dd, $J = 4.5$ and 9.5 Hz, 1H), 7.15–7.62 (m, 5H). ^{13}C NMR: 19.88, 31.83, 32.01, 109.08, 127.99, 128.54, 128.72, 136.54, 143.71, 172.05. Anal. Calcd for $C_{12}H_{13}NO$: C, 76.96; H, 6.99; N, 7.48. Found: C, 76.81; H, 7.02, N; 7.20.

1,3-Dimethyl-6-phenyl-3,4-dihydro-1*H*-pyridin-2-one (3c). Yield: 53%. IR (film): 1670, 1625. ^{1}H NMR: 1.25 (d, $J = 6$ Hz, 3H), 2.10–2.43 (m, 3H), 2.88 (s, 3H), 5.30 (dd, $J = 4.5$ and 6.5 Hz, 1H), 7.18–7.50 (m, 5H). ^{13}C NMR: 15.57, 28.00, 32.35, 35.63, 108.35, 127.93, 128.51, 128.75, 136.78, 143.35, 175.06. Anal. Calcd for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.33; H, 7.46; N, 6.73.

1-Methyl-3,4,5,6,7,8-hexahydro-1*H*-quinolin-2-one (3d).[7b] Yield: 49%. IR (film): 1675, 1620. ^{1}H NMR: 1.45–1.80 (m, 4H), 1.95–2.20 (m, 6H), 2.30–2.60 (m, 2H), 3.10 (s, 3H). ^{13}C NMR: 22.22, 23.05, 25.48, 25.78, 28.06, 29.00, 31.61, 114.47. 132.04, 170.65. Anal. Calcd for $C_{10}H_{15}NO$: C, 72.69; H, 9.15; N, 8.48. Found: C, 72.60; H, 8.98; N, 8.21.

1-Phenyl-3,4,5,6,7,8-hexahydro-1*H*-quinolin-2-one (3e).[7c] Yield: 57%.

1,4-Dimethyl-3,4,5,6,7,8-hexahydro-1*H*-quinolin-2-one (3f). Yield: 49%. IR (film): 1665, 1610. ^{1}H NMR: 0.93 (d, $J = 7$ Hz, 3H), 1.53–1.75 (m, 4H),

1.95–2.15 (m, 5H), 2.35–2.45 (m, 2H), 3.00 (s, 3H). ^{13}C NMR: 17.24, 22.38, 23.04, 24.84, 25.87, 27.12, 30.77, 39.10, 119.42, 139.63, 170.13. Anal. Calcd for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.58; H, 9.63; N, 7.80.

1-Methyl-4-phenyl-3,4,5,6,7,8-hexahydro-1*H*-quinolin-2-one (3g). Yield: 54%. IR (film): 1670, 1610. ^{1}H NMR: 1.33–2.40 (m, 9H), 2.58–2.87 (m, 2H), 3.05 (s, 3H), 7.10–7.30 (m, 5H). ^{13}C NMR: 21.16, 21.86, 24.93, 2 × 26.91, 38.25, 41.23, 115.38, 125.99, 126.47, 127.87, 131.82, 140.95, 168.12. Anal. Calcd for $C_{16}H_{19}NO$: C, 79.63; H, 7.93; N, 5.81. Found: C, 79.61; H, 7.82; N, 5.53.

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