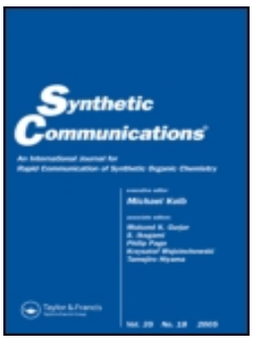

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Studies on the Preparation of 4-Ethoxyalkyliden and 4-Aminoalkyliden-5(4*H*)-oxazolones

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ABSTRACT

Optimized conditions for the preparation of 4-ethoxyalkyliden-5(4*H*)-oxazolones were developed. A considerable steric hindrance was observed on the nucleophilic substitution of the ethoxy group by amines.

Key Words: Oxazolones; Nucleophilic substitution; 4-aminoalkyliden-5(4*H*)-oxazolones; *E*/*Z*-configuration; Heterocycles.

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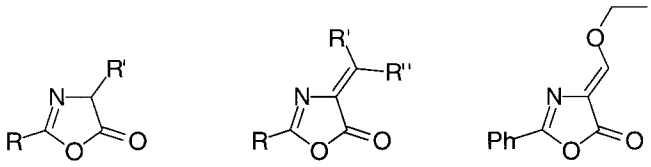
5(4*H*)-Oxazolones **1** and **2** are versatile substrates in organic synthesis.[1] Some recent applications of this type of compounds include the synthesis of heterocycles,[2] α-aminoacids,[3] peptides,[4] α,β-dehydro-α-aminoacids,[5] and other units.[6] Among them, 4-ethoxymethylene-2-phenyl-5(4*H*)-oxazolone **3a** has found wide use as a synthon for different heterocycles due to the ease of substitution of the ethoxy group by halogen,[7] nitrogen,[1c,2a,2b,4a,8] sulphur,[3d,9] and carbon[10] nucleophiles.



1 **2** **3a**

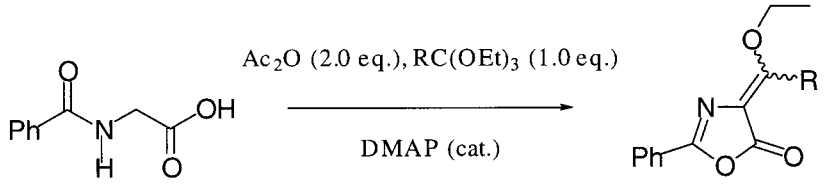
4-Alkyl-5(4*H*)-oxazolones **1** and the unsaturated 5(4*H*)-oxazolones **2** have been prepared, respectively, by dehydration of the *N*-acylated aminoacids[3c,4c] and by the Erlenmeyer method. This last method, works as a one-pot synthesis by heating the aldehyde, acylglycine, acetic anhydride with the additives sodium acetate,[1,11] $Pb(OAc)_4$[12] or zinc chloride.[13] The ethoxymethylene-2-phenyl-5(4*H*)-oxazolone **3a** has been formerly prepared in 34% yield by the Erlenmeyer method using hippuric acid, ethyl orthoformate and acetic anhydride.[14] In spite of this fact, our attempts to prepare the analogues **3b–3d** under the same conditions[14] were unsuccessful. However, the use of 4-(dimethylamino)-pyridine (DMAP) and the control of the reaction time and temperature allowed us to obtain the 5(4*H*)-oxazolones **3a–3d** in moderate to high yields (Table 1).

The observed effect of DMAP on the formation of 5(4*H*)-oxazolones **3a–3d** can be easily explained by an activation of the acetic anhydride, which promotes the formation of the intermediate 2-phenyl-5(4*H*)-oxazolone enol form, which then reacts with the activated ortho ester. We have also noticed that the preparation of **3b** and **3c** required lower reaction temperature for better conversions (Entries 2 and 3).

The reactivity of the 5(4*H*)-oxazolones **3a–3d** towards nucleophilic substitution was further explored using representative amines (Table 2).

The substitution with benzylamine occurred readily at 0°C for the 5(4*H*)-oxazolones **3a–3c**, but for **3d** (*R*=Ph), only moderate conversion

Table 1. Optimized conditions for the preparation of the 5(4*H*)-oxazolones **3a–3d** from hippuric acid.



3a-3d

Entry	Temperature (°C)	Time	Product	Yield[a] (%)
1	140	30 min	**3a** $R=H$	88[b]
2	90	1 h	**3b** $R=Me$	39[b]
3	90	1 h	**3c** $R=Et$	48[b]
4	140	4 h	**3d** $R=Ph$	30[c]

[a]Isolated yield after purification by flash chomatography and crystallization.
[b]Isolated only one isomer.
[c]Isolated as a 4.9:1.0 mixture of isomers.

was obtained at room temperature (Entry 11). For the more hindered dibenzylamine, the required reaction temperature increased with the bulkiness of the substituent R of the 5(4*H*)-oxazolones (R=H at 0°C; R=Me at 40°C, R = Et at 80°C and R=Ph at 110°C). In the case of the preparation of **3d** we have also isolated the ring opened compound **9,** formed by a competitive attack of the dibenzylamine on the carbonyl group.

The lower reactivity observed for **3b** and **3c**, when compared with **3a**, should be due to the steric hindrance on the attack of the amino group on the C1′ carbon. For **3d** (R=Ph) the observed lowest reactivity, is consistent both with the steric hindrance and the predicted less electrofillic character of the C1′ carbon due to extended conjugation with the phenyl group.

When concerning the stability of the 5(4*H*)-oxazolones, in general, the more stable isomer corresponds to the case were the bulkier group is *cis* relative to the nitrogen atom of the 5(4*H*)-oxazolone.[1d] Reported examples of general structure **10** ($R^2=H$) with the *Z*-configuration includes for R^1 = Aryl,[1d,11,7a,15] Alkyl,[1d,16] OH,[7b] OEt,[14] OAc,[7b] OPiv,[7b] SPh,[3d,7a] and $NMe_{[2]}$.[17] On the other hand, in case of monoalkylated amino groups, the more stable isomer corresponds to the *E*-configuration, due to the formation of intramolecular hydrogen bond with the carbonyl

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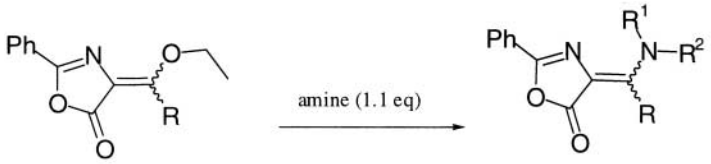
Table 2. Substitution of 5(4*H*)-oxazolones **3a**-**3d** with amines.



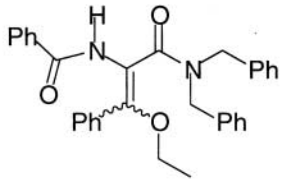
3a R = H

3b R = Me

3c R = Et

3d R = Ph

	R	R^1R^2N
4a	H	benzylamino
5a	H	*(R)*-1-phenylethylamine
6a	H	diethylamine
7a	H	morpholino
8a	H	dibenzylamino
4b	Me	benzylamino
5b	Me	*(R)*-1-phenylethylamine
8b	Me	dibenzylamino
4c	Et	benzylamino
8c	Et	dibenzylamino
4d	Ph	benzylamino
8d	Ph	dibenzylamino



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Entry	Substrate	Amine	Solvent	Temp.	Time	Product	Yield[a] (%)
1	**3a** *R* = H	Benzylamine	CH_2Cl_2	0°C	5 h	**4a**	69[b]
2	**3a** *R* = H	(R)-(+)-1-Phenylethylamine	CH_2Cl_2	r.t.	24 h	**5a**	55[b]
3	**3a** *R* = H	Diethylamine	CH_2Cl_2	Reflux	2.5 h	**6a**	93[b]
4	**3a** *R* = H	Morpholine	CH_2Cl_2	Reflux	3.7 h	**7a**	76[b]
5	**3a** *R* = H	DiBenzylamine	CH_2Cl_2	0°C	20 h	**8a**	69[b]
6	**3b** *R* = Me	Benzylamine	CH_2Cl_2	0°C	7 h	**4b**	86[c]
7	**3b** *R* = Me	(R)-(+)-1-Phenylethylamine	CH_2Cl_2	r.t.	24 h	**5b**	51[d]
8	**3b** *R* = Me	DiBenzylamine	CH_2Cl_2	Reflux	12 days	**8b**	9[b,e]
9	**3c** *R* = Et	Benzylamine	CH_2Cl_2	0°C	6 h	**4c**	62[f]
10	**3c** *R* = Et	DiBenzylamine	Benzene	Reflux	12 days	**8c**	57[g]
11	**3d** *R* = Ph	Benzylamine	CH_2Cl_2	r.t.	4 days	**4d**	34[h]
12	**3d** *R* = Ph	DiBenzylamine	Toluene	Reflux	6 days	**8d**	13[i]

[a]Isolated yield obtained after purification by flash chomatography and crystallization; [b]Isolated only one isomer; [c]Isolated as a 2.0:1.0 mixture of isomers; [d]Isolated as a 1.7:1.0 mixture of isomers; [e]Recovered starting substrate **3b** in 36%; [f]Isolated as a 1.3:1.0 mixture of isomers; [g] Recovered starting substrate **3c** in 19%; [h]Isolated as a 5.7:1.0 mixture of isomers; [i]Isolated the ring opened product **9** in 35%.

Table 3. $^{3}J_{\text{C-5,H-1}'}$ and E/Z configurations determined from ^{13}C NMR.

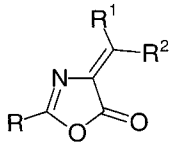
Entry	Compound	δ C_5 (ppm)	$^{3}J_{\text{C-5,H-1}'}$ (Hz)	E/Z configuration
1	**3a**	168.3	2.2	*Z*
2	**4a**	168.2	9.4	*E*
3	**5a**	167.7	2.2	*Z*
4	**12**	167.5	5.5	*Z*

oxygen as has been illustrated for **10** ($R = $ Ph, $R^1 = $ H, $R^2 = $ NHBzl, NHAlk).[17]

The assignment of the *E*,*Z*-configuration of 5(4*H*)-oxazolones of the general structure **10** where R^1 or $R^2 = $ H is possible by means of ^{13}C NMR by measuring the $^{3}J_{\text{C-5,H-1}'}$ vicinal coupling constant between the carbonyl carbon and the olefinic β proton. For the **3a** related compounds with an aryl substituent instead of the ethoxy group, as for example in the case of the isomers **11** and **12** it has been shown that there is a significant difference between the $^{3}J_{\text{C-5,H-1}'}$ coupling of *trans*- and *cis*-isomers of 12.5 Hz and 5.5 Hz respectively.[15] Compound **12** was therefore prepared and its $^{3}J_{\text{C-5,H-1}'}$ coupling constant measured in the proton coupled ^{13}C NMR spectra, obtained through the inverse gated decoupling technique. A value of 5.5 Hz was measured which when compared with the previous reported values indicates that the *Z* isomer was obtained (Table 3, Entry 4).[15] This methodology was then further employed to determine the configuration of compounds **3a**, **4a**, and **5a**. The values of the coupling constants obtained are reported in Table 3.

The value of the coupling constant measured for **3a** ($^{3}J_{\text{C-5,H-1}'} = 2.2$ Hz, Entry 1) indicates that the *Z* isomer was obtained, being this assignment also in agreement with the previous reported spectral and physical data.[14] In case of the 4-aminomethylen-5(4*H*)-oxazolone **4a** the higher value of the measured coupling constant ($^{3}J_{\text{C-5,H-1}'} = 9.4$ Hz, Entry 2) indicates that the isomer with the *E* configuration was obtained. As was mentioned previously, the possibility of formation of an intramolecular hydrogen bond between the amine proton and the carbonyl oxygen should account for the higher stability of this isomer. Unexpected was however the result obtained for **5a**, which corresponds to the isomer *Z* according to the NMR data ($^{3}J_{\text{C-5,H-1}'} = 2.2$ Hz, Entry 3), but where the same stabilization effect of an intramolecular hydrogen bond leading to formation of the *E* isomer was expected. The 4-aminomethylen-5(4*H*)-oxazolones **6a–8a** should correspond to the *E*-isomers on basis of the expected more stable isomer.

The compound **3b** correspond to the *E*-isomer by comparison with reported physical data. The new compound **3c** should correspond to the *E*-isomer by comparison of the ^{13}C NMR with the **3b** and the expected effect of the ethyl group. For the other derivatives **4b**, **5b**, **8b**, **4c**, and **8c**, we have isolated a mixture of isomers which is rationalized on the basis of competitive steric effect of the methyl and ethyl groups.



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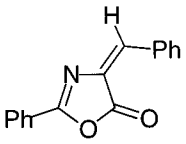

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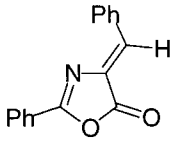

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In summary, the conditions presented here allowed the preparation of 5(4*H*)-oxazolones **3b–3d** in moderate yields and an improved yield for the preparation of the 5(4*H*)-oxazolones **3a**. The study presented on the nucleophilic substitution of the ethoxy group by amines, also showed that the nucleophilic substitution on the C1′ carbon by simple amines is strongly dependent of the steric hindrance on the reactive center. These results suggest that a careful choice of the reaction conditions is essential for the preparation 4-aminoalkyliden-5(4*H*)-oxazolones.

EXPERIMENTAL

All glassware was oven dried and cooled in a desiccator (P_2O_5 desiccant) prior to use. Dichloromethane was distilled from P_2O_5 powder under a nitrogen atmosphere. Triethylamine was distilled from NaOH powder under a nitrogen atmosphere. Commercially supplied reagents were used as supplied. Anhydrous toluene, benzene and tetrahydrofuran were prepared by distillation from sodium/benzophenone ketyl under argon. Flash column chromatography was carried out using Merck 60 silica gel (70–240 μm). Thin layer chromatography was carried out using Merck Kieselgel 60 F_{254} precoated, glass backed plates. The plates were visualized using ultraviolet light (254 nm), $KMnO_4$ solution, ninhydrin or iodine as appropriate.

^{1}H NMR spectra were recorded on Brüker ARX 400 spectrometer. Chemical shifts are reported downfield in parts per million (ppm) from a tetramethyl silane reference. ^{13}C NMR spectra were recorded on

Brüker ARX 400 spectrometer at 100 MHz. ^{13}C NMR spectra for the determination of the $^{3}J_{\text{C-5,H-1}'}$ coupling constants were recorded on a Bruker DRX 399 spectrometer. The inverse gated decoupling technique was employed. Infrared (IR) spectra were recorded on a Buck Scientific M-500 spectrometer as thinly dispersed films (from CH_2Cl_2) between sodium chloride plates unless otherwise stated. Low resolution (EI/FAB) mass spectra were recorded using a Fisons Autospec or Kratos mass spectrometer. Optical rotations were carried out using a Optical Activity Mod. AA-1000 digital polarimeter with a cell path length of 5 cm. Melting points were carried out on a Gallenkamp melting point apparatus and are uncorrected.

Preparation of 4*Z*-(ethoxymethylen)-2-phenyl-5(4*H*)-oxazolone 3a: To a stirred mixture of hippuric acid (2.47 g, 13.8 mmol), ethyl orthoformate (2.3 mL, 13.8 mmol),4-(dimethylamino)pyridine (catalytic amount aprox. 3 mg) at room temperature and under an argon atmosphere was added acetic anhydride (2.6 mL, 27.6 mmol) and then refluxed for 30 min. The reaction mixture was concentrated under vacuo and the obtained brown oil was purified by column chromatography (SiO_2, ethyl acetate/*n*-hexane 2:8) and crystallized from *n*-hexane to give **3a** (2.65 g, 88%), orange needles, m.p. 94–96°C; Lit.[14] m.p. 94–95°C; $R_f = 0.36$ (ethyl acetate/*n*-hexane 2:8); IR and ^{1}H NMR similar to those reported.[14] ^{13}C NMR 100 MHz ($CDCl_3$): δ 168.3 (>*C*=O), 159.2 (-N=*C*-), 152.5 (=*C*H-), 132.2 (=*C*H-, Ar), 128.6 (=*C*H-, Ar), 127.5 (=*C*H-, Ar), 125.7 (-*C*-, Ar), 117.6 (-HC=*C*<), 72.7 (-O*C*H$_2$-), 15.1 (-*C*H$_3$). Compound **3a** was slowly dissolved (2 days) in *iso*-propanol, left at room temperature for 24 days and then new crystals of 4-(*iso*-propoxymethylen)-2-phenyl-5(4*H*)-oxazolone were obtained as yellow plates, m.p. 122–124°C; IR (film): 3065, 3025, 2985, 2930, 1790 (C=O), 1620 (C=N), 1280, 1225, 1150, 980, 940, 830, 770, 715 cm^{-1}; ^{1}H NMR 400 MHz ($CDCl_3$): δ 8.07 (1H, d, $J = 7.6$, Ar), 7.54 (1H, dd, $J = 7.2$, 7.0, Ar), 7.60–7.40 (3H, m, Ar), 7.40 (1H, s, vinyl *H*), 5.13 (0.5H, heptet, $J = 6.2$, C*H*Me$_2$), 4.62 (0.5H, heptet, $J = 6.2$, C*H*Me$_2$), 1.48 (3H, d, $J = 6.2$, CH(C*H*$_3$)$_2$), 1.31 (3H, d, $J = 6.2$, CH(C*H*$_3$)$_2$); ^{13}C NMR 100 MHz ($CDCl_3$): δ 168.6, 159.2, 151.7, 132.3, 128.7, 127.7, 125.9, 117.5, 81.0, 22.4; Anal. calcd. for $C_{13}H_{13}NO_3$: C, 67.5; H, 5.7; N, 6.1. Found: C, 67.7; H, 5.7; N, 5.9.

Preparation of 4-(1′-ethoxyethylen)-2-phenyl-5(4*H*)-oxazolone 3b: To a stirred mixture of hippuric acid (2.00 g, 11.2 mmol), triethyl orthoacetate (2.1 mL, 11.2 mmol), 4-(dimethylamino)pyridine (catalytic amount aprox. 3 mg) at room temperature and under an argon atmosphere was added acetic anhydride (2.1 mL, 21.1 mmol) and heated to 90°C (oil bath temperature) for 1 h. The reaction mixture was concentrated under vacuo and the obtained brown oil was purified by column chromatography

(SiO_2, ethyl acetate/*n*-hexane 1:9) and crystallized from ethyl acetate to give **3b** (1.01 g, 39%), yellow needles, m.p. 112–114°C; Lit.[1d] m.p. 112–113°C for *E* isomer and 136–138°C for *Z* isomer; $R_f = 0.97$ (ethyl acetate/*n*-hexane 2:8); IR (film): 3050, 2990, 2920, 1745 (C=O), 1620 (C=N), 1574, 1540, 1440, 1380, 1280, 1150, 1053, 973, 890, 790 cm^{-1}; ^1H NMR 400 MHz ($CDCl_3$): δ 8.00 (2H, d, $J = 7.1$, Ar), 7.49–7.43 (3H, m, Ar), 4.74 (2H, q, $J = 7.0$, CH_2O), 2.53 (3H, s, C=CCH_3), 1.47 (3H, t, $J = 7.0$, CH_3CH_2O); ^{13}C NMR 100 MHz ($CDCl_3$): δ 168.2, 166.6, 154.9, 131.2, 128.3, 126.7, 126.2, 114.6, 68.69, 17.1, 15.01; Anal. calcd. for $C_{13}H_{13}NO_3$: C, 67.5; H, 5.7; N, 6.1. Found: C, 67.4; H, 5.7; N, 6.1.

Preparation of 4-(1′-ethoxypropylen)-2-phenyl-5(4*H*)-oxazolone 3c: To a stirred mixture of hippuric acid (1.62 g, 8.94 mmol), triethyl orthopropionate (1.8 mL, 8.9 mmol), 4-(dimethylamino)pyridine (catalytic amount aprox. 3 mg) at room temperature and under an argon atmosphere was added acetic anhydride (1.7 mL, 17.4 mmol) and heated to 90°C (oil bath temperature) for 1 h. The reaction mixture was concentrated under vacuo and the obtained brown oil was purified by column chromatography (SiO_2, ethyl acetate/*n*-hexane 0.5:9.5) and the product crystallized from ethyl acetate to give **3c** (0.55 g, 48%), plates, m.p. 58–59°C; $R_f = 0.54$ (ethyl acetate/*n*-hexane 1:9); IR (film): 3050, 2990, 2967, 2922, 2866, 1778 (C=O), 1642 (C=N), 1585, 1563, 1450, 1393, 1308, 1250, 1150, 1211, 1075, 970, 883, 770, 700 cm^{-1}; ^1H NMR 400 MHz ($CDCl_3$): δ 7.97 (2H, d, $J = 7.1$, Ar), 7.49–7.42 (3H, m, Ar), 4.87 (2H, q, $J = 7.0$, CH_2O), 2.90 (2H, q, $J = 7.4$, CH_2C=C), 1.44 (3H, t, $J = 7.0$, CH_3CH_2O), 1.20 (2H, t, $J = 7.5$, CH_3CH_2C=C); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 168.3, 154.9, 131.4, 128.6, 126.9, 126.6, 113.8, 70.0, 25.0, 15.3, 11.6; Anal. calcd. for $C_{14}H_{15}NO_3$: C, 68.6; H, 6.2; N, 5.7. Found: C, 68.5; H, 6.2; N, 5.5.

Preparation of 4-(1′-ethoxy-1′-phenylmethylen)-2-phenyl-5(4*H*)-oxazolone 3d: To a stirred mixture of hippuric acid (1.49 g, 8.32 mmol), triethyl orthobenzoate (1.9 mL, 8.32 mmol), 4-(dimethylamino)pyridine (catalytic amount aprox. 3 mg) at room temperature and under an argon atmosphere was added acetic anhydride (1.5 mL, 16.2 mmol) and then was refluxed for 4 h. The reaction mixture was concentrated under vacuo and the obtained brown oil was purified by column chromatography (SiO_2, ethyl acetate/*n*-hexane 1:9) to give **3d** (735 mg, 30%) as viscous yellow oil; mixture of isomers in the ratio of 4.9:1.0 determined by ^1H NMR; $R_f = 0.64$ (ethyl acetate/*n*-hexane 1:9); IR (film): 3058, 2980, 2900, 2930, 2840, 1790 (C=O), 1630 (C=N), 1597 (C=C), 1495, 1450, 1300, 1290, 1195, 1098, 996, 883, 849, 770 cm^{-1}; ^1H NMR 400 MHz ($CDCl_3$): δ 8.06 (0.34H, d, $J = 7.1$, Ar), 8.01 (1.66H, d, $J = 7.1$, Ar), 7.91–7.89 (2H, m, Ar), 7.58–7.42 (6H, m, Ar), 4.69 (0.34H, q, $J = 7.0$, MeCH_2O), 4.29 (1.66H, q, $J = 7.0$, MeCH_2O), 1.46 (3H, t, $J = 7.0$, CH_3CH_2O); ^{13}C NMR 100 MHz

($CDCl_3$): δ 165.1, 164.9, 158.1, 131.9, 131.4, 130.5, 129.5, 128.6, 128.3, 127.3, 126.2, 121.8, 70.5, 70.1, 15.5; Acc Mass (FAB): $C_{18}H_{16}NO_3$ (MH^+); calcd. 294.1130 found 294.1110.

Preparation of (*E*)-4-(*N*-benzylaminomethylen)-2-phenyl-5(4*H*)-oxazolone 4a: To a stirred solution of **3a** (501 mg, 2.31 mmol) in anhydrous dichloromethane (10 mL) at 0°C and under an argon atmosphere was added dropwise benzylamine (277 μL, 2.54 mmol). After 5 h the solvent was removed under vacuo and the crude product crystallized from ethyl acetate to give **4a** (440 mg, 69%), plates, m.p. 141–143°C; Lit.[17] m.p. 136–138°C (ethanol); $R_f = 0.34$ (ethyl acetate/*n*-hexane 3:7); IR and ^{1}H NMR similar to those reported;[17] ^{13}C NMR 100 MHz ($CDCl_3$): δ 168.2 (>*C*=O), 155.3, 147.2 (=*C*H-), 135.9, 130.5, 129.1, 128.6, 128.4, 127.6, 127.0, 126.1, 110.4 (-HC=*C*<), 52.9 (-*C*H_2Ph); Anal. calcd. for $C_{17}H_{14}N_2O_2$: C, 73.4; H, 5.1; N, 10.1. Found: C, 73.3; H, 5.1; N, 9.7.

Preparation of (1′*R*)-(*Z*)-4-[*N*-(1′-phenylethylamino)-methylen]-2-phenyl-5(4*H*)-oxazolone 5a: To a stirred solution of **3a** (481.4 mg, 2.2 mmol) in anhydrous dichloromethane (5 mL) at room temperature and under an argon atmosphere was added dropwise (*R*)-(+)-1-phenylethylamine (314 μL, 2.4 mmol). After 24 h the solvent was evaporated under *vacuo*. The crude product was purified by column chromatography (SiO_2, diethyl ether/*n*-hexane 3:7) and crystallized from ethyl acetate/*n*-hexane to give **5a** (355 mg, 55%), yellow plates, m.p. 114–118°C; $R_f = 0.40$ (diethyl ether/*n*-hexane 3:7); $[\alpha]_D^{20} = -174.0$ (*c* 1.0, $CHCl_3$); IR (KBr): 3262 (NH), 3062, 2976, 1742 (C=O), 1644 (C=N), 1492, 1449, 1323, 1291, 1199, 1110, 984, 894, 845, 754, 697 cm^{-1}; ^{1}H NMR 400 MHz ($CDCl_3$): δ 7.94 (2H, d, $J = 7.5$, Ar), 7.47–7.26 (8H, m, vinyl *H* and Ar), 6.5 (1H, d, $J = 9.0$, N–H), 4.65 (1H, m, MeC*H*NH), 1.68 (3H, d, $J = 6.8$, CH_3HC); ^{13}C NMR 100 MHz ($CDCl_3$): δ 167.8 (>*C*=O), 155.3 (-*C*-, Ar), 141.5 (=*C*H-), 140.9, 131.0, 129.2, 128.7, 128.4, 126.9 (-*C*-, Ar), 126.6, 126.3, 110.0 (-HC=*C*<), 57.1 (-*C*H-), 22.7 (-*C*H_3); Anal. calcd. for $C_{18}H_{16}N_2O_2$: C, 74.0; H, 5.5; N, 9.6. Found: C, 74.0; H, 5.4; N, 9.6.

Preparation of 4-(*N*,*N*-diethylaminomethylen)-2-phenyl-5(4*H*)-oxazolone 6a: To a stirred solution of **3a** (100 mg, 0.46 mmol) in anhydrous dichloromethane (1 mL) at reflux and under an argon atmosphere was added dropwise diethylamine (52 μL, 0.51 mmol). After 2.5 h the solvent was evaporated under vacuo and the crude product was purified by column chromatography (SiO_2, ethyl acetate/*n*-hexane 2:8) to give **6a** (105 mg, 93%), yellow viscous liquid at room temperature, solid in the fridge, m.p. 45–50°C; Lit.[7b] oil, $R_f = 0.83$ (ethyl acetate/*n*-hexane 2:8); Spectral data (IR, ^{1}H and ^{13}C NMR) identical to those reported[7b]; MS (FAB) *m*/*z* 245 (MH^+), 244, 229, 128, 111; Acc Mass (FAB): $C_{14}H_{17}N_2O_2$ (MH^+); calcd. 245.12900. Found: 245.12905.

Preparation of 4-(*N*-morpholinomethylen)-2-phenyl-5(4*H*)-oxazolone 7a: To a stirred solution of **3a** (200 mg, 0.92 mmol) in anhydrous dichloromethane (4 mL) at reflux and under an argon atmosphere was added dropwise morpholine (88 μL, 0.10 mmol). After 3.7 h the solvent was evaporated under vacuo and crystallized from ethyl acetate/*n*-hexane to give **7a** (180 mg, 76%), prisms, m.p. 157–158°C; $R_f = 0.84$ (ethyl acetate/*n*-hexane 4:6); IR (film): 3014, 2971, 2910, 1750 (C=O), 1643 (C=N), 1266, 740 cm^{-1}; ^1H NMR 400 MHz ($CDCl_3$): δ 7.93–7.89 (2H, m, Ar), 7.44–7.38 (4H, m, Ar), 7.07 (1H, s, vinyl *H*), 4.42 (2H, dd, $J = 4.8$, 4.4, CH_2N), 3.81 (4H, dd, $J = 4.4$, 9.6, CH_2O), 3.50 (2H, dd, $J = 4.8$, 4.4, CH_2N); ^{13}C NMR 100 MHz ($CDCl_3$): δ 170.2, 153.6, 140.7, 130.8, 128.6, 127.1, 126.5, 107.9, 66.9, 66.3, 54.3, 47.6; Acc Mass (EI): $C_{14}H_{14}N_2O_3$ (M^+); calcd. 259.1083. Found: 259.1069.

Preparation of 4-(*N*,*N*-dibenzylaminomethylen)-2-phenyl-5(4*H*)-oxazolone 8a: To a stirred solution of **3a** (101.6 mg, 0.47 mmol) in anhydrous dichloromethane (3.5 mL) at 0°C and under an argon atmosphere was added dropwise dibenzylamine (99 μL, 0.52 mmol). After 20 h the solvent was removed under vacuo and the crude product was crystallized from ethyl acetate to give **8a** (118.4 mg, 69%), plates, m.p. 164–165°C; $R_f = 0.65$ (ethyl acetate/*n*-hexane 3:7); IR (film): 3024, 2990, 2910, 2840, 1733 (C=O), 1640 (N=C), 1585, 1574, 1450, 1390, 1325, 1235, 1210, 1130, 1064, 974, 860, 758, cm^{-1}; ^1H NMR 400 MHz ($CDCl_3$): δ 7.93 (2H, d, $J = 6.5$, Ar), 7.41–7.34 (12H, m, Ar and vinyl *H*), 7.22 (2H, d, $J = 7.6$, Ar), 5.28 (2H, s, CH_2NR_2), 4.40 (2H, s, CH_2NR_2); ^{13}C NMR 100 MHz ($CDCl_3$): δ 170.3, 153.7, 142.2, 135.8, 134.6, 130.7, 129.1, 128.9, 128.6, 128.5, 128.1, 127.0, 127.1, 126.5, 108.2, 59.2, 51.5; Anal. calcd. for $C_{24}H_{20}N_2O_2$: C, 78.2; H, 5.5; N, 7.6. Found: C, 78.0; H, 5.3; N, 7.4.

Preparation of 4-[1′-(*N*-benzylamino)-ethylen]-2-phenyl-5(4*H*)-oxazolone 4b: To a stirred solution of **3b** (370 mg, 1.6 mmol) in anhydrous dichloromethane (10 mL) at 0°C and under an argon atmosphere was added dropwise benzylamine (192 μL, 1.8 mmol). After 7 h the solvent was evaporated under vacuo and the crude product was crystallized from ethyl acetate to give **4b** (400.7 mg, 86%), yellow needles, m.p. 143–145°C; mixture of isomers in the ratio of 2.0:1.0 determined by ^1H NMR; Lit.[1d,18] *Z*-isomer m.p. 127–129°C; $R_f = 0.40$ (ethyl acetate/*n*-hexane 3:7); IR (film): 3270 (NH), 3047, 3024, 2920, 1720 (C=O), 1630 (N=C), 1574, 1550, 1450, 1430, 1360, 1325, 1087, 1053, 985, 940, 860, 735, 700 cm^{-1}; ^1H NMR 400 MHz ($CDCl_3$): δ 8.83 (1H, s, NHR_2), 7.93 (2H, dd, $J = 4.7$ and 3.5, Ar) 7.40–7.26 (8H, m, Ar), 4.6 and 4.55 (2H, d, $J = 5.6$, CH_2NH), 2.52 and 2.45 (3H, s, $H_3CC{=}C$); ^{13}C NMR

100 MHz ($CDCl_3$): δ 166.6, 157.0, 153.0, 136.4, 130.4, 130.0, 129.0, 128.5, 128.0, 127.1, 127.0, 126.8, 126.3, 125.9; 108.2, 47.3, 46.8, 14.2, 12.4; Anal. calcd. for $C_{18}H_{16}N_2O_2$: C, 74.0; H, 5.5; N, 9.6. Found: C, 74.0; H, 5.6; N, 9.6.

Preparation of (1″*R*)-4-[1′-[*N*-(1″-phenylethylamino)-]-methylen]-2-phenyl-5(4*H*)-oxazolone 5b: To a stirred solution of **3b** (183.9 mg, 0.80 mmol) in anhydrous dichloromethane (4 mL) at room temperature and under an argon atmosphere was added dropwise (*R*)-(+)-1-phenylethylamine (113 μL, 0.88 mmol). After 24 h the solvent was evaporated under vacuo and the crude product was purified by column chromatography (SiO_2, ethyl acetate/*n*-hexane 3:7) to give **5b** (123 mg, 51%), as a yellow viscous liquid, mixture of isomers in the ratio of 1.7:1.0 determined by ^{1}H NMR; $R_f = 0.40$ (diethyl ether/*n*-hexane 3:7); $[\alpha]_D^{20} = -495.6$ (*c* 1.5, $CHCl_3$); IR (film): 3365 (NH), 3062, 2979, 2929, 1728 (C=O), 1626 (C=N), 1494, 1418, 1325, 1232, 1123, 1087, 969, 880, 768, 694 cm^{-1}; ^{1}H NMR 400 MHz ($CDCl_3$): δ 8.80 (2H, d, $J = 7.4$, N–H), 7.99–7.91 (2H, m, Ar), 7.41–7.11 (8H, m, Ar), 4.79 (1H, m, PhC*H*Me), 2.36 and 2.29 (3H, s, CH_3C=C), 1.60 (3H, d, $J = 6.8$, PhCHCH_3); ^{13}C NMR 100 MHz ($CDCl_3$): δ 167.8, 166.4, 159.3, 156.5, 152.5, 151.2, 142.7, 142.6, 130.3, 129.8, 128.9, 128.4, 127.6, 127.4, 127.1, 126.2, 126.0, 125.8, 125.3, 109.4, 108.0, 53.5, 52.8, 24.1, 23.8, 14.4, 14.0; MS (FAB) *m*/*z* 307 (MH^+), 306, 203, 202, 105; Acc Mass (EI): $C_{19}H_{18}N_2O_2$ (M^+); calcd. 306.13683. Found: 306.13835.

Preparation of 4-[1′-(*N*,*N*-dibenzylamino)-ethylen]-2-phenyl-5(4*H*)-oxazolone 8b: To a stirred solution of **3b** (446 mg, 1.9 mmol) in anhydrous dichloromethane (10 mL) at 0°C and under an argon atmosphere was added dropwise dibenzylamine (408 μL, 2.1 mmol). After 3 h at 0°C and 18 h at room temperature (no reaction by TLC) the reaction mixture was refluxed. After 12 days, the solvent was evaporated under vacuo and the crude product was purified by column chromatography (SiO_2, ethyl acetate/*n*-hexane 2:8) and crystallized from ethyl acetate/*n*-hexane to give recovered **3b** (162.6 mg, 36%) and **8b** (63.5 mg, 9%), as white plates, m.p. 188–190°C; $R_f = 0.8$ (ethyl acetate/*n*-hexane 3:7); IR (film): 3100, 3090, 3060, 3035, 3015, 2990, 1700 (C=O), 1640 (N=C), 1619, 1560, 1545, 1505, 1450, 1430, 1390, 1257, 962, 690 cm^{-1}; ^{1}H NMR 400 MHz ($CDCl_3$): δ 7.79 (2H, d, $J = 6.7$, Ar), 7.40–7.25 (13H, m, Ar), 4.5–5.5 (4H, br, PhCH_2N), 2.74 (3H, s, CH_3C=C); ^{13}C NMR 100 MHz ($CDCl_3$): 169.2, 156.5, 150.5, 130.1, 128.9, 128.5, 127.7, 127.4, 126.9, 126.2, 108.3, 54.7, 16.2; Anal. calcd. for $C_{25}H_{22}N_2O_2$: C, 78.5; H, 5.8; N, 7.3. Found: C, 78.5; H, 5.6; N, 7.2.

Preparation of 4-[1′-(*N*-benzylamino)-propylen]-2-phenyl-5(4*H*)-oxazolone 4c: To a stirred solution of **3c** (73 mg, 0.30 mmol) in anhydrous

dichloromethane (3 mL) at 0°C and under an argon atmosphere was added dropwise benzylamine (36 μL, 0.33 mmol). After 6 h the solvent was evaporated under vacuo and the crude product was crystallized from ethyl acetate to give **4c** (55.2 mg, 62%), yellow needles, m.p. 105–108°C; $R_f = 0.60$ (ethyl acetate/*n*-hexane 3:7); mixture of isomers in the ratio of 1.3:1.0 determined by ^{1}H NMR; IR (film): 3260 (NH), 3035, 3024, 2970, 2920, 2870, 1710 (C=O), 1642 (N=C), 1600, 1585, 1563, 1540, 1506, 1460, 1390, 1340, 1235, 1166, 1087, 1030, 883, 725 cm^{-1}; ^{1}H NMR 400 MHz ($CDCl_3$): δ 8.76 and 7.05 (1H, s, N*H*), 7.93 (2H, d, $J = 7.6$, Ar), 7.40–7.25 (8H, m, Ar), 4.61 (1.12H, d, $J = 6.6$, PhCH_2NH), 4.59 (0.88H, d, $J = 8.3$, PhCH_2NH), 3.00 (1.12H, q, $J = 7.4$, CH_3CH_2), 2.88 (0.88H, q, $J = 7.4$, CH_3CH_2), 1.28 (1.68H, t, $J = 7.4$, CH_3CH_2), 1.27 (1.32H, t, $J = 7.4$, CH_3CH_2); ^{13}C NMR 100 MHz ($CDCl_3$): δ 167.0, 164.8, 162.1, 136.8, 130.4, 129.9, 129.1, 129.0, 128.5, 128.2, 128.0, 127.7, 127.1, 126.8, 126.3, 126.0, 118.0, 109.0, 107.0, 47.0, 46.6, 21.1, 19.3, 12.4, 12.3; Anal. calcd. for $C_{19}H_{18}N_2O_2$: C, 74.5; H, 5.9; N, 9.1; Found: C, 74.5; H, 5.8; N, 9.1.

Preparation of 4-(*N*,*N*-dibenzylaminopropylen)-2-phenyl-5(4*H*)-oxazolone 8c: To a stirred solution of **3c** (339 mg, 1.4 mmol) in anhydrous benzene (3 mL) at room temperature and under an argon atmosphere was added dropwise dibenzylamine (291 μL, 1.5 mmol) and refluxed for 12 days. The solvent was evaporated under vacuo and the crude product was purified by column chromatography (SiO_2, ethyl acetate/*n*-hexane 3:7) and crystallized from ethyl acetate/*n*-hexane to give recovered **3c** (65.6 mg, 19%) and **8c** (314.5 mg, 57%), plates, m.p. 140–142°C; $R_f = 0.50$ (ethyl acetate/*n*-hexane 3:7); IR (film): 3070, 3050, 3020, 1700 (C=O), 1670 (N=C), 1565, 1560, 1460, 1420, 1240, 1120, 1100, 1008, 940, cm^{-1}; ^{1}H NMR 400 MHz ($CDCl_3$): δ 7.79 (2H, d, $J = 5.6$, Ar), 7.38–7.25 (13H, m, Ar), 4.6–5.5 (4H, br, PhCH_2N), 3.19 (2H, q, $J = 6.5$, CH_2CH_3), 1.29 (3H, t, $J = 6.5$, CH_2CH_3); ^{13}C NMR 100 MHz ($CDCl_3$): δ 168.4, 162.1, 150.8, 136.7, 130.1, 129.0, 128.5, 127.8, 127.5, 126.9, 126.2, 107.5, 54.1, 22.5, 13.3; Anal. calcd. for $C_{26}H_{24}N_2O_2$: C, 78.7; H, 6.1; N, 7.1. Found: C, 79.4; H, 6.2; N, 7.1.

Preparation of 4-[1′-(*N*-benzylamino)-1′-phenylmethylen]-2-phenyl-5(4*H*)-oxazolone 4d: To a stirred solution of **3d** (513 mg, 1.8 mmol) in anhydrous dichloromethane (3 mL) at 0°C and under an argon atmosphere was added dropwise benzylamine (210 μL, 1.9 mmol). After 6 h at 0°C and 4 days at room temperature the solvent was evaporated under vacuo purified by column chromatography (SiO_2, dichloromethane/*n*-hexane 7:3) and the crude product was crystallized from ethyl acetate/*n*-hexane to give **4d** (217 mg, 34%), as yellow plates, m.p. 144–146°C; $R_f = 0.45$ (dichloromethane/*n*-hexane 7:3); mixture of

isomers in the ratio of 5.7:1.0 determined by ^{1}H NMR; IR (film): 3260 (N–H), 3110, 3090, 3045, 3024, 1710 (C=O), 1642 (N=C), 1620, 1563, 1540, 1495, 1450, 1430, 1390, 1221, 1098, 1007, 962, 883, 769 cm^{-1}; ^{1}H NMR 400 MHz 8.89 (1H, s, N*H*), 7.88 (0.3H, m, Ar), 7.87 (1.7H, m, Ar), 7.51–7.18 (13H, m, Ar), 4.47 (1.7H, q, $J = 6.4$, CH_2N), 4.33 (0.3 H, q, $J = 6.4$, CH_2N); ^{13}C NMR 100 MHz ($CDCl_3$): δ 169.0, 160.0, 137.3, 130.7, 130.5, 130.2, 129.4, 128.9, 128.8, 128.6, 128.5, 128.4, 127.8, 127.3, 127.2, 126.9, 126.6, 126.3, 110.3, 48.8, 48.1; Anal. calcd. for $C_{23}H_{18}N_2O_2$: C, 78.0; H, 5.2; N, 7.9. Found: C, 77.9; H, 5.1; N, 7.9.

Preparation of 4-[1′-(*N*-dibenzylamino)-1′-phenylmethylen]-2-phenyl-5(4*H*)-oxazolone 8d: To a stirred solution of **3d** (422 mg, 1.4 mmol) in anhydrous toluene (6 mL) at room temperature and under an argon atmosphere was added dropwise dibenzylamine (304 μL, 1.6 mmol) and was refluxed for 6 days. The solvent was evaporated under vacuo and the crude product was purified by column chromatography (SiO_2, ethyl acetate/*n*-hexane 3:7) to give **8d** (80 mg, 13%) as viscous yellow oil, $R_f = 0.80$ (ethyl acetate/*n*-hexane 3:7) and the opened product **9** (246 mg, 35%), as plates, m.p. 145–150°C; $R_f = 0.25$ (ethyl acetate/*n*-hexane 3:7); **8d**: IR (film): 3060, 3027, 2925, 2858, 1747 (C=O), 1616 (N=C), 1536, 1448, 1328, 1294, 1193, 1106, 1072, 1008, 933 cm^{-1}; ^{1}H NMR 400 MHz ($CDCl_3$): 7.95 (2H, d, $J = 6.9$, Ar), 7.94 (2H, d, $J = 7.7$, Ar), 7.54–7.22 (16H, m, Ar), 5.6 and 4.2 (4H, s, PhCH_2N); ^{13}C NMR 100 MHz ($CDCl_3$): δ 167.4, 156.8, 152.8, 133.6, 130.4, 129.8, 128.9, 128.7, 128.6, 128.4, 127.7, 126.3, 109.1, 53.9; MS (EI) *m*/*z* 444 (M^+), 353, 335, 105, 91, 77; Acc Mass (EI): $C_{30}H_{24}N_2O_2$ (M^+); calcd. 444.18378, found 444.18466; **9:** IR (KBr): 3239 (N–H), 3060, 3027, 2975, 1660 (C=O), 1610 (C=O), 1515, 1481, 1444, 1305, 1108, 1076, 1027 cm^{-1}; ^{1}H NMR 400 MHz ($CDCl_3$): δ 8.22 (1H, s, N*H*), 7.85 (2H, d, $J = 7.4$, Ar), 7.54–6.82 (18H, m, Ar), 4.45 (2H, s, PhCH_2N), 4.27 (2H, s, PhCH_2N), 3.74 (2H, q, $J = 6.7$, CH_2CH$_3$), 1.29 (3H, t, $J = 6.7$, CH$_2$CH_3); ^{13}C NMR 100 MHz ($CDCl_3$): δ 165.8, 163.7, 142.6, 136.1, 135.7, 134.0, 131.8, 131.6, 129.2, 129.0, 128.6, 128.4, 128.3, 128.0, 127.2, 126.9, 117.5, 65.7, 52.0, 46.7, 15.6; Anal. calcd. for $C_{32}H_{26}N_2O_3$: C, 79.0; H, 5.4; N, 5.8. Found: C, 78.2; H, 6.0; N, 5.7.

Preparation of 4*Z*-(phenyl-methylen)-2-phenyl-5(4*H*)-oxazolone 12: This compound was prepared from hippuric acid following reported procedure,[13] m.p. 163–164°C; Lit.[15] m.p. 165–166°C, Lit.[13] m.p. 170°C, IR and ^{1}H NMR similar to those reported[13]; ^{13}C NMR 100 MHz ($CDCl_3$): δ 167.6 (>*C*=O) (C5, $J_{C5,H1'} = 5.4$ Hz), 163.5, 134.1, 133.5, 133.2, 132.5, 131.9, 131.7 (-HC=*C*<), 130.9, 130.4, 129.7, 129.2, 128.1, 127.5, 125.6 (=*C*H-).

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