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Stereoselective Preparation of Enaminone Lithium Dianions: Synthesis of N,N-Dimethylcarbamoylenaminones.

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Abstract: A simple regio- and stereoselective synthesis of *N,N*-dimethylcarbamoylenaminones **2** by acylation of enaminone lithium dianions **1"** with *N,N*-dimethylcarbamoyl chloride is reported. The mechanism for the stereoselective preparation of the enaminone lithium dianions **1"** and successive acylation was investigated. The carbamoylenaminones **2** are selectively cyclized to 4-amino-2-pyranones **3** or hydrolyzed to carbamoyl diketones **4** in acidic conditions.

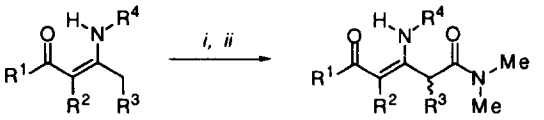
The γ-acylation of 1,3-diketones is a highly useful synthetic operation in organic synthesis, especially in the field of natural products.[1-3] Recently we have found several methods for the acylation of lithium enamines [4,5] or the regioselective acylation of β-enamino ketones [6,7] affording the regioselective preparation of polyketone derivatives.

Now we wish to report the regio- and stereoselective acylation of lithium dianions of β-enamino ketones with N,N-dimethylcarbamoyl chloride affording carbamoyl-β-enamino ketones **2** (see scheme of **Table 1**). This methodology can avoid the synthetic difficulties that are generally associated with the preparation of ketoamide derivatives.[8] In the case of enaminone **1e** (R^4 = H) we have obtained the γ-*C* and *N* diacylated product **2e** in low yield (entry 5) as already known in literature for primary amine.[9]

The acylation can be performed regioselectively on enaminones **1f,g**, prepared from acetylacetone and the appropriate amine. The kinetic lithium α'-dianion, obtained from enaminone **1f** by metallation with LiTMP/THF (B conditions [10]), allowed the preparation of the α'-carbamoylenaminone **2f** while the thermodynamic γ-dianion, obtained from enaminone **1g** by metallation with MeLi/TMEDA/THF (C conditions [10]), allowed the preparation of the γ-carbamoylenaminone **2g** with good yields.

The γ-acylation can be stereoselectively performed on enantiopure enaminones **1j-l** prepared by the use of (*R*)-(+)-α-methylbenzylamine. This convenient chiral auxiliary allowed the stereoselective preparation of the relative lithium γ-dianions by metallation with MeLi/HMPA/THF (D conditions [11, 12]).

Table 1. Reaction of enaminone **1a-l** lithium dianions with N,N-dimethylcarbamoyl chloride.



1 **2**

i: B^- (A, B, C or D conditions [a]); *ii*: N,N-Dimethylcarbamyl chloride, - 80 °C to 20 °C, 60 min.

Entry	**1**	R^1	R^2	R^3	R^4	Metallation condition [a]	**2**	Yield [b] (%)
1	**1a**	Ph	H	H	Me	A	**2a**	72
2	**1b**	Ph	H	H	Pri	A	**2b**	82
3	**1c**	Ph	H	H	Bu	A	**2c**	88
4	**1d**	Ph	H	H	Ph	A	**2d**	93
5	**1e**	Ph	H	H	H	A	**2e** [c]	25
6	**1f**	Me	H	H	Ph	B	**2f** [d]	73
7	**1g**	Me	H	H	Me	C	**2g**	67
8	**1h**	Ph	H	Bn	Me	C	**2h**	40
9	**1i**	Ph	H	H	R*	D	**2i**	93
10	**1j**	Ph	H	Me	R* [e]	D	(*S*)-**2j**	88 [f]
11	**1k**	Ph	$(CH_2)_2$		R* [e]	D	(*S*)-**2k**	82 [f]
12	**1l**	Ph	$(CH_2)_3$		R* [e]	D	(*S*)-**2l**	78 [f]

[a] Metallation conditions: A) LDA/THF, 1 h, 0 °C [10]; B) LTMP/THF, 30 min, 20 °C [10]; C) MeLi/TMEDA/THF, 1 h, 20 °C [10]; D) MeLi/HMPA/THF, 1 h, 40 °C.[11, 12] [b] Yields of the pure isolated compounds. [c] The γ-C and N bisacylation compound was been obtained. [d] The α'-C acylation compound was been obtained. [e] R* = (*R*)-α-methylbenzyl. [f] Yields of the enantiopure isolated compounds.

All the new enantiopure isolated compounds (*S*)-**2j-l** are unknown in literature neither as such nor as the usual derivatives. Therefore the absolute configuration of the new chiral isolated compounds were determined by X-ray diffraction of the single crystal for the compound (α*R*,2*S*)-**2j** [13] (see **Figure 1**). The absolute configuration of the other isolated compounds was determined by ^1H and ^{13}C NMR correlations. The (*R*)-**2j-l** carbamoyl enaminones were not observed in detectable amount. All the carbamoylenaminones **2**, with the exception of **2j**, show simple ^1H and ^{13}C NMR ($CDCl_3$) spectra indicating the presence of only one conformation. The spectra of carbamoylenaminone **2j** show the two conformation depicted in the **Figure 1** coexisting in $CDCl_3$ solution in the ratio of 4.3:1 (This experimental finding is in agreement with PM3 molecular modelling calculations [14] were the two conformers differ by 1.4 Kcal mol^{-1}; the more stable is the one present in the crystal).

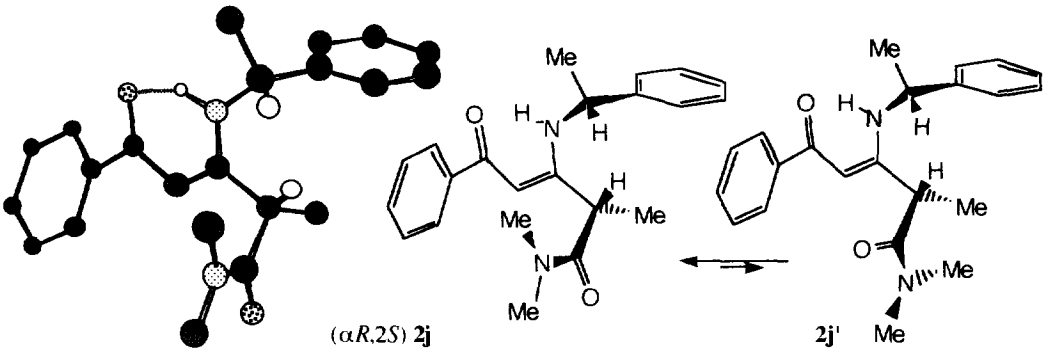
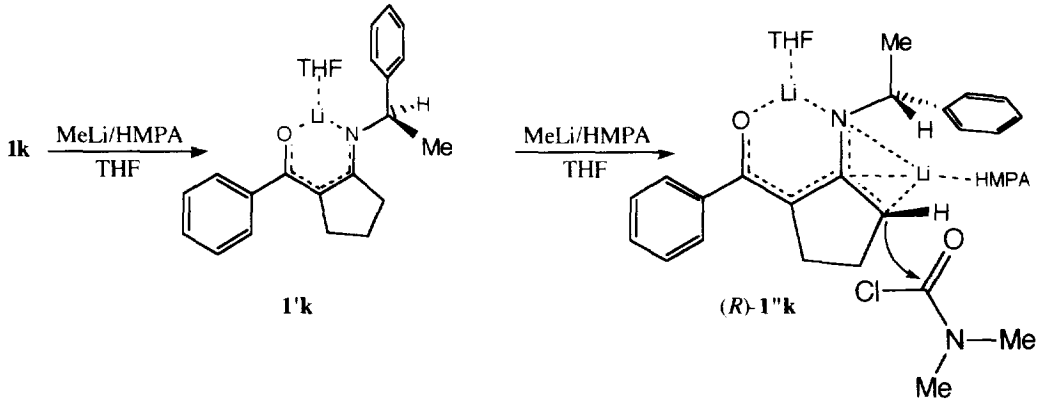


Figure 1. Ball and stick depiction of the single crystal X-ray structure of (α*R*,2*S*)-**2j** (most of the hydrogen atoms have been omitted for clarity). The less stable conformer **2j'** is also present in $CDCl_3$ solution.

A possible explanation of the asymmetric induction in the stereoselective synthesis of carbamoylenaminones (*S*)-**1j-l** can be proposed, involving the steric aspect of the formation process of the chiral enaminone lithium dianion (**1"k** in the **Scheme 1**). The first coordinated lithium ion in the monoanion **1'k** constrains the aza-allylic sistem in the *syn* configuration and provides the conformational rigidity necessary for a high asymmetric induction. The chiral substituent at the N atom directs the second metallation process to the less hindered side (back face of **1'k** in the case of the (*R*)-amine). In this medium the lithium enaminones are present as reactive monomers, coordinated with HMPA and THF.[15] In the dianion **1"k** the *re* face of the (*E*)-azaallylic system is highly hindered by the second lithium atom, strongly coordinated with the bulky and powerful ligand HMPA, preventing the attack of the electrophile on the same face. Thus the approach of the electrophilic carbamyl chloride takes place preferentially from the *si* face[11] affording the stereoselective synthesis of the γ-carbamoylenaminones (*S*)-**2j-l**.

Scheme 1. Stereoselective formation process of the chiral enaminone lithium dianion (*R*)**1"k** and nucleophilic attack of this to the N,N-dimethylcarbamyl chloride.



Molecular modelling calculations show the intermediate (*R*)-**1"k** to be more stable by 1.2 kcal mol^{-1} if compared with the diastereomer (*S*)-**1"k** (these structures, minimized with semi empirical AM1 calculation,[14] are the most stable among the possible conformations). The greater stability of the dianion (*R*)-**1"k** can be explained with a π-donating effect of the phenyl group on the lithium ion. In addition it is noteworthy that the intermediate (*R*)-**1"k** offers less steric hindrance to the *anti* attack of the electrophile as can be seen in the models of **Figure 2**.

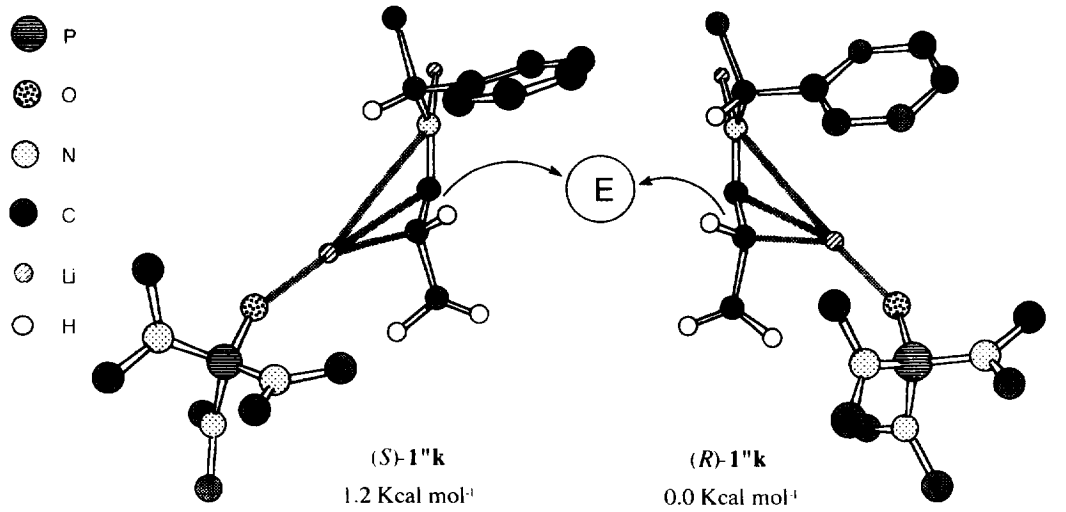
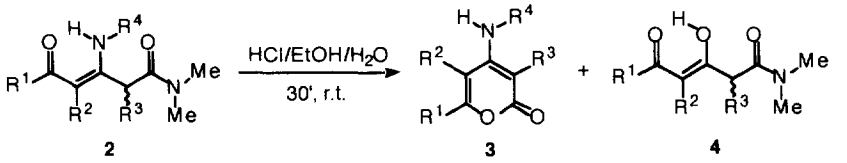


Figure 2 The AM1 minimized intermediate lithium dianions (*S*)- and (*R*)-**1"k** (simplified representations of the minimized structures are depicted for clarity).

In the attempt to hydrolyze the carbamoylenaminones **2** in acidic conditions (HCl/EtOH/H_2O, 30 min at room temperature) we have observed cyclization to 4-alkylamino-2-pyranones **3** with high yields. Only in the case of the carbamoylenaminone **2d,e,l** no alkylaminopyranones **3** were detected, but the 3,5-dioxoamides **4d,l** were obtained in good yields. In these cases hydrolysis was the preferred pathway because of the obvious steric hindrance in the cyclic **2l** or because the decreased basicity of the N atom results in a reduced nucleophilicity of the O atom on enaminones **2d,e**. The structure of 4-alkylamino-2-pyranones **3** were confirmed by X-ray diffraction of the single crystal for the compound **3b** [16] (see **Figure 3**).

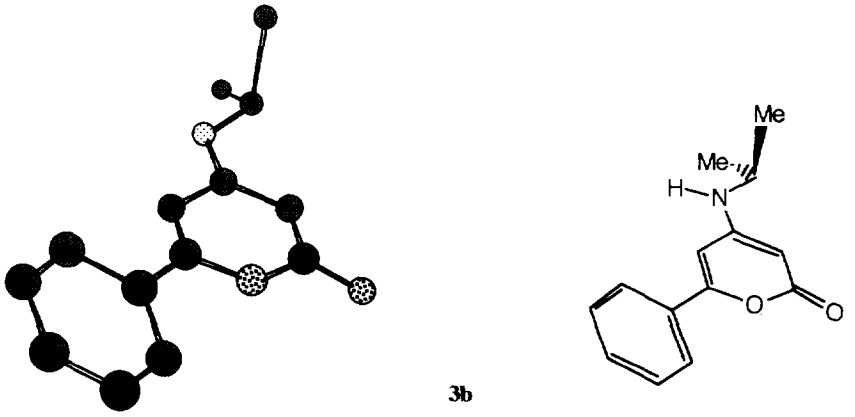
Both **3** and **4** are useful as synthetic intermediates,[17-20] and can be selectively prepared with our methodology by choice of the appropriate amine. The presence of a six-membered oxygenated heterocyclic ring in a range of naturally occurring compounds provided the incentive for the development of synthetic routes to these compounds. In a previous work we have found the synthesis of 4-imino-2,3-dihydropyranones by cyclization of δ-hydroxyenamino ketones.[12] It is noteworthy that 4-amino-2*H*-pyran-2-one derivatives, useful synthon in heterocyclic chemistry, [21] cannot be synthesized by reaction of 4-hydroxy-2-pyrones with amines, because the nucleophile reacts preferentially with the lactone carbonyl group at C-2 and only at C-4 through a second attack.[22, 23]

Table 2. Cyclization of γ-Carbamylenaminones **2** to 4-alkylamino-2-pyranones **3** or hydrolysis to 3,5-dioxoamide **4**.



Entry	**2**	R^1	R^2	R^3	R^4	**3**	Yield[a] (%)	**4**	Yield[a] (%)
1	**2a**	Ph	H	H	Me	**3a**	79		
2	**2b**	Ph	H	H	Pri	**3b**	75		
3	**2c**	Ph	H	H	Bn	**3c**	84		
4	**2d**	Ph	H	H	Ph			**4d**	79
5	**2e**	Ph	H	H	$CONMe_2$			**4d**	94
6	**2g**	Me	H	H	Me	**3g**	77		
7	**2h**	Ph	H	Bn	Me	**3h**	78		
8	**2j**	Ph	H	Me	R*	**3j**	72		
9	**2l**	Ph	$(CH_2)_3$		R*			**4l**	65

[a] Yields of the pure isolated compounds.

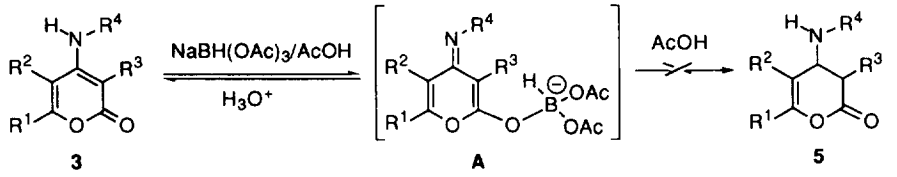


3b

Figure 3. Ball and stick depiction of the single crystal X-ray structure of **3b** (the hydrogen atoms have been omitted for clarity).

We have treated the 4-amino-2-pyranone **3** with sodium triacetoxyborohydride in acetic acid, for the reduction of the enamine function,[24] but starting material was recovered. The triacetoxyborohydride could react with 4-amino-2-pyranone **3** but the possible intermediate diacetoxyborohydride **A** (see **Scheme 2**) is unable to perform the intramolecular hydride transfer to 4-amino-3,4-dihydropyranone **5** because of the *s-trans* constraint of the enaminonic system in **3** (as already we observed for tetronic acid imine [24]).

Scheme 2



In conclusion we have found the conditions for the regio- and stereoselective acylation of β-enamino ketones with carbamoyl chloride. The carbamoylenaminones **2**, obtained with good yields, are selectively cyclized to 4-amino-2-pyranones **3** or hydrolyzed to carbamoyl diketones **4** in acidic conditions. The mechanism for the stereoselective preparation of enantiopure enaminone lithium dianions **1"** and successive acylation was explained.

EXPERIMENTAL SECTION

^{1}H and ^{13}C-NMR spectra were recorded with a Varian VXR 300 instrument. Chemical shifts are given in ppm downfield from Me_4Si in $CDCl_3$ solution. Coupling constants are given in Hertz. IR spectra were recorded with a Perkin-Elmer 257 spectrometer. GC-MS analyses were performed with an HP 59970 workstation formed by an HP-5890 gas chromatograph equipped with a methyl silicone capillary column and by an HP-5970 mass detector. Optical rotations were measured with a Perkin-Elmer 241 polarimeter using 10 cm cells. THF was dried by refluxing over sodium wires until the blue colour of benzophenone ketyl persisted and then distilling into a dry receiver under nitrogen atmosphere. Commercial methyllithium and butyllithium solutions (Aldrich) were employed under dry atmosphere. Commercial HMPA, TMEDA and TMP (Aldrich) were dried and distilled before use. The (*R*)-(+)-1-phenylethylamine 98% $[\alpha]^{23}$ +38°(neat) were purchased from Aldrich and used without further purification. LDA and LTMP was prepared from equimolecular amounts of buthyllithium or 2,2,6,6-tetramethylpiperidine in THF at 0 °C.

Preparation of starting enaminones 1a-l.

The enaminones **1a-i** were prepared from benzoylacetone or acetylacetone and the appropriate amine according to Singh and Tandon's procedure.[25] The enaminone **1j** was prepared by γ methylation of enaminone **1i** according to our procedure previously reported.[10] The enaminones **1k,l** were prepared by benzoylation of (*R*)-N-(α-methylbenzyl)-cyclopentaneimine or (*R*)-N-(α-methylbenzyl)-cyclohexaneimine according to our procedure previously reported.[4]

General procedure for the condensation of the enaminones 1a-l with N,N-dimethylcarbamoyl chloride.

Lithium dianions were prepared treating the enaminone **1** (5 m mol) in THF (5 mL) with the suitable base (see **Table 1**) (12.5 m mol) in THF (5 mL) under nitrogen atmosphere at 0 °C and allowing to react under the following conditions: A conditions, LDA, 1h, 0 °C; B conditions, LTMP, 0.5 h, 20 °C; C conditions, MeLi (1.6

M in diethylether)/TMEDA (12.5 mmol), 1h, 20 °C; D conditions, MeLi (1.6 M in diethylether)/HMPA (12.5 mmol), 1h, 40 °C[40]. The mixture was cooled at -90 °C and then treated with N,N-dimethylcarbamoyl chloride (12.5 mmol) in THF (3 mL) for 30'. The temperature was slowly allowed to rise to 0 °C (1 h) followed by quenching with a water solution of ammonium chloride (10 mL). The reaction mixture was partitioned, at room temperature, between water (50 ml) and dichloromethane (100 mL). The organic layer was dried (Na_2SO_4), evaporated under reduced pressure and the residue obtained was submitted to column chromatographic separation (n-hexane/ethyl acetate, 80:20 as eluent). The yields of the pure isolated carbamoylenaminones **2** are reported in Table 1.

N,N-Dimethyl-3-methylamino-5-oxo-5-phenyl-3-pentenamide (2a): mp 117-120°C (CH_2Cl_2/n-hexane); IR (nujol) 3360, 1630, 1590, 1220, 730 cm^{-1}; ^1H NMR δ 3.02 (s, 3H), 3.05 (s, 3H), 3.08 (s, 3H), 3.45 (s, 2H), 5.65 (bs, 1H), 7.30-7.55 (m, 3H), 7.80-8.00 (m, 2H), 11.45 (bs, 1H); ^{13}C NMR δ 30.49, 35.19, 38.28, 38.64, 92.68, 123.16, 127.43, 128.63, 131.04, 140.76, 162.63, 188.80; MS *m/z* (%) 201 (M^+-45,100), 173 (69), 144 (53), 124 (14), 105 (32); Anal. Calcd for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.39; H, 7.52; N, 11,45.

N,N-Dimethyl-3-isopropylamino-5-oxo-5-phenyl-3-pentenamide (2b): oil; IR (neat) 3430, 1625, 1570, 1310, 1130 cm^{-1}; ^1H NMR δ 1.29 (d, 6H, J =6.4 Hz), 3.00 (s, 3H), 3.06 (s, 3H), 3.44 (s, 2H), 3.77 (d sept, 1H, J = 9.3, 6.4 Hz), 5.58 (s, 1H), 7.20-7.35 (m, 3H), 7.85-7.95 (m, 2H), 11.50 (d, 1H, J =8.6 Hz); ^{13}C NMR δ 24.00, 35.84, 37.80, 38.28, 45.43, 91.46, 126.87, 128.10, 130.48, 140.24, 159.82, 167.56, 188.00; MS *m/z* (%) 274 (M^+,17), 229 (28), 202 (15), 186 (21), 169 (85), 105 (100); Anal. Calcd for $C_{16}H_{22}N_2O_2$: C, 70.04; H, 8.08; N, 10.21. Found: C, 70.27; H, 8.13; N, 10.15.

N,N-Dimethyl-3-benzylamino-5-oxo-5-phenyl-3-pentenamide (2c): mp 92-96°C (CH_2Cl_2/n-hexane); IR (nujol) 3350, 1630, 1580, 1325 cm^{-1}; ^1H NMR δ 2.96 (s, 3H), 2.98 (s, 3H), 3.45 (s, 2H), 4.56 (d, 2H, J = 6.2 Hz), 5.70 (bs, 1H), 7.20-7.50 (m, 8H), 7.80-7.95 (m, 2H), 11.80 (bs, 1H); ^{13}C NMR δ 36.29, 38.18, 39.00, 47.78, 93.25, 127.49, 127.53, 127.93, 128.66, 129.39, 121.23, 138.21, 140.58, 161.67, 167.95, 189.21; Anal. Calcd for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.70; H, 6.62; N, 8.87.

N,N-Dimethyl-3-anilino-5-oxo-5-phenyl-3-pentenamide (2d): mp 105-107°C (CH_2Cl_2/n-hexane); IR (nujol) 3300, 1610, 1540, 1260, 1240 cm^{-1}; ^1H NMR δ 2.82 (s, 3H), 2.93 s, 3H), 3.45 (s, 2H), 5.95 (s, 1H), 7.13-7.50 (m, 8H), 7;85-7.95 (m, 2H), 13.00 (bs, 1H); ^{13}C NMR δ 36.18, 38.02, 38.73, 94.31, 125.98, 126.96, 127.72, 128.74, 129.73, 131.57, 133.00, 138.54, 159.47, 168.53, 189.80; MS *m/z* (%) 263 (M^+-45,100), 235 (82), 234 (92), 105 (43); Anal. Calcd for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.08. Found: C, 73.95; H, 6.32; N, 9.22.

N,N-Dimethyl-3-(N,N-dimethylcarbamoyl)amino-5-oxo-5-phenyl-3-pentenamide (2e): mp 140-144°C (CH_2Cl_2/n-hexane); IR (nujol) 3300, 1610, 1260, 1135 cm^{-1}; ^1H NMR δ 3.00 (s, 3H), 3.08 (s, 9H), 3.96 (s, 2H), 6.02 (s, 1H), 7.41-7.50 (m, 3H), 7.80-7.90 (m, 2H), 13.02 (s, 1H); ^{13}C-NMR δ 36.05, 37.15, 38.00, 40.26, 78.17, 101.81, 128.04, 128.91, 132.50, 139.40, 154.77, 157.00, 169.13, 191.86; MS *m/z* (%) 303 (M^+, 6), 160 (100), 84 (73); Anal. Calcd for $C_{16}H_{21}N_3O_3$: C, 63.35; H, 6.98; N, 13.85. Found: C, 63.27; H, 7.08; N, 13.56.

N,N-Dimethyl-5-anilino-3-oxo-4-hexenamide (2f): oil; IR (neat) 3400, 1550, 1290, 1100 cm^{-1}; ^1H NMR δ 1.98 (s, 3H), 2.96 (s, 3H), 3.04 (s, 3H), 3.43 (s, 2H), 5.23 (s, 1H), 7.00-7.20 (m, 5H), 12.40 (bs, 1H); ^{13}C NMR δ 20.38, 36.02, 38.63, 49.26, 96.98, 125.27, 126.42, 129.61, 138.75, 162.53, 169.01, 190.94; MS *m/z* (%) 246 (M^+,23), 202 (68), 160 (47); Anal. Calcd for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.50; H, 7.21; N, 11.13.

N,N-Dimethyl-3-methylamino-5-oxo-3-hexenamide (**2g**): mp 95-98°C (CH_2Cl_2/n-hexane); IR (nujol) 3300, 1590, 1270 cm^{-1}; ^{1}H-NMR δ 2.00 (s, 3H), 2.94 (d, 3H, J=5.2), 3.00 (s,3 H), 3.04 (s, 3H), 3.29 (s, 2H), 4.95 (bs, 1H), 10.80 (bs, 1H); ^{13}C-NMR δ 29.49, 30.17, 36.22, 38.06, 38.18, 95.80, 160.86, 167.96, 195.95; MS *m/z* (%) 184 (M^+,53), 140 (80), 98 (45), 72 (100); Anal. Calcd for $C_9H_{16}N_2O_2$: C, 58.67; H, 8.75; N, 15.20. Found: C, 58.53; H, 8.80; N, 15.03.

N,N-Dimethyl-2-benzyl-3-methylamino-5-oxo-5-phenyl-3-pentenamide (**2h**): mp 148-50 °C (CH_2Cl_2/n-hexane); IR (nujol) 3300, 1625, 1520, 1195 cm^{-1}; ^{1}H-NMR δ 2.78 (d, 3 H, J = 4.9 Hz), 2.87 (s, 3H), 2.97 (s, 3H), 3.02 (dd, 1H, J = 13.7, 6.9 Hz), 3.50 (dd, 1H, J = 13.7, 6.9 Hz), 3.78 (t, 1H, J = 6.9 Hz), 5.90 (s, 1H), 7.15-7.50 (m, 8H), 7.82-7.92 (m, 2H), 11.58 (br s, 1H); ^{13}C-NMR δ 30.06, 36.39, 37.60, 38.67, 41.30, 89.24, 126.76, 127.07, 128.10, 128.19, 129.22, 130.76, 138.80, 139.93, 163.16, 169.39, 188.27; MS *m/z* (%) 291 (M^+-45, 100), 263 (29), 186 (25), 105 (42); Anal. Calcd for $C_{21}H_{24}N_2O_2$: C, 74.97; H, 7.19; N, 8.33. Found: C, 74.79; H, 7.28; N, 8.49.

(*R*)-N,N-Dimethyl-3-α-methylbenzylamino-5-oxo-5-phenyl-3-pentenamide (**2i**): mp 76-78 °C (CH_2Cl_2/n-hexane); IR (nujol) 3350, 1640, 1595, 1330, 1130 cm^{-1}; ^{1}H NMR δ 1.62 (d, 3H, J = 6.9 Hz), 2.76 (s, 3H), 2.92 (s, 3H), 3.18 (d, 1H, J = 16.1 Hz), 3.30 (d, 1H, J = 16.1 Hz), 4.79 (dq, 1H, J = 7.1, 6.9 Hz), 5.65 (s, 1H), 7.20-7.65 (m, 8H), 7.80-7.90 (m, 2H), 11.90 (d, 1H, J = 7.1 Hz); ^{13}C NMR δ 25.44, 36.21, 38.04, 39.26, 54.00, 92.79, 126.15, 127.53, 127.94, 128.69, 129.46, 131.26, 140.54, 144.70, 161.19, 168.04, 189.16; MS *m/z* (%) 291 (M^+-45,57), 159 (13), 105 (100); Anal. Calcd for $C_{21}H_{24}N_2O_2$: C, 74.97; H, 7.19; N, 8.33. Found: C, 74.84; H, 7.33; N, 8.50.

(α*R*,2*S*)-N,N-Dimethyl-2-methyl-3-α-methylbenzylamino-5-oxo-5-phenyl-3-pentenamide (**2j**): mp 122-124 °C (CH_2Cl_2/n-hexane); $[\alpha]^{20}_D$ = - 570 (c = 1.2, $CHCl_3$); IR (nujol) 3360, 1640, 1580, 1270 cm^{-1}; ^{1}H NMR δ, major conformer: 1.12 (d, 3H, J = 6.9 Hz), 1.63 (d, 3H, J = 6.8 Hz), 2.80 (s, 3H), 2.93 (s, 3H), 3.56 (q, 1H, J = 6.9 Hz), 4.89 (dq, 1H, J = 8.5, 6.8 Hz), 5.80 (s, 1H), 7.20-7.40 (m, 8H), 7.80-7.90 (m, 2H), 12.2 (d, 1H, J = 8.5 Hz); minus conformer: 1.47 (d, 3H, J = 7.0 Hz), 1.54 (d, 3H, J = 6.7 Hz), 3.01 (s, 3H), 3.22 (s, 3H), 4.49 (q, 1H, J = 6.7 Hz), 5.48 (s, 1H), 6.10 (q, 1H, J = 7.0 Hz); ^{13}C NMR δ major conformer:17.55, 26.10, 36.63, 37.40, 41.31, 53.58, 90.61, 125.99, 127.58, 127.89, 128.72, 129.38, 131.35, 140.43, 144.36, 167.09, 170.86, 189.53; MS *m/z* (%) 305 (M^+-45, 99), 277 (17), 173 (55), 105 (100); Anal. Calcd for $C_{22}H_{26}N_2O_2$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.33; H, 7.63; N, 8.04.

(α*R*,3*S*)-1-Benzoyl-2-α-methylbenzylamino-3-N,N-dimethylcarbamoyl-cyclopentene (**2k**): mp 100-102 °C (CH_2Cl_2/n-hexane); $[\alpha]^{20}_D$ = - 274 (c = 4.1, $CHCl_3$); IR (nujol) 3400, 1630, 1590, 1310 cm^{-1}; ^{1}H NMR δ 1.41 (d, 3H, J = 6.9 Hz), 1.52-2.00 (m, 2H), 2.37-2.85 (m, 2H), 2.52 (s, 3H), 2.86 (s, 3H), 3.35 (dd, 1H, J = 9.6, 5.0 Hz), 4.42 (quint, 1H, J = 6.6 Hz), 7.15-7.24 (m, 8H), 7.52-7.55 (m, 2H), 10.75 (d, 1H, J = 6.1 Hz); ^{13}C-NMR δ 25.25, 28.22, 30.26, 35.67, 37.18, 47.44, 54.41, 106.73, 125.66, 127.27, 127.78, 128.43, 128.84, 129.49, 142.11, 144.89, 166.06, 171.54, 189.73; MS *m/z* (%) 362 (M^+, 5), 257 (100), 212 (47), 105 (85); Anal. Calcd for $C_{23}H_{26}N_2O_2$: C, 76.21; H, 7.23; N, 7.73. Found: C, 76.30; H, 7.18; N, 7.84.

(α*R*,3*S*)-1-Benzoyl-3-N,N-dimethylcarbamoyl-2-α-methylbenzylaminocyclohexene (**2l**): mp 49-51°C (CH_2Cl_2/n-hexane); $[\alpha]^{20}_D$ = - 432 (c = 1.1, $CHCl_3$); IR (nujol) 3400, 1625, 1580, 1260, 1130 cm^{-1}; ^{1}H NMR δ 1.52 (d, 3H, J = 6.7 Hz), 1.56-1.70 (m, 4H), 2.22-2.36 (m, 2H), 2.83 (s, 3H), 3.00 (s, 3H), 3.43 (t, 1H, J = 5.1 Hz), 4.40 (quint, 1H, J = 6.3 Hz), 7.20-7.50 (m, 10H), 12.45 (bs, 1H); ^{13}C-NMR δ 20.79, 26.09, 26.61, 28.44, 36.43, 37.80, 40.91, 53.58, 102.81, 125.91, 127.17, 127.76, 128.28, 129.12, 129.44, 143.51, 145.56, 160.90,

172.17, 195.70; MS *m/z* (%) 376 (M^+,1), 271 (100), 226 (87), 198 (13), 105 (100); Anal. Calcd for $C_{24}H_{28}N_2O_2$: C, 76.56; H, 7.50; N, 7.44. Found: C, 76.42; H, 7.61; N, 7.38.

General procedure for the carbamoylenaminone 2 cyclization to 4-alkylamino-2-pyranone 3 or hydrolysis to carbamoyldiketones 4. The carbamoylenaminone **2** (2 m mol) in EtOH (10 mL) were treated with HCl (1 mL, 5 M in water) for 30 min at room temperature. The reaction mixture was partitioned between sodium carbonate saturated water solution (20 ml) and dichloromethane (50 mL). The organic layer was dried (Na_2SO_4), evaporated under reduced pressure and the residue obtained was submitted to column chromatographic separation (n-hexane/ethyl acetate, 50:50 as eluent). The yields of the pure isolated 4-alkylamino-2-pyranones **3** and carbamoyldiketones **4** are reported in Table 2.

4-methylamino-6-phenylpyran-2-one (3a): mp 178-180°C (CH_2Cl_2/n-hexane); IR (nujol) 3250, 1650, 1530, 1040 cm^{-1}; ^{1}H-NMR δ 2.90 (s, 3H), 5.10 (d, 1H, J = 1.9 Hz), 5.46 (bs, 1H), 6.30 (d, 1H, J = 1.9 Hz), 7.32-7.42 (m, 3H), 7.70-7.80 (m, 2H); ^{13}C-NMR δ 29.48, 81.11, 96.96, 125.56, 128.71, 130.51, 131.66, 156.38, 158.83, 164.88; Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51; N, 6.96. Found: C, 71.48; H, 5.83; N, 7.08.

4-isopropylamino-6-phenylpyran-2-one (3b): mp 172-174°C (CH_2Cl_2/n-hexane); IR (nujol) 3230, 1640, 1520 cm^{-1}; ^{1}H-NMR δ 1.27 (d, 6H, J = 6.3 Hz), 3.65 (sept, 1H, J = 6.3 Hz), 4.95 (br s, 1 H), 5.12 (d, 1H, J = 1.8 Hz), 6.22 (d, 1H, J = 1.8 Hz), 7.35-7.45 (m, 3H), 7.75-7.80 (m, 2H); ^{13}C-NMR δ 22.12, 44.21, 81.53, 97.25, 125.54, 128.69, 130.46, 131.71, 156.77, 159.20, 164.92; MS *m/z* (%) 229 (M^+,47), 186 (100), 159 (19), 105 (64); Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.48; H, 6.33; N, 6.23.

4-Benzylamino-6-phenylpyran-2-one (3c): mp 198-200°C (CH_2Cl_2/n-hexane); IR (nujol) 3260, 1650, 1540 cm^{-1}; ^{1}H-NMR δ 4.38 (s, 2H), 5.20 (bs, 1H), 5.22 (d, 1H, J = 1.8 Hz), 6.26 (d, 1H, J = 1.6 Hz), 7.30-7.50 (m, 8H), 7.75-7.82 (m, 2H); ^{13}C-NMR δ 47.10, 82.49, 96.73, 125.60, 127.55, 128.04, 128.75, 128.97, 130.59, 131.60, 136.34, 153.00, 157.70, 164.25; Anal. Calcd for $C_{18}H_{15}NO_2$: C, 77.96; H, 5.45; N, 5.05. Found: C, 78.12; H, 5.59; N, 4.98.

6-Methyl-4-methylaminopyran-2-one (3g): mp 120-122 °C (CH_2Cl_2/n-hexane); IR (nujol) 3240, 1670, 1545, 1285 cm^{-1}; ^{1}H-NMR δ 2.14 (s, 3H), 2.83 (s, 3H), 4.96 (d, 1H, J = 1.9 Hz), 5.20 (bs, 1H), 5.60 (d, 1H, J = 1.9 Hz); ^{13}C-NMR δ 19.81, 29.25, 79.88, 99.10, 159.02, 160.78, 165.63; MS *m/z* (%) 139 (M^+,85), 124 (21), 111 (59), 82 (46), 68 (100); Anal. Calcd for $C_7H_9NO_2$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.37; H, 6.74; N, 10.23.

3-Methyl-4-(α-methylbenzyl)amino-6-phenylpyran-2-one (3j): mp 169-172°C (CH_2Cl_2/n-hexane); $[\alpha]^{20}_D$ = +10.6 (c=3.1, $CHCl_3$); IR (nujol) 3400, 1620, 1550, 1010 cm^{-1}; ^{1}H NMR δ 1.63 (d, 3H, J = 6.6 Hz), 2.04 (s, 3H), 4.63 (d, 1H, J = 5.9 Hz), 4.77 (quint, 1H, J = 6.3 Hz), 6.25 (s, 1H), 7.20-7.45 (m, 8H), 7.50-7.65 (m, 2H); ^{13}C NMR δ 9.78, 25.23, 53.57, 92.73, 94.19, 125.89, 128.27, 129.16, 129.68, 129.70, 130.74, 132.48, 144.00, 154.29, 158.41, 164.86; MS *m/z* (%) 305 (M^+,28), 173 (35), 105 (100); Anal. Calcd for $C_{20}H_{19}NO_2$: C, 78.66; H, 6.27; N, 4.59. Found: C, 78.73; H, 6.12; N, 4.81.

3-Benzyl-4-methylamino-6-phenylpyran-2-one (3h): mp 202-204°C (CH_2Cl_2/n-hexane); IR (nujol) 3310, 1635, 1540, 1115 cm^{-1}; ^{1}H-NMR δ 2.92 (d, 3H, J = 5.0 Hz), 3.85 (s, 2H), 4.63 (br q, 1H, J = 5.0 Hz), 6.45 (s, 1H), 7.12-7.31 (m, 5H), 7.39-7.51 (m, 3H), 7.79-7.91 (m, 2 H); ^{13}C-NMR δ 29.91, 30.13, 92.48, 94.58, 125.65, 126.38, 127.88, 128.68, 128.76, 130.51, 132.02, 138.79, 155.63, 159.08, 164.53; Anal. Calcd for $C_{19}H_{17}NO_2$: C, 78.33; H, 5.88; N, 4.81. Found: C, 78.18; H, 5.99; N, 4.67.

N,N-Dimethyl-3,5-dioxo-5-phenylpentanamide (4d): oil; IR (neat) 3330, 1600, 1540, 1250, 1220, 800 cm^{-1}; ^{1}H-NMR δ 1.90 (br s, 1H) 2.97 (s, 3H), 3.06 (s, 3H), 3.56 (s, 2H), 6.30 (s, 1H), 7.41-7.60 (m, 3H), 7.80-8.00

(m, 2H); ^{13}C-NMR δ 35.65, 38.04, 46.27, 96.50, 127.04, 128.51, 132.53, 133.87, 166.91, 181.58, 191.79; MS *m/z* (%) 188 (M^+-45, 18), 160 (28), 105 (100); Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.50; H, 6.57; N, 6.32.

2-Benzoyl-6-N,N-Dimethylcarbamoylcyclohexanone (4l): mp 144-146 °C (CH_2Cl_2/n-hexane); IR (nujol) 3470, 1640, 1285 cm^{-1}; ^{1}H-NMR δ 1.70-2.60 (m, 6H), 2.92 (s, 3H), 3.01 (s, 3H), 4.05 (dd, 1H, *J* = 8.8, 6.2 Hz), 4.74 (t, 1H, *J* = 5.9 Hz), 7.35-7.67 (m, 3H), 7.87-7.98 (m, 2H); ^{13}C-NMR δ 21.19, 26.66, 30.43, 37.65, 46.57, 58.89, 108.47, 128.20, 129.11, 131.08, 133.65, 170.13, 187.43, 198.93; MS *m/z* (%) 273 (M^+, 9), 180 (22), 105 (100); Anal. Calcd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.12. Found: C, 70.53; H, 7.19; N, 4.96.

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