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Photoreductive Cyclization of N,N-Dialkyl-β-Oxoamides: Synthesis of Piperidines and δ-Lactams

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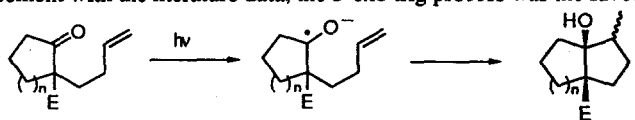
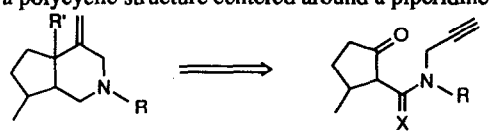
Abstract: The photoreductive cyclization of N,N-unsaturated dialkyl-β-oxoamides produced δ-lactams in good yields. On the contrary the photoreductive cyclization of N,N-unsaturated dialkyl-β-aminoketones produced substituted piperidines in poor yields.

Recently, we described that bicyclic cycloalkanols were prepared in good yields by an intramolecular radical addition, using a photochemically induced electron transfer from hexamethylphosphoramide (HMPA) or triethylamine (NEt_3) in acetonitrile to δ,ε-unsaturated ketones [1]. The reaction was stereo-, chemo- and regioselective. In agreement with the literature data, the 5-exo trig process was the favoured one [2].



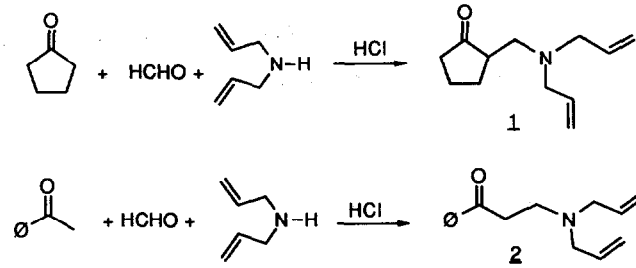
A great variety of alkaloids, such as monoterpenic alkaloids (e.g.: actinidine, tecomanine, isooxyskytanthine) possess a polycyclic structure centered around a piperidine ring such as A.



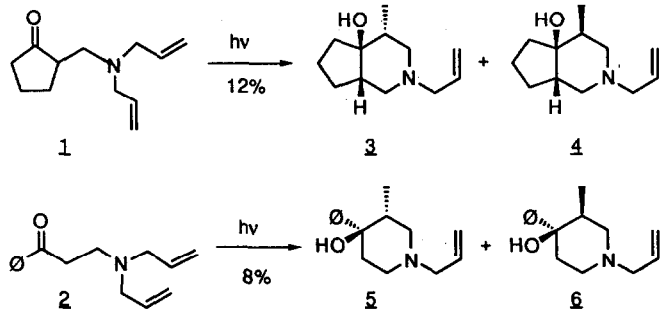
The synthesis of systems such as A can thus be envisioned to result from the irradiation of N,N-unsaturated dialkyl-β-aminoketones or N,N-unsaturated dialkyl-β-oxoamides of type B in the presence of an electron donor.

Results

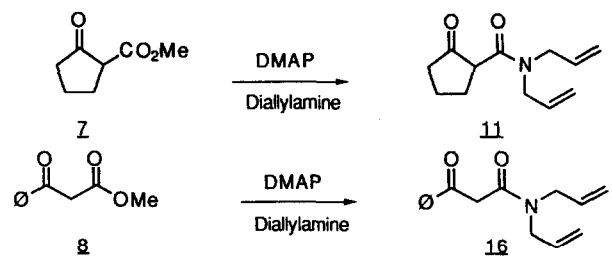
The synthesis of N,N-unsaturated dialkyl-β-aminoketones 1 and 2 was accomplished by condensing the corresponding ketones with formaldehyde and N,N-diallylamine hydrochloride via a Mannich reaction [3].



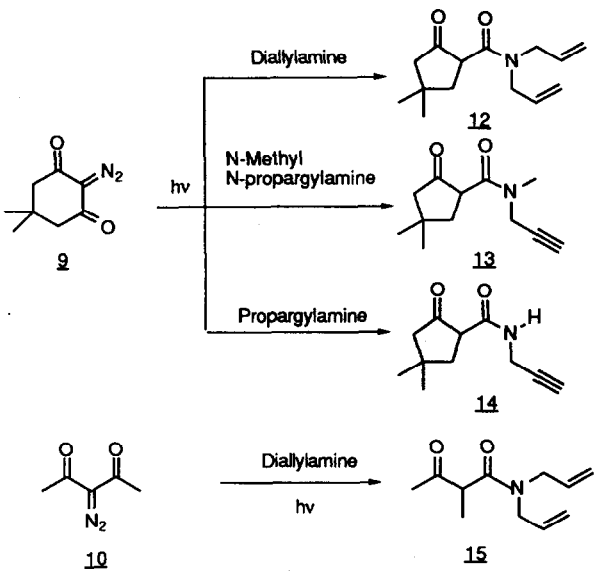
Compounds 1 and 2 were irradiated in acetonitrile (3×10^{-2} M) in the presence of NEt_3 (10 equiv) in a quartz vessel (low pressure mercury lamp; 254 nm; 3 hours). Under these conditions, 1 afforded two isomeric products 3 and 4 (12 % in a ratio 9:1) [4]. In the case of 2 a 1.7:1 mixture of the substituted piperidines 5 and 6 [5] was obtained in only 8% yield, together with polymeric material and unreacted (ca. 20%) starting material.



The β-ketoamides 11 and 16 were synthesized in the following way. Treatment of the β-ketoesters 7 and 8 with N,N-diallylamine in the presence of a catalytic amount of DMAP (4-dimethylaminopyridine) in refluxing toluene [6] produced the corresponding β-ketoamides 11 and 16 in 80% and 85% yield respectively.



An alternative approach for the preparation of β-ketoamides 12-15 involved a Wolff rearrangement [7] as shown below. Irradiation of diazodiketone 9 at 254 nm in the presence of a primary or secondary amine led to the formation of the corresponding β-ketoamides 12-14. In the case of 13, two rotamers were detected in its NMR spectra. Similarly, the irradiation of 10 with N,N-diallylamine provided β–ketoamide 15 (70%).



The irradiation of β-ketoamides 11-15, under photoreductive conditions, in acetonitrile (5×10^{-2} M) in the presence of NEt3 (10 equiv) gave the products 17-23 shown in the Scheme.

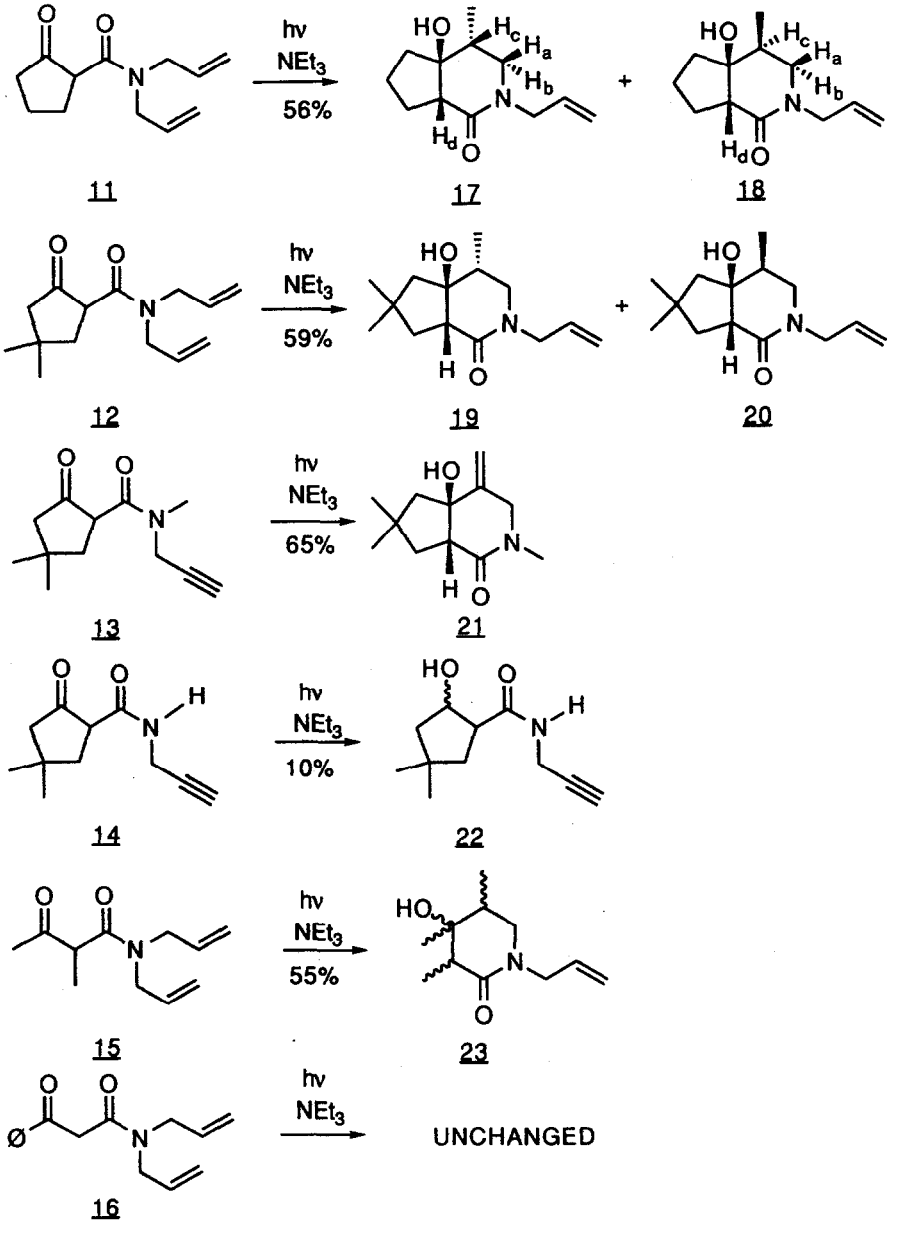
Starting from 11, a 1.8:1 mixture of the bicyclic lactams 17 and 18 was obtained. These compounds could be separated on tlc (silica gel) and their structures were determined by spectroscopic analysis. The relative configurations of compounds 17 and 18 were established by their ^{1}H NMR spectra with the help of nOe experiments and by determining the coupling constants between protons Ha, Hb, Hc and Hd. A trans relative configuration of the substituents of the bridgehead centers C(1) and C(6) of 17 and 18 would be prohibitive for the five-membered ring [8]. Furthermore MM2 force-field calculations have shown that the strain energy of the transition state structure for the trans ring closures was markedly higher than that of their cis counterparts [9].

In compound 17, the cis relationship between the methyl group and Hb was established by nOe experiments. Irradiation of the methyl group of protons led to a 10% increase in the integration of the signal attributed to Hb (δ_H = 2.90 ppm) and to a 5% increase in the integration of the signal attributed to Ha (δ_H = 3.05 ppm). The signal for Hd (δ_H = 2.77 ppm) is broadened because of coupling with protons Hc (δ_H = 2.04 ppm) and Ha. The vicinal coupling constants between Ha, Hb and Hc are as follows: for Ha-Hc : J = 5.0 Hz, for Ha-Hb: J = 13.0 Hz and for Hb-Hc: J = 12.0 Hz. A trans relative configuration of the methyl group and of the hydroxyl group was deduced from these data.

In compound 18, irradiation of the ^{1}H NMR signal of the methyl group of protons showed a 15% increase in the integration of the signal attributed to Ha (δ_H = 2.87 ppm) and a 5% increase only of the integration of the signal attributed to Hb (δ_H = 2.85 ppm). In this product the coupling constants between Ha, Hb and Hc are as follows: for Ha-Hc: J = 8.0 Hz, for Ha-Hb: J = 12.5 Hz and for Hb-Hc: J = 4.0 Hz. This confirmed that the methyl and the hydroxyl groups in 18 have a cis relationship.

The irradiation of 12 under the photoreductive conditions led to the formation of a 2.3:1 mixture of 19 and 20. The relative configurations of these two products were deduced from their ^{1}H NMR spectra and by

SCHEME: Irradiation of N,N-dialkyl-β-oxamides.



comparison of the coupling constants between Ha, Hb and Hc with those measured in the ^1H NMR spectra of 17 and 18.

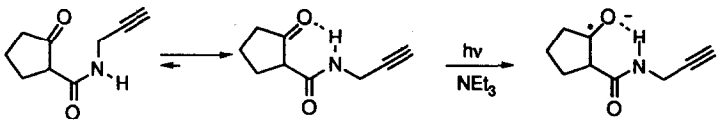
The photocyclization of 13 (Scheme) led to a single product 21 (isolated in 65% yield), the structure of which was established from its spectral data (see the experimental section).

In the case of the acyclic β-ketoamide 15 a mixture of stereoisomers 23 was obtained in 55% yield. With N-propargyl-β-ketoamide 14, no trace of the bicyclic lactam could be seen in the crude reaction mixture. Most of the starting material was recovered together with 10% of isomeric alcohols 22. A similar observation was made with 16, for which no cyclized product was detected after 5 hours of irradiation (90% of the starting material was recovered under these conditions).

These experiments demonstrate that when this photocyclization process is successful, the photoreductive cyclization is highly regioselective. In agreement with literature data, the 6-exo trig process and the 6-exo dig process were the favoured modes of cyclization [2].

Discussion

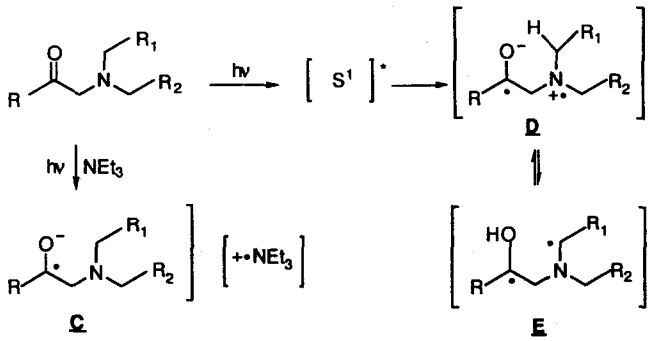
The N-propargyl-β-ketoamide 14 did not lead to the expected cyclized product. Instead, photoreduction of compound 14 was observed, providing alcohols 22 in 10% yield. The low reactivity of this compound can be interpreted in terms of species in which intramolecular hydrogen bonding occurs between the hydrogen of the amide moiety and the ketone group. This may lead to an efficient deactivation of the excited state of the carbonyl chromophore. It also favours an *s-trans* conformation for the N-propargylamide moiety which retards the addition of the intermediate radical-anion 24 onto the acetylenic group.



14 *s-cis* 14 *s-trans* 24

The non-reactivity of 16 is probably due to the favorable enolization of this ketone in acetonitrile, a property established by its ^1H NMR spectrum.

Even if the irradiation of N,N-dialkylamino-β-ketoamides 11-13 and 15 and N,N-dialkylaminoketones 1-2 produced the desired cyclized products, we have to recognize that the yields are much lower in the case of N,N-dialkylaminoketones than for N,N-dialkyl-β-ketoamides. In the case of aminoketones, two processes can compete with the desired reductive cyclization. The first one is an intermolecular transfer of an electron from the triethylamine to the carbonyl moiety of the aminoketone to produce the radical-anion C. The second one is an intramolecular electron transfer from the nitrogen center of the amino group of 1 and 2 to the carbonyl group. This intramolecular process is probably faster than the intermolecular one. We suggest that the intermediate produced via the intramolecular electron transfer would form an ion pair or a zwitterion D. Transfer of a proton from the N-alkyl group to the ketyl radical followed by electron reorganization would produce a 1,4-diradical E. Proton transfer occurring in D should be highly favorable because the zwitterionic character of this intermediate should enhance both the nucleophilicity of the carbonyl oxygen atom and the electrophilicity of the proton α to the nitrogen. A back electron transfer from D is also possible.



In the case of amides, the intramolecular transfer is suppressed because acylation of the amines raises the ionization energy of the n electrons of the nitrogen moiety [10, 11]. Consequently, yields of the cyclized products are substantially increased.

Conclusion

The photoinduced reductive cyclization of N,N-unsaturated dialkylaminoketones led to substituted piperidines in poor yields. In contrast, the corresponding non-enolized N,N-diallyl and N-methyl-N-propargyl-β-ketoamides produced the corresponding 6-hydroxy-3-azabicyclo[4.3.0]nonan-2-ones in yields up to 50%. Thus, the photoreductive cyclization of β-ketoamides may become a convenient method for the preparation of monoterpenic alkaloids [12].

EXPERIMENTAL SECTION

All experiments were run under an argon atmosphere. ^1H NMR spectra were recorded at 300 MHz, ^{13}C NMR spectra at 75 MHz in $CDCl_3$. Chemical shift data for ^1H and ^{13}C NMR spectra were measured relative to tetramethylsilane. Chemical shifts are reported in ppm and coupling constants in Hz. IR spectra were recorded on a Pye Unicam spectrometer. THF was distilled from sodium / benzophenone. Toluene, acetonitrile (CH_3CN) and triethylamine (NEt_3) were distilled from CaH_2. Flash chromatography was carried on Kieselgel 60 (230-400 mesh) and preparative tlc on Merck silica Kielselgel 60 PF 254-366 nm.

Synthesis of β-aminoketones [3].

Paraformaldehyde (1.5g, 50 mmol, 0.5 equiv) was added to a solution of ketone (100 mmol, 1 equiv) diallylamine (9.71g, 100 mmol, 1 equiv) and hydrochloric acid (5N, 14.6 mL) in ethanol (24 mL). After 3 h reflux, more paraformaldehyde (1.5g, 50 mmol, 0.5 equiv) was added. After heating under reflux for 14 h, the solution was evaporated in *vacuo*. $CHCl_3$ (10 mL) and then hydrochloric acid 1N (10 mL) were added to the aqueous phase. The aqueous phase was separated and treated with concentrated aqueous solution of Na_2CO_3 (10 mL). It was then extracted with $CHCl_3$. The organic phase was dried over $MgSO_4$ and evaporated in *vacuo*.

2-(Diallylaminomethyl) cyclopentanone 1. Yield = 43%. IR (film): 1730; 1700; 1640;1450; 1400; 1150; 996 cm^{-1}. ^1H NMR: δ 1.61-2.50 (m, 8H); 2.52-2.89 (m, 1H); 2.91-3.06 (m, 2H); 3.14-3.27 (m, 2H); 5.06-5.21 (m, 4H); 5.27-5.91 (m, 2H). ^{13}C NMR: δ 20.5 (t); 29.5 (t); 38.1 (t); 47.9 (d); 53.1 (t); 56.9 (t); 117.1 (2t); 135.4 (2d); 220.3 (s). MS m/e = 193 (M^+, 10); 164 (30); 152 (20); 110 (100); 96 (18); 81 (10); 41 (70). High resolution MS calcd.: 193.1466. Found: 193.1472.

2-(Diallylaminomethyl) acetophenone **2** [3]. Purification by flash chromatography. Rf = 0.3 (CH_2Cl_2 / EtOAc: 90 / 10). Yield : 54%. IR: 1690; 1680; 1640; 1600; 1450; 1000 cm^{-1}. ^1H NMR: δ 2.50-3.25 (m, 6H); 5.00-5.35 (m, 4H); 5.50-6.15 (m, 2H); 7.25-8.25 (m, 5H). ^{13}C NMR: δ 36.4 (t); 48.4 (t); 56.9 (t); 117.4 (2t); 127.9 (2d); 128.4 (2d); 132.8 (d); 135.4 (2d); 136.9 (s); 199.3 (s). MS m/e = 229 (M^+, 1); 202 (6); 188 (100); 110 (90); 105 (60); 77 (40).

Synthesis of β-ketoamides

Method A: The amine (2-5 eq) was added to a degassed solution of 2-diazo-1,3-dione [13] (3 mmol, 1 equiv) in acetonitrile (60 mL, 5 x 10^{-2} M). The solution was irradiated at 254 nm in a merry-go-round system equipped with 12 low-pressure mercury Philips TUV 15 lamps. 10 mm o.d. quartz tubes were used. After evaporation of the solvent, the crude material was purified by flash chromatography.

Method B: A solution of β-ketoester (20 mmol, 1 equiv) amine (40 mmol, 2 equiv) and 4-dimethylaminopyridine (4-DMAP) (6 mmol, 0.3 equiv) in toluene (16 mL) was heated under reflux for 16 h. The solvent was evaporated under reduced pressure and the residue purified by flash chromatography on silica gel.

N,N-Diallyl-2-oxocyclopentanecarboxamide **11**. Prepared according to method B. Purification by flash chromatography. Rf = 0.30 (AcOEt / hexane: 20 / 80). Yield = 80%. IR: 1730; 1625; 1470; 1405; 1310; 1290; 1200; 990; 920 cm^{-1}. ^1H NMR: δ 1.80-2.60 (m, 6H); 3.35-3.45 (t, *J* = 2.0 Hz, 1H); 3.65-3.90 (m, 2H); 4.25-4.40 (m, 2H); 5.10-5.25 (m, 4H); 5.65-5.90 (m, 2H). ^{13}C NMR: δ 21.1 (t); 27.6 (2t); 38.72 (t); 48.4(t); 49.4 (d); 116.5 (t); 117.0 (t); 132.8 (d); 133.4 (d); 169.1 (s); 214.8 (s). MS m/e = 209 (M^+, 15); 208 (90); 207 (15); 166 (30); 152 (30); 124 (22); 111 (42); 98 (40); 97 (55); 96 (100); 70 (50); 56 (100). Anal. calcd. for $C_{12}H_{17}NO_2$: C 69.53; H 8.27; N 6.76. Found: C 69.56; H 8.29; N 6.81.

N,N-Diallyl-4,4-dimethyl-2-oxocyclopentanecarboxamide **12**. Prepared according to method A from 2-diazodimedone and diallylamine (3 equiv). Purification by flash chromatography (AcOEt / hexane: 20 / 80). Yield = 91%. IR: 1740; 1650; 1635; 1470; 1415; 1370; 1305; 1285; 1125; 990; 925 cm^{-1}. ^1H NMR: δ 1.03 (s, 3H); 1.25 (s, 3H); 1.89-1.98 (m, 1H); 2.15 (d, *J* = 17.5 Hz, 1H); 2.25 (d, *J* = 17.5 Hz, 1H); 2.41-2.51 (m, 1H); 3.61 (dd, *J* = 10.5 and 8.0 Hz, 1H); 3.65-3.88 (m, 2H); 4.25-4.38 (m, 2H); 5.10-5.25 (m, 4H); 5.67-5.88 (m, 2H). ^{13}C NMR: δ 28.1 (q); 29.1 (q); 34.4 (s); 41.0 (t); 48.5 (t); 49.4 (t); 51.5 (d); 53.5 (t); 116.5 (t); 117.0 (t); 132.7 (d); 133.3 (d); 169.0 (s); 214.1 (s). MS m/e = 235 (M^+, 30); 152 (27); 139 (22); 98 (22); 97 (33); 96 (100); 70 (20); 56 (94); 55 (33). Anal. calcd. for $C_{14}H_{21}NO_2$: C 71.45; H 8.99; N 5.95. Found: C 71.49; H 9.01; N 5.97.

N-Methyl-N-propargyl-4,4-dimethyl-2-oxocyclopentanecarboxamide **13**. Prepared according to method A from 2-diazodimedone and N-methyl-N-propargylamine (3 equiv). Purification by flash chromatography (AcOEt / hexane: 20 / 80). Yield = 88%. Two rotamers are present, their ratio was determined by ^1H NMR in $CDCl_3$ at 20° C (1.8 : 1). IR: 3310; 1740; 1640; 1460; 1400; 1370; 1340; 1280; 1110 cm^{-1}. ^1H NMR: - Major rotamer: δ 1.00 (s, 3H); 1.17 (s, 3H); 3.15 (s, 3H). - Minor rotamer: δ 1.01 (s, 3H); 1.17 (s, 3H); 2.97 (s, 3H). - For the two rotamers: δ 1.87-2.45 (m, 5H); 3.60-3.72 (m, 1H), 3.80-4.60 (m, 2H). ^{13} C NMR: - Major rotamer: δ 28.1 (q); 29.1 (q); 34.3 (s); 35.0 (q); 36.9 (t); 40.6 (t); 51.4 (d); 53.5 (t); 72.0 (d); 78.6 (s); 168.5 (s); 213.6 (s). - Minor rotamer: δ 28. 1 (q); 29.1 (q); 34.1 (q); 34.3 (s); 39.6 (t); 40.6 (t); 51.4 (d); 53.5 (t); 73.0 (d); 78.3 (s); 168.1 (s); 213.3 (s). MS m/e = 207 (M^+, 17); 124 (73); 123 (18); 97 (10); 70 (15); 69 (16); 68 (100); 55 (33). Anal. calcd.for $C_{12}H_{17}NO_2$: C 69.54; H 8.26; N 6.75. Found: C 69.43; H 8.23; N 6.76.

N-Propargyl-4,4-dimethyl-2-oxocyclopentanecarboxamide 14. Prepared according to method A from 2-diazodimedone and N-propargylamine (3 equiv). Purification by flash chromatography (AcOEt / hexane: 15 / 85). Yield 71%. IR (CCl_4) = 3380; 3310; 1735; 1670; 1520; 1460; 1400; 1370; 1280; 1130 cm^{-1}. ^1H NMR: δ 1.06 (s, 3H); 1.17 (s, 3H); 2.00-2.45 (m, 5H); 3.20 (t, *J* = 2.0 Hz; 1H); 3.82-3.93 (m, 2H); 7.00 (sl, 1H). ^{13}C NMR: δ 27.8 (q); 28.8 (q); 29.3 (t); 34.0 (s); 39.3 (t); 52.6 (t); 53.6 (d); 71.6 (d); 79.4 (s); 116.2 (s); 216.1 (s). MS m/e = 193 (M^+, 12); 178 (17); 123 (10); 110 (100); 97 (25); 56 (55); 54 (20). Anal. calcd. for $C_{11}H_{15}NO_2$: C 68.36; H 7.82; N 7.25. Found: C 68.17; H 7.71; N 7.21.

N,N-Diallyl-2-methyl-3-oxobutanamide 15. Prepared according to method A from 3-diazopentan-2,4-dione and diallylamine. Purification by flash chromatography. Rf = 0.4 (AcOEt / hexane: 30 / 70). Yield = 70%. IR: 1700; 1620; 1450; 1420; 1405; 1350; 980; 910 cm^{-1}. ^1H NMR: δ 1.37 (d, *J* = 7.0 Hz, 3H); 2.37 (s, 3H); 3.60 (q, *J* = 7.0 Hz, 1H); 3.81-4.17 (m, 4H); 5.10-5.27 (m, 4H); 5.70-5.87 (m, 2H). ^{13}C NMR: δ 13.92 (q); 27.01 (q); 48.13 (t); 49.30 (t); 51.52 (d); 116.81 (t); 117.43 (t); 132.62 (d); 132.74 (d); 170.37 (s); 205.04 (s). MS m/e : 195 (M^+, 28); 154 (19); 152 (18); 97 (22); 96 (77); 82 (26); 70 (34); 56 (100). Anal. calcd. for $C_{11}H_{17}NO_2$: C 66.66; H 8.77; N 7.17. Found: C 66.65; H 8.70; N 7.18.

N,N-Diallyl-3-phenyl-3-oxopropanamide 16. Prepared according to method B from diallylamine. Purification by flash chromatography (AcOEt / hexane: 20 / 80). Yield = 85%. IR: 1680; 1620; 1480; 1230; 990 cm^{-1}. ^1H NMR: δ 3.90-4.20 (m, 4H); 4.10 (s, 1H); 5.20-5.30 (m, 4H); 5.30-5.90 (m, 2H); 5.30 (s, 1H); 7.50-8.10 (m, 5H). ^{13}C NMR: - Ketone form: δ 47.8 (t); 49.2 (2t); 116.9 (2t); 128.1 (2d); 128.5 (2d); 132.1 (d); 132.9 (2d); 136.1 (s); 172. (s); 194.0 (s). - Enol form: δ 49.8 (2t); 89.9 (d); 116.8 (2t); 125.8 (2d); 128.5 (2d); 130.1 (d); 133.4 (2d); 134.7 (s); 167.0 (s); 171.4 (s). MS m/e = 243 (M^+, 10); 202 (12); 147 (18); 105 (100); 96 (60); 77 (62); 56 (45).

Irradiation

Triethylamine (14.5 mmol, 10 equiv) was added to a degassed solution of β-ketoamine or β-ketoamide (1.45 mmol, 1 equiv) in acetonitrile (30 mL, 5 x 10^{-2} M). The solution was irradiated for 5 h at 254 nm in a merry-go-round apparatus equipped with 12 low pressure mercury Philips TUV 15 lamps. Two 10 mm o.d. quartz tubes were used. After evaporation of the solvent, the crude material was purified by flash chromatography.

4-Allyl-4-azabicyclo[4.3.0]nonan-1-ols 3 *and* 4. Purification by flash chromatography ($CHCl_3$ / MeOH: 91 / 9). Yield: 12%. Ratio: 3 / 4: 9 / 1. IR (film): 3406 cm^{-1}. ^1H NMR: - Major isomer: δ 0.94 (d, *J* = 6.8 Hz, 3H). - Minor isomer: δ 0.93 (d, *J* = 6.8 Hz, 3H). - For the two isomers: δ 1.20-2.18 (m, 10H); 2.31-2.88 (m, 3H); 2.91-3.18 (m, 2H); 5.13-5.32 (m, 2H); 5.81-5.98 (m,1H). ^{13}C NMR: - Major isomer: δ 12.3 (q); 19.6 (t); 26.2 (t); 28.7 (t); 39.0 (d); 45.7 (d); 57.6 (t); 58.3 (t); 61.1 (t); 83.3 (s); 117.7 (t); 134.5 (d). - Minor isomer: δ 13.2 (q); 19.9 (t); 26.8 (t); 36.5 (t); 39.2 (d); 47.2 (d); 56.5 (t); 58.2 (t); 61.5 (t); 83.5 (s); 118.2 (t); 134.8 (d). High resolution MS calcd. for $C_{12}H_{21}NO$: 195.1623. Found: 195.1626.

1-Allyl-3-methyl-4-phenylpiperidin-4-ols 5 *and* 6. Purification by tlc (AcOEt: 100%). Yield= 8%. Ratio 5/6: 1.7/1. IR: 3100; 1700; 1470; 1400 cm^{-1}. ^1H NMR: - Major isomer: δ 1.60 (d, *J* = 7.5 Hz, 2H). - Minor isomer: δ 1.50 (d, *J* = 6.5 Hz, 2H). - For the two isomers: δ 2.50-4.10 (m, 10H); 5.50-6.00 (m, 2H); 6.20-6.51 (m, 1H); 7.50-8.20 (m, 5H). ^{13}C NMR: - Major isomer: δ 13.4 (q); 34.7 (t); 45.1 (t); 49.3 (t); 56.2(t); 65.5 (d); 77.9 (s); 116.7 (t); 126.8 (d); 127.5 (2d); 127.9 (2d); 138.8 (d); 144.7 (s). - Minor isomer: δ 13.9 (q); 32.3 (t); 45.0 (t); 49.7 (t); 56.5 (t); 63.7 (d); 78.9 (s); 116.7 (t); 126.3 (2d); 127.2 (2d); 127.7 (d); 128.3 (d); 144.9 (s). High resolution MS calcd. for $C_{15}H_{21}NO$: 231.1623. Found: 231.1620.

3-Allyl-6-hydroxy-5-methyl-3-azabicyclo[4.3.0]nonan-2-ones 17 *and* 18. Purification by flash chromatography ($CHCl_3$ / MeOH : 93 / 7). Ratio 17/18: 1.8/1). Yield = 56%. IR (film): 3390; 1620; 1480; 1350; 1260 cm^{-1}. ^1H NMR: - Major isomer: δ 1.02 (d, *J* = 6.8 Hz, 3H); 2.90 (dd, *J* = 13.0 and 12.0 Hz, Hb); 3.05 (dd, *J* = 13.0 and 5.0 Hz, Ha). - Minor isomer: δ 1.00 (d, *J* = 6.8 Hz, 3H); 2.80 (dd, *J* = 12.5 and 4.0 Hz, Hb); 2.87 (dd, *J* = 12.5 and 8.0 Hz, Ha); 3.25 (t, *J* = 12.0 Hz, 1H). - For the two isomers: δ 1.40-1.90 (m,3H); 2.00-2.25 (m,4H); 2.75-2.80 (m,1H); 3.80-4.20 (m, 2H); 4.70 (s, exchangeable, 1H); 5.12-5.21 (m, 2H); 5.60-5.75 (m,1H). ^{13}C NMR: - Major isomer: δ 12.6 (q); 23.0 (t); 30.5 (t); 36.0 (t); 37.4 (d); 49.3 (t); 49.8 (t); 50.2 (d); 81.9 (s); 117.4 (t); 132.7 (d); 172.8 (s). - Minor isomer: δ 11.4 (q); 22.7 (t); 30.2 (t); 36.0 (d); 39.1 (t); 49.1 (t); 49.9 (t); 53.7 (d); 80.2 (s); 117.2 (t); 132.9 (d); 171.6 (s). MS m/e = 209 (M^+, 25); 194 (100); 103 (25); 70 (70). Anal. calcd. for $C_{12}H_{19}NO_2$: C 68.86; H 9.15; N 6.69. Found: C 68.85; H 9.10; N 6.71.

3-Allyl-6-hydroxy-5,8,8-trimethyl-3-azabicyclo[4.3.0]nonan-2-ones 19 *and* 20. Purification by flash chromatography ($CHCl_3$ / MeOH : 93 / 7). Yield = 59%. Ratio 19/20 : 2.3/1. IR: 3590; 3400 (broad); 1650; 1620; 1490; 1355; 1275; 990; 925 cm^{-1}.^1H NMR: - Major isomer: δ 0.98 (d, *J* = 6.8 Hz, 3H); 0.99 (s, 3H); 1.20 (s, 3H); 3.08 (dd, *J* = 13.0 and 5.0 Hz, Ha); 2.92 (dd, *J* = 13.0 and 11.0 Hz, Hb) - Minor isomer: δ 0.96 (d, *J* = 7.0 Hz, 3H); 1.03 (s, 3H); 1.17 (s, 3H); 2.85 (dd, *J* = 12.5 and 4.0 Hz, Hb); 2.86 (dd, *J* = 12.5 and 8.0 Hz, Ha). - For the two isomers: δ 1.40-1.90 (m, 3H); 2.00-2.25 (m, 2H); 2.60 (s exchangeable, 1H); 2.75-2.80 (m, 1H); 3.80-4.20 (m, 2H); 5.12-5.23 (m, 2H); 5.66-5.80 (m, 1H). ^{13}C NMR: - Major isomer: δ 12.4 (q); 29.6(q); 30.8 (q); 37.8 (s); 39.1 (d); 45.6 (t); 47.9 (t); 49.6 (t); 50.1 (t); 52.8 (d); 83.3 (s); 117.9 (t); 132.8 (d); 172.9 (s). - Minor isomer: δ 11.1 (q); 29.3 (q); 30.5 (q); 37.2 (s); 37.7 (d); 45.3 (t); 47.9 (t); 49.3 (t); 49.8 (t); 53.6 (d); 80.7 (s); 117.4 (t); 132.9 (d); 171.7 (s). MS m/e = 237 (M^+, 23); 222 (100); 112 (23); 100 (260); 70 (62); 56 (29); 55 (23). High resolution MS calcd.: 237.1729. Found: 237.1746.

6-Hydroxy-5-methylene-3,8,8-trimethyl-3-azabicyclo[4.3.0]nonan-2-one 21. Purification by flash chromatography ($CHCl_3$ / MeOH: 93 /7). Yield: 65%. mp = 96-97° C. IR: 3580; 3380; 1655; 1630; 1500; 1400; 1310; 1140; 1050; 920 cm^{-1}.^1H NMR: δ 1.10 (s, 3H); 1.21 (s, 3H); 1.68 (d, *J* = 14.2 Hz, 1H); 1.85 (dd, *J* = 13.0 and 7.0 Hz, 1H); 1.90 (d, *J* = 14.2 Hz, 1H); 2.13 (dd, *J* = 13.0 and 8.0 Hz, 1H); 2.75 (s exchangeable, 1H); 2.80 (t, *J* = 7.5 Hz, 1H); 2.96 (s, 3H); 3.95 (s, 2H); 5.08 (d, *J* = 0.5 Hz, 1H); 5.29 (d, *J* = 0.5 Hz, 1H). ^{13}C NMR: δ 30.6 (q); 31.0 (q); 34.5 (q); 37.9 (s); 44.7 (t); 52.7 (t); 53.3 (t); 55.7 (d); 81.9 (s); 110.4 (t); 144.3 (s); 171.8 (s). MS m/e = 209 (M^+, 36); 194 (33); 152 (32); 125 (58); 124 (63); 112 (95); 110 (54); 98 (42); 97 (58); 96 (52); 95 (32); 70 (100); 55 (53). High resolution MS calcd.: 209.1416. Found: 209.1426.

N–Propargyl-4,4-dimethyl-2-hydroxycyclopentanecarboxamide 22. Purification by flash chromatography (AcOEt / hexane: 60 / 40). Yield: 10%. IR: 3300; 1630; 1530 cm^{-1}.^1H NMR: - Major isomer: δ 1.00 (s, 3H); 1.15 (s, 3H); 4.30-4.35 (m, 1H). - Minor isomer: δ 1.05 (s, 3H); 1.10 (s, 3H); 4.40-4.50 (m, 1H). - For the two isomers: δ 2.00-2.35 (m, 5H); 2.70-2.90 (m, 1H); 3.92-4.12 (m, 2H); 4.20 (s exchangeable, 1H); 6.30 (s exchangeable, 1H). ^{13}C NMR: - Major isomer: δ 27.86 (q); 29.85 (q); 29.32 (t); 34.05 (s); 39.50 (t); 53.61 (t); 53.66 (d); 71.59 (d); 75.68 (d); 79.48 (s); 166.85 (s). - Minor isomer: δ 27.75(q); 29.80(q); 29.25 (t); 34.00 (s); 39.35 (t); 53.54 (t); 53. 68 (d); 71.56 (d); 75.70 (d); 79.50 (s); 166.87 (s). MS m/e = 171 (M+1, 5); 140 (10); 123 (10); 112 (100); 95 (30); 81 (35); 57 (60).

1-Allyl-4-hydroxy-3,4,5-trimethylpiperidin-2-one 23. Purification by flash chromatography. Rf = 0.3 ($CHCl_3$ / MeOH: 93 / 7). Yield = 55%. Mixture of 2 stereoisomers, ratio (^1H NMR) 2/1. IR: 3390; 1620; 1480; 1350; 1270; 970 cm^{-1}. ^1H NMR: - Major isomer: δ 0.98 (d, *J* = 6.8 Hz, 3H); 1.15 (d, *J* = 6.8 Hz, 3H). - Minor isomer : δ 1.05 (d, J = 6.8 Hz, 3H); 1.10 (d, *J* = 6.8 Hz, 3H). - For the two isomers: δ 2.00-2.60 (m, 4H); 2.60-

3.60 (m, 2H); 3.80 (m, 2H); 5.00-5.10 (m,2H); 5.60-6.00 (m,1H). ^{13}C NMR: - Major isomer: δ 13.3 (q); 14.9 (q); 24.0 (q); 29.8 (d); 46.2 (d); 50.4 (t); 117.7 (t); 132.8 (d); 173.3 (s). - Minor isomer: d 12.0 (q); 15.8 (q); 24.8 (q); 32.4 (d); 49.1 (d); 49.4 (t); 50.9 (t); 117.5 (t); 132.8 (d); 173.1 (s). MS m/e = 197 (40); 182 (100); 164 (40); 85 (80); 60 (100). Anal. calcd. for $C_{17}H_{19}NO_2$: C 66.97; H 9.80; N 7.17. Found: C 66.99; H 9.80; N 7.15.

Reduction of 17 and 18 by $LiAlH_4$. To a solution of 17 and 18 (0.140g, 0.67 mmol) in THF (4 mL) was added $LiAlH_4$ 1M (0.057 g, 1.5 mmol) at 0° C. After 3 h at room temperature, water was added at 0° C (20 mL). The reaction was extracted with ethyl acetate. After evaporation of the organic phase, the residue was purified by tlc ($CHCl_3$ / MeOH : 91 / 9) to give 3 and 4 with a yield of 57%.

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