Pergamon

Tetrahedron 56 (2000) 3857–3866

TETRAHEDRON

Regioselective Synthesis of *N*-Substituted 4-Methylene-2-oxazolidinones and 4-Oxazolin-2-ones. Study of Reactivity in Thermal Michael Conjugate Additions

Rafael Martínez, Hugo A. Jiménez-Vázquez and Joaquín Tamariz*

Departamento de Química Orgánica, Escuela Nacional de Ciencias Biológicas, I.P.N. Prol. Carpio y Plan de Ayala, 11340 Mexico, DF, Mexico

Received 3 March 2000; accepted 19 April 2000

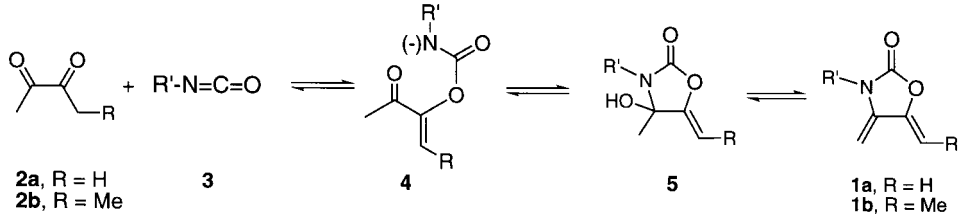
Abstract—*N*-Substituted 4-methylene-2-isoxazolidinones **9a**–**9e** have been prepared from the tandem condensation of isocyanates **3** with α-ketol **7**. In a more polar solvent (DMF) the same reaction led to stereoisomeric alcohols **11** and **12**, which could be transformed to the thermodynamically more stable isomers 4-oxazolin-2-ones **10** in good yield. Thermal conjugate additions of both heterocycles **9a** and **10a** to enone **13** provided the C-5 adduct **15**. When the reaction was carried out with the captodative olefin **17**, the unexpected aniline **18** was isolated. The regiochemistry of the Michael addition was rationalized in terms of FMO theory by ab initio calculations.

Introduction

We have recently developed a promising methodology for the one-step synthesis of novel *N*-substituted *exo*-2-oxazolidinone dienes **1**, which involves a tandem condensation of aliphatic α-diketones **2** to isocyanates **3**, and intramolecular cyclization of the carbamate anion intermediate **4** to give the 4-hydroxy-5-methylene-oxazolidinone **5** (Scheme 1).[1] Dehydration of the latter leads to dienes **1** in fair yields. When the unsymmetrical α-diketone **2b** was treated under these conditions, dienes **1b** were formed as a single regio- and stereo-isomer.

The versatility of this method might be further improved by taking advantage of this cascade process with a new class of substrate **6** that would bear, like the α-diketones **2**, potential nucleophilic and electrophilic centers. One could consider 3-hydroxy-2-butanone (**7**) as a synthetic equivalent of **6**, considering that the hydroxy group would be the nucleophilic group, and the carbonyl group, the electron deficient center (Scheme 2). Isocyanates **3** would play the role of the counterpart. These species may provide either 4-methylene-2-oxazolidinones **9** or 4-oxazolin-2-ones **10**, depending on the orientation of the dehydration step, and if this could be selective. The latter are useful synthons and precursors for a variety of aldehydes, amino ketones, and alcohols.[2] They have also been used as protecting groups,[3] and the *N*-aryl 5-*t*-butyl-4-chloro-4-oxazolin-2-ones derivatives have significant herbicide activity.[4]

Owing to the importance of these heterocycles, several methodologies have been designed for their selective synthesis,[5] such as the cyclization of *O*-propargylic carbamates catalyzed by metal ions,[6] the condensation of tertiary propargylic alcohols with isocyanates,[7] reaction of α-monosubstituted oximes with methyl carbonate,[8] and



Scheme 1.

Keywords: 4-methylene-2-oxazolidinones; 4-oxazolin-2-ones; Michael addition; FMO theory.
* Corresponding author. Fax: +52-55866621; e-mail: jtamariz@woodward.encb.ipn.mx

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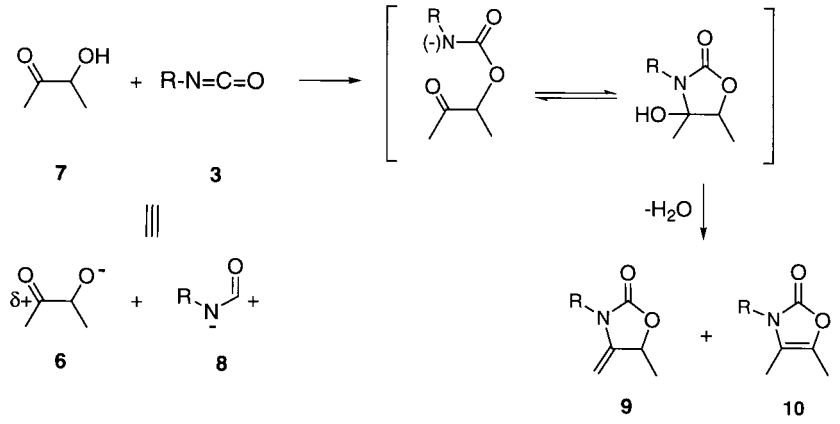


Scheme 2.

introduction of carbon dioxide into acetylenic amines.[9] To the best of our knowledge, only two examples have been reported using the reaction between α-hydroxy ketones and isocyanates; however, they are limited to the preparation of either 4-oxazolin-2-ones,[10] or 4-methylene-5,5-dimethyl-2-oxazolidinones.[11]

Herein, we report that the condensation and intramolecular cyclization of α-ketol **7** with isocyanates **3** can be a very efficient methodology for the regioselective preparation of *N*-substituted 4-methylene-2-oxazolidinones **9**, or *N*-substituted 4-oxazolin-2-ones **10**, depending on the polarity of the solvent. Additional information about the reactivity of these compounds toward Michael acceptors, and the possible role of frontier molecular orbitals in explaining the regiochemistry, is also provided.

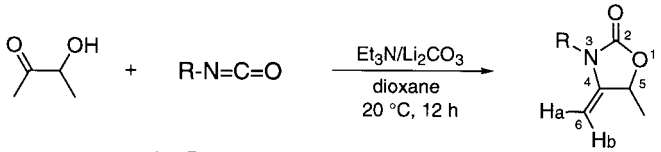
Results and Discussion

The reaction of isocyanates **3a**–**3e** with α-ketol **7** was found to proceed smoothly under mild conditions (dioxane/Li_2CO_3, room temperature, 12 h), similar to those used for the preparation of dienes **1**, to give *N*-substituted 4-methylene-2-oxazolidinones **9a**–**9e** in fair yields (57–86%) as the exclusive regioisomer (Scheme 3). The endocyclic isomeric olefin **10** was not detected in the crude reaction mixtures. An increase of the temperature (100°C) does not seem to have a significant effect either on the outcome of the process, or on the regiochemistry of the dehydration. The use of another solvent of low polarity, such as toluene, furnished comparable results. We also investigated the effect of molecular sieves (4 Å) as an alternative dehydrating agent, giving also the exocyclic olefinic heterocycle in comparable yield.

These compounds were fully characterized by spectroscopy, and the structure of derivative **9b** was also determined by X-ray crystallography (Fig. 1). It is noteworthy that the chemical shifts for the vinylic protons H-6a and H-6b are reversed in comparison to those analogous to dienic protons of **1a** and **1b**. Thus, in compounds **9**, proton H-6a was located down-field with respect to H-6b (ca. 0.1 ppm). In comparison, for the corresponding protons of dienes **1**, H-6a was shielded up-field with respect to H-6b to a greater extent (ca. 0.4 ppm), whatever the substituent be at the nitrogen atom.

When a more polar solvent (DMF) was used, under similar conditions of additive, temperature, and reaction time (Li_2CO_3, 25°C, 12 h), the reaction provided a mixture of alcohols **11/12**. Scheme 4 summarizes the results, showing that the process was stereoselective, since the *anti* dimethyl alcohol **11** was the major epimer. The structure was established by nOe experiments, detecting an enhancement of the signal of the methyl Me-4 when the proton H-5 was irradiated. This assignment was confirmed by X-ray crystallography of alcohol **11d** (Fig. 1).

The dehydration step was carried out by heating to reflux a DMSO solution of the mixture of alcohols **11/12**,[12] yielding almost quantitatively the endocyclic elimination products



7

3a, R = Ph
3b, R = C_6H_4p-Cl
3c, R = C_6H_4p-CH_3
3d, R = C_6H_4p-OMe
3e, R = C_2H_4Cl

9a-9e

Scheme 3.

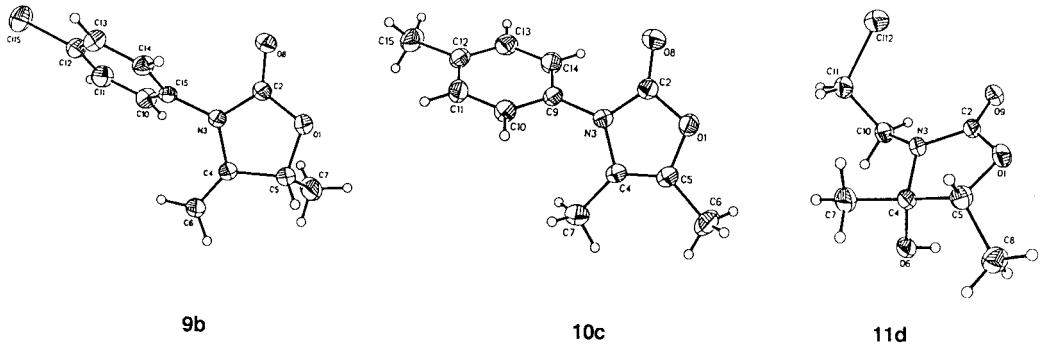


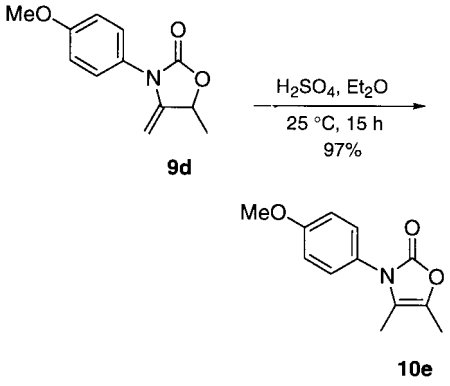
Figure 1. X-Ray structures of compounds **9b**, **10c**, and **11d**.

10 (Scheme 4). In the ^{1}H and ^{13}C NMR spectra of all the derivatives, the methyl group Me-6 on C-4 is shifted upfield with respect to methyl group Me-7, as established by nOe and HETCOR experiments. The X-ray structure of **10c** is depicted in Fig. 1.

The preference of the *anti* isomer **11** may be accounted for possibly by thermodynamic control at the cyclization step. The conformational intermediates **13a** and **13b**, which derived from the first addition of the alkoxide of **7** to isocyanates **3**, may be interconverting by C–C bond rotation, the equilibrium being shifted to **13a**, in order to maintain the *anti* relationship of the methyl groups (Scheme 4).

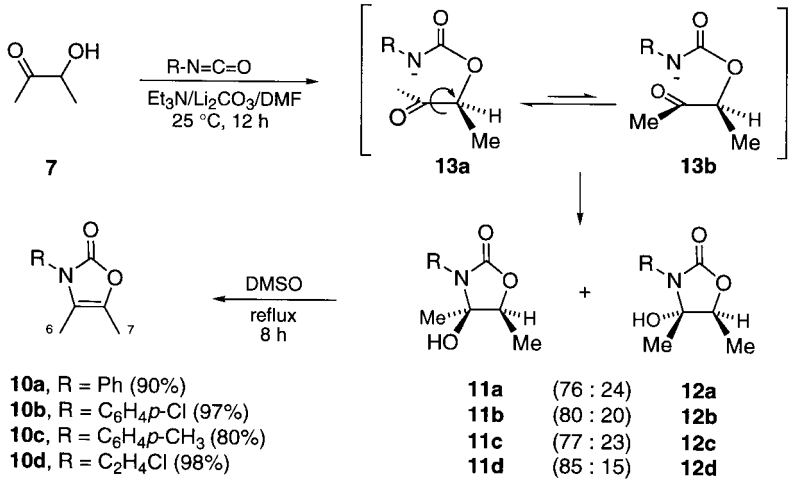
According to the importance of the dehydrating agent for the preparation of dienes **1**,[1a] we investigated the effect of molecular sieves (4 Å) in the reaction of alcohol **7** with isocyanates, in order to obtain the 4-oxazolin-2-ones, **10**, directly. Even though a small amount of **10** is formed, alcohols **11/12** remained largely the major products.

The regioselectivity in the dehydration step by thermal treatment with DMSO suggests a thermodynamic control, consistent with a carbenium ion intermediate.[12] In addition, the direct formation of the exocyclic elimination products **9a**–**9e** seems to be under kinetic control, since compound **9d** was converted to the *endo* isomer **10e** by acid catalyzed treatment in high yield (Eq. (1)).



(1)

The higher stability of regioisomer **10** has been confirmed by ab initio calculations (RHF/3-21G and 6-31G*), showing small differences of energy for the pairs **9a/10a**, and **9e/10d** (Table 1). At the 6-31G* level this difference is slightly larger. Electron lone pair delocalization through the double bond by both heteroatoms, nitrogen and oxygen, may be invoked as the reason of this stabilization. The strain generated by the *endo* double bond, though, and the destabilizing nonbonding van der Waals interactions between the methyl groups in compounds **10**, might be the origin of the relative small differences in energy with respect to isomers **9**.



Scheme 4.

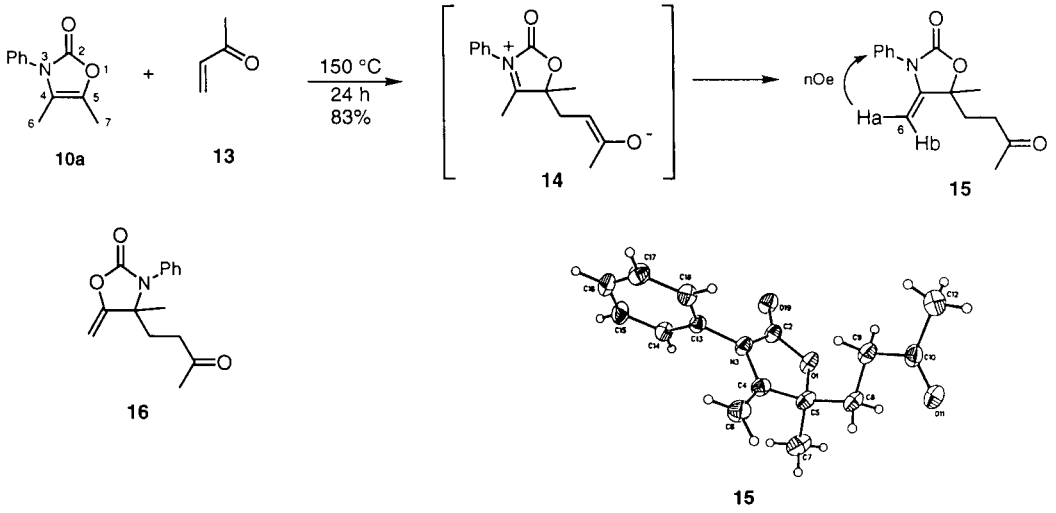
Table 1. Relative electronic energies (ΔE, kcal/mol) for the pairs **9a/10a**, and **9e/10d**, calculated by RHF/3-21G and 6-31G*

	ΔE (**9a**–**10a**)	ΔE (**9e**–**10d**)
3-21G	0.47	0.05
6-31G*	1.72	1.24

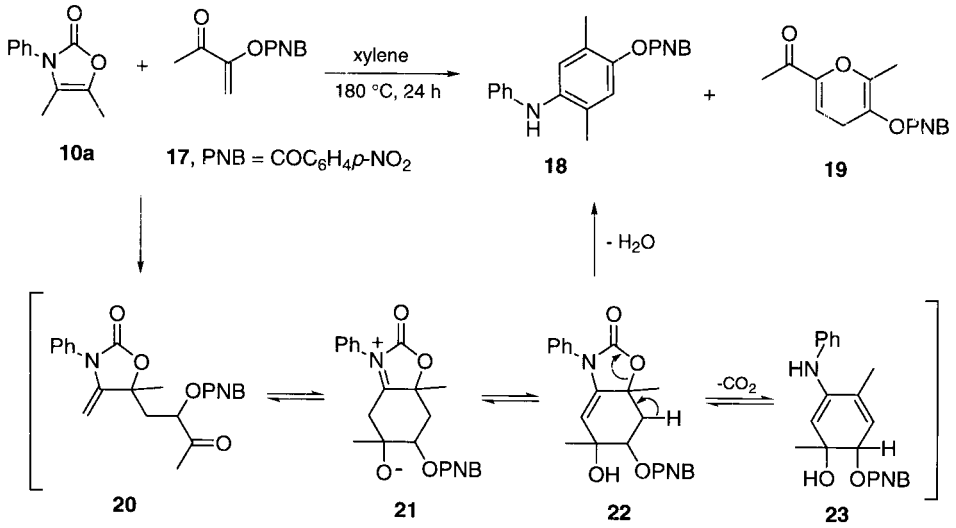
Considering the relative stability of the double bond in isomers **9** and **10**, and the fact that it may be considered as a part of both an enamide and an enol ester moiety, we examined the reactivity of these compounds with conjugate acceptors. Thermal (150°C, 24 h) addition of **10a** to methyl vinyl ketone (**13**) led to the conjugate adduct **15** in 83% yield, as a colorless crystalline product (Scheme 5). This product would arise from zwitterion **14**, that is later stabilized by proton abstraction from the C-6 methyl, and by proton enolate trapping. Further heating to high temperature (250°C, 24 h) of **15** failed to promote internal cyclization, recovering the starting material.

The reaction was highly regioselective, in view of the presence of a single product, since the alternative adduct **16**, arising from the addition of C-4 to electrophile **13**, was not detected in the crude reaction mixture. The nOe experiments carried out in compound **15** showed that the double bond was placed at the C-4 position, as a consequence of the enhancement of the phenyl group signal when the olefinic proton H-6a was irradiated. The structure of **15** was confirmed by X-ray crystallography (Scheme 5).

Similarly, addition of isomer **9a** to **13**, under analogous reaction conditions, gives rise to the same adduct **15** in 76% yield. This result may be accounted for as a consequence of a previous thermal isomerization of the *exo* double bond to the *endo* position to give isomer **10a**. The isomerization process seems to be faster than the addition to enone **13**, since lower reaction temperatures (100°C) did not prevent the slow conversion to isomer **10a**, but under these conditions the addition did not take place.



Scheme 5.



Scheme 6.

The captodative olefin 3-(*p*-nitrobenzoyloxy)-3-buten-2-one (**17**) has proven to be a very reactive dienophile,[13] and dipolarophile[14] in cycloaddition reactions. Oxazolinone **10a** reacted with olefin **17** in xylene at 180°C for 24 h to yield a mixture of two main products: diarylamine **18**, and the dimeric product of the olefin, **19**[15] (Scheme 6). The former product was likely formed by a consecutive series of reactions, including the intramolecular nucleophilic addition of the enamide moiety to the carbonyl group of **20**, the first formed adduct by Michael addition, to give a series of intermediate species **21**, **22**, and **23**, successively.[16] The latter gives rise to **18** after losing water. It is surprising to see that this kind of product was not observed in the reaction with **13**.

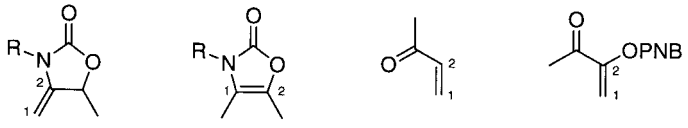
Other Michael acceptors, such as methyl propiolate (**24**), methyl acrylate (**25**), and tetracyanoethylene (**26**), were submitted to the same addition conditions with **10a**, however, none of the expected reaction products were detected. Starting materials were recovered, along with a dense dark residue, seemingly coming from the olefin polymerization.

Given the enamide and enol ester character of the double bond, and the fact that both heteroatoms polarize the double bond in the opposite direction in compounds **10**, these experiments would support the hypothesis of a stronger effect from the nitrogen atom in Diels–Alder additions.[1a] This is probably due to the higher polarizability of the nitrogen lone pair. In order to evaluate this by a theoretical method, we calculated the energy of the MOs for the *exo*- and *endo*-olefinic heterocycles **9a/10a**, and **9e/10d**. Table 2 summarizes the HOMO/LUMO energies and the corresponding coefficients for each one of them. In addition, the same parameters for enones **13** and **17** are included.[17] Geometries were fully optimized using the AM1 semi-empirical method[18] and employed as the starting point for ab initio optimization, using the 3-21G and 6-31G* basis sets.[19] From the FMO energies, it appears that the HOMO-heterocycle/LUMO-olefin interaction is preferred (Table 3). Moreover, in principle, the *endo*-double bond heterocycles **10a** and **10d** should be more reactive than isomers **9a** and **9e**, respectively, due to a smaller energy gap between the interacting FMOs (i.e. the HOMOs of compounds **9** are more stable, see Table 2). In contrast to the values shown in Table 3, where the HOMO-**10**/LUMO-**17** energy gaps are smaller than those for olefin **13**, the reactivity of olefin **17** was lower, since any conversion of starting material takes place below 180°C.

On the basis of coefficient differences for the proper frontier orbital interaction between heterocycle **10** and Michael acceptor (HOMO-heterocycle/LUMO-olefin), regioselectivity could be assessed. It can be observed that the relative value of the coefficient C_2 on C-5 is bigger than C_1 on carbon C-4 in the HOMO of both **10a** and **10d**. The lower electronegativity and higher releasing effect of the nitrogen lone pair, in comparison with the oxygen atom, would explain the polarization of the π-system. Therefore, the main interaction to be predicted is that between carbon C-5 of heterocycle **10** with the terminal carbon C-1 of olefins **13** and **17**, since the largest LUMO coefficients of the latter are located on this carbon (Fig. 2).

A lower reactivity found in methyl propiolate (**24**) and methyl acrylate (**25**) with respect to **13** and **17** may be due

Table 2. Ab initio 3-21G and 6-31G* calculations of energies (eV) and coefficients (C_i) of the Frontier Molecular Orbitals for heterocycles **9a**, **9e**, **10a**, and **10d**, and olefins MVK (**13**) and **17**. These are the values of the $2p_z$ coefficients, the relative $2p_z'$ contributions and their ΔC_i are analogous. For the calculations of olefins **13** and **17** see Ref. 17.



9a, R = Ph
9e, R = CH_2Cl_2

10a, R = Ph
10d, R = CH_2Cl_2

13

17

		HOMO[a]				LUMO[b]			
Compd[c]	Level	*E*(eV)	C_1	C_2	ΔC_i[d]	*E*(eV)	C_1	C_2	ΔC_i[d]
9a	3-21G	−8.8440	−0.2322	−0.1405	0.0917	4.5762	0.2437	−0.3004	−0.0567
	6-31G*	−8.9132	−0.2991	−0.1934	0.1057	4.6382	0.2804	−0.3635	−0.0831
9e	3-21G	−9.4710	−0.3060	−0.2014	0.1046	4.2284	0.2506	−0.3176	−0.0670
	6-31G*	−9.3891	0.3650	0.2417	0.1233	4.2733	0.2785	−0.3729	−0.0944
10a	3-21G	−8.5058	−0.2497	−0.2888	−0.0391	5.2630	0.3203	−0.3291	−0.0088
	6-31G*	−8.3736	0.2768	0.3283	−0.0515	5.3190	0.3623	−0.3708	−0.0085
10d	3-21G	−8.7409	−0.2437	−0.2875	−0.0438	4.8450	0.2813	−0.2893	−0.0080
	6-31G*	−8.6846	0.2943	0.3426	−0.0483	4.8426	0.2516	−0.2545	−0.0029
13	3-21G	−10.5391	0.2935	0.3031	−0.0096	2.9002	−0.2690	0.1745	0.0945
	6-31G*	−10.4895	−0.3464	−0.3669	−0.0205	2.9222	0.3109	−0.2069	0.1040
17	3-21G	−11.0460	−0.2991	−0.2873	0.0118	2.2417	0.2548	−0.1972	0.0576
	6-31G*	−11.0123	−0.3593	−0.3565	0.0028	2.4588	0.2940	−0.2386	0.0554

[a] Energies and coefficients of 2NHOMOs of olefin **17**, since the HOMOs and NHOMOs do not have a p_z contribution.
[b] Energies and coefficients of 2NLUMOs of **9a**, and **10a**, and NLUMO of **17**, since the LUMOs do not have a p_z contribution, at the 3-21G and 6-31G* levels.
[c] The FMOs of the most stable non-planar *s-trans* conformation for **17** and *s-cis* for **13**.
[d] Carbon 1–carbon 2 for the double bonds.

Table 3. Energy gaps (eV) of frontier orbitals for heterocycles **10a** and **10d** and olefins **13** and **17**

Heterocycle	Method	**13**[a]		**17**[a]	
		HOMO–LUMO	LUMO–HOMO	HOMO–LUMO	LUMO–HOMO
10a	3-21G	11.4060	15.8021	10.7475	16.3090
	6-31G*	11.2958	15.8085	10.8324	16.3313
10d	3-21G	11.6411	15.3841	10.9826	15.8910
	6-31G*	11.6068	15.3321	11.1434	15.8549

[a] HOMO-heterocycle/LUMO-olefin and LUMO-heterocycle/HOMO-olefin. The gaps for olefin **17** were calculated with the 2NHOMO, since its HOMO does not have any p_z contribution in the olefin, and 2NLUMOs of **10a**, and NLUMO of **17**, in both levels.

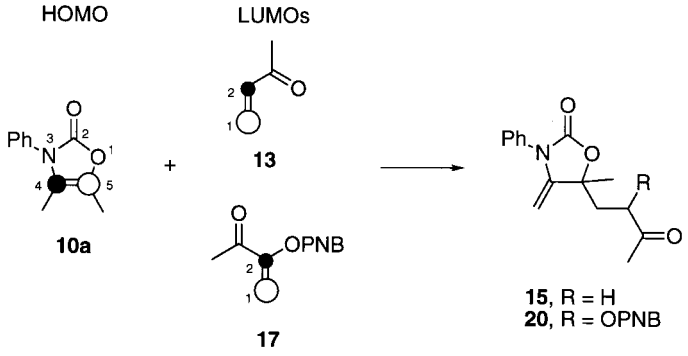


Figure 2. Ab initio RHF/6-31G* frontier orbital interactions for the Michael addition of **10a** with olefins **13** and **17**.

to less stable LUMOs for the former compounds.[1a] Although this argument could not be invoked for the case of tetracyanoethylene (**26**), however, steric factors might be controlling the approach of this electrophile toward the already crowded nucleophilic C-5 quaternary center of **10**. This is also suggested by the reactivity differences between **13** and **17**, the latter being the less reactive olefin, though its LUMO is the most stable (Table 2).

Conclusion

A new series of 4-methylene-2-oxazolidinones **9a**–**9e**, and 4-oxazolin-2-ones **10a**–**10e**, have been prepared from 3-hydroxy-2-butanone (**7**) in the presence of isocyanates **3**, using a regioselective methodology. The polarity of the solvent seems to play an important role in the formation of either heterocycles **9** or the alcohol precursors **11/12**, that are selectively dehydrated to the *endo* olefinic heterocycle **10**. These results contribute to confirm the tandem pathway between two potential dipolar species as a versatile strategy for the preparation of functionalized heterocycles related to cyclic carbamates. These compounds proved to be efficient nucleophilic enamides before the presence of some Michael acceptor enones. The regioselectivity shown by **10a** and **10d** was rationalized by FMO calculations, which showed a good fit between the proper coefficients in both reactants for the most stable HOMO-heterocycle/LUMO-olefin interaction.

Experimental

General

Melting points (uncorrected) were determined with an Electrothermal capillary melting point apparatus. IR spectra were recorded on a Perkin–Elmer 1600 spectrophotometer. ^{1}H and ^{13}C NMR spectra were obtained on a Varian Gemini-300 (300 MHz) instrument, with $CDCl_3$ as solvent and TMS as internal standard. The mass spectra (MS) were taken on a Hewlett–Packard 5971A spectrometer. X-Ray crystallographic structures were obtained on a Siemens P4 diffractometer.[20] Microanalyses were performed by M-H-W Laboratories (Phoenix, AZ). All air moisture sensitive reactions were carried out under nitrogen using oven-dried glassware. Dioxane, ethyl ether, toluene, and xylene were freshly distilled from sodium; methylene chloride, DMF, and DMSO from calcium hydride prior to use. Li_2CO_3 was dried overnight at 120°C before use. All other reagents were used without further purification.

General procedure for the preparation of *N*-substituted 5-methyl-4-methylene-2-oxazolidinones, 9a–9e

A solution of 3-hydroxy-2-butanone (**7**) (0.31 g, 3.5 mmol) in dry dioxane (3 mL) was added to a suspension of triethylamine (0.70 g, 7.0 mmol) and dry Li_2CO_3 (0.31 g, 4.2 mmol) in dry dioxane (2 mL), under an N_2 atmosphere and at room temperature. The mixture was stirred for 30 min, and a solution of the isocyanate **3** (5.2 mmol) in dry dioxane (2 mL) was added dropwise. The mixture was stirred for 12 h at room temperature, filtered, and the solvent was removed under vacuum. The residue was purified by column chromatography on silica gel treated with triethylamine (10%) in hexane (30 g per gram of crude) (hexane/EtOAc, 9:1).

5-Methyl-4-methylene-*N*-phenyl-2-oxazolidinone (9a). Using the general procedure with 0.62 g of **3a** gave 0.43 g (67%) of **9a** as colorless crystals (hexane/CH_2Cl_2, 3:7): R_f 0.51 (hexane/EtOAc, 7:3); mp 87–88°C [lit.[21]

89.5–90.5°C], IR (KBr) 1759, 1646, 1390, 1318, 1195, 1072, 754, 692 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.60 (d, J=6.4 Hz, 3H, Me-7), 4.08 (dd, J=2.8, 2.0 Hz, 1H, H-6b), 4.19 (dd, J=2.8, 2.5 Hz, 1H, H-6a), 5.20–5.30 (m, 1H, H-5), 7.33–7.55 (m, 5H, PhH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 21.0 (C-7), 74.9 (C-5), 81.8 (C-6), 126.8 (C-9), 128.1 (C-11), 129.4 (C-10), 133.8 (C-8), 147.4 (C-4), 155.1 (C-2); MS (70 eV) 189 (M^+, 66), 143 (20), 144 (39), 130 (100), 103 (21), 77 (44). Anal. Calcd for $C_{11}H_{11}NO_2$: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.77; H, 5.93; N, 7.63.

***N*-(*p*-Chlorophenyl)-5-methyl-4-methylene-2-oxazolidinone (9b).** Using the general procedure with 0.80 g of **3b** gave 0.46 g (61%) of **9b** as colorless crystals (hexane/CH_2Cl_2, 3:7): R_f 0.52 (hexane/EtOAc, 7:3); mp 102–103°C, IR (KBr) 1715, 1591, 1489, 1393, 1224, 1173, 1088, 817 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.61 (d, J=6.4 Hz, 3H, Me-7), 4.11 (dd, J=2.8, 2.2 Hz, 1H, H-6b), 4.20 (dd, J=2.8, 2.4 Hz, 1H, H-6a), 5.18–5.26 (m, 1H, H-5), 7.22–7.29 (m, 2H, ArH), 7.38–7.44 (m, 2H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 21.1 (C-7), 75.1 (C-5), 82.1 (C-6), 128.3 (C-9), 129.8 (C-10), 132.5 (C-8), 134.0 (C-11), 147.3 (C-4), 154.7 (C-2); MS (70 eV) 225 (M^++2, 17), 223 (M^+, 52), 178 (12), 166 (33), 164 (100), 144 (51), 137 (62), 111 (31), 102 (15), 75 (25). Anal. Calcd for $C_{11}H_{10}ClNO_2$: C, 59.07; H, 4.51; N, 6.26. Found: C, 59.14; H, 4.64; N, 6.40.

5-Methyl-4-methylene-*N*-(*p*-tolyl)-2-oxazolidinone (9c). Using the general procedure with 0.69 g of **3c** gave 0.40 g (57%) of **9c** as colorless crystals (hexane/CH_2Cl_2, 3:7): R_f 0.52 (hexane/EtOAc, 7:3); mp 72–73°C, IR (KBr) 1757, 1649, 1514, 1405, 1322, 1208, 1079, 980, 819 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.61 (d, J=6.6 Hz, 3H, Me-7), 2.39 (s, 3H, CH_3Ar), 4.03 (dd, J=2.8, 2.2 Hz, 1H, H-6b), 4.16 (dd, J=2.7, 2.4 Hz, 1H, H-6a), 5.19–5.26 (m, 1H, H-5), 7.19–7.33 (m, 4H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 21.1 (C-7 or CH_3Ar), 21.2 (CH_3Ar or C-7), 75.0 (C-5), 79.2 (C-6), 126.8 (C-9), 130.2 (C-10), 131.1 (C-8), 138.4 (C-11), 147.8 (C-4), 155.4 (C-2); MS (70 eV) 203 (M^+, 63), 158 (24), 144 (100), 117 (43), 91 (35), 65 (23). Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.91; H, 6.45; N, 6.89. Found: C, 70.74; H, 6.52; N, 6.89.

***N*-(*p*-Anisyl)-5-methyl-4-methylene-2-oxazolidinone (9d).** Using the general procedure with 0.77 g of **3d** gave 0.52 g (69%) of **9d** as colorless crystals (hexane/CH_2Cl_2, 3:7): R_f 0.49 (hexane/EtOAc, 7:3); mp 77–78°C, IR (KBr) 1767, 1514, 1402, 1243 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.61 (d, J=6.4 Hz, 3H, Me-7), 3.83 (s, 3H, MeOAr), 4.05 (ddd, J=2.6, 2.0, 0.7 Hz, 1H, H-6b), 4.12 (dd, J=2.6, 2.4 Hz, 1H, H-6a), 5.20–5.28 (m, 1H, H-5), 6.97–7.00 (m, 2H, ArH), 7.22–7.27 (m, 2H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 21.2 (C-7), 55.5 (MeO), 74.9 (C-5), 81.6 (C-6), 114.9 (C-10), 126.5 (C-8), 128.4 (C-9), 148.2 (C-4), 155.8 (C-2), 159.4 (C-11); MS (70 eV) 219 (M^+, 17), 160 (6), 148 (100), 111 (9), 92 (15), 77 (25). Anal. Calcd for $C_{12}H_{12}NO_3$: C, 65.78; H, 5.98; N, 6.39. Found: C, 65.90; H, 6.08; N, 6.55.

***N*-(2-Chloroethyl)-5-methyl-4-methylene-2-oxazolidinone (9e).** Using the general procedure with 0.55 g of **3e** gave 0.52 g (86%) of **9e** as a pale brown oil: R_f 0.62 (hexane/EtOAc, 7:3); IR (KBr) 2974, 1769, 1671, 1441, 1405, 1344, 1190, 1072, 1031, 815 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.41 (d, J=6.5 Hz, 3H, Me-7), 3.57–3.64 (m, 2H, H-8), 3.67–3.74 (m, 2H, H-9), 4.01–4.05 (m, 1H, H-6b), 4.14–4.18 (m, 1H, H-6a), 4.98–5.06 (m, 1H, H-5); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 20.7 (C-7), 39.0 (C-8), 42.4 (C-9), 74.7 (C-5), 80.4 (C-6), 145.7 (C-4), 155.8 (C-2); MS (70 eV) 177 (M^++2, 9), 175 (M^+, 30), 126 (41), 113 (52), 104 (30), 63 (37), 42 (100). Anal. Calcd for $C_7H_{10}ClNO_2$: C, 47.88; H, 5.74; N, 7.98. Found: C, 47.65; H, 5.89; N, 7.82.

General procedure for the preparation of *N*-substituted 4-hydroxy-4,5-dimethyl-2-oxazolidinones, 11a–11d and 12a–12d

A solution of 3-hydroxy-2-butanone (**7**) (0.31 g, 3.5 mmol) in dry DMF (3 mL) was added to a suspension of triethylamine (0.70 g, 7.0 mmol) and dry Li_2CO_3 (0.31 g, 4.2 mmol) in dry DMF (2 mL), under an N_2 atmosphere and at room temperature. The mixture was stirred for 30 min, and a solution of the isocyanate **3** (5.2 mmol) in dry DMF (2 mL) was added dropwise. The mixture was stirred for 12 h at room temperature, filtered, and the solvent was removed under vacuum. The residue was purified by column chromatography on silica gel treated with triethylamine (10%) in hexane (30 g per gram of crude) (hexane/EtOAc, 9:1).

(4*R,5*S**)-4-Hydroxy-4,5-dimethyl-*N*-phenyl-2-oxazolidinone (11a). (4*R**,5*R**)-4-Hydroxy-4,5-dimethyl-*N*-phenyl-2-oxazolidinone (12a).** Using the general procedure with 0.62 g of **3a** gave a mixture of **11a/12a** (76:24), which after recrystallization (hexane/CH_2Cl_2, 1:1) yielded 0.39 g (56%) of **11a** as colorless crystals: R_f 0.55 (hexane/EtOAc, 1:1); mp 97–99°C, IR (KBr) 3310, 1728, 1647, 1593, 1495, 1233, 1162, 759, 694 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.29 (d, J=6.6 Hz, 3H, Me-7), 1.35 (s, 3H, Me-6), 4.42 (q, J=6.6 Hz, 1H, H-5), 4.98 (br s, 1H, OH), 7.25–7.50 (m, 5H, PhH). Signals attributed to minor isomer **12a**: 1.31 (d, J=6.6 Hz, Me-7), 1.34 (s, Me-6), 4.49 (q, J=6.6 Hz, H-5); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 12.5 (C-7), 23.2 (C-6), 80.9 (C-5), 89.2 (C-4), 127.2 (C-9), 127.3 (C-11), 128.8 (C-10), 134.7 (C-8), 156.8 (C-2). MS (70 eV) 207 (M^+, 19), 189 (19), 164 (4), 120 (100), 92 (20), 77 (52). Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 5.87; N, 6.27; Found: C, 63.88; H, 5.79; N, 6.51.

(4*R,5*S**)-*N*-(*p*-Chlorophenyl)-4-hydroxy-4,5-dimethyl-2-oxazolidinone (11b). (4*R**,5*R**)-*N*-(*p*-Chlorophenyl)-4-hydroxy-4,5-dimethyl-2-oxazolidinone (12b).** Using the general procedure with 0.80 g of **3b** gave a mixture of **11b/12b** (80:20), which after recrystallization (hexane/CH_2Cl_2, 1:1) yielded 0.51 g (62%) of **11b** as colorless crystals: R_f 0.47 (hexane/EtOAc, 1:1); mp 105–106°C, IR (KBr) 3369, 1732, 1490, 1392, 1232, 1150, 1083 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.28 (d, J=6.6 Hz, 3H, Me-7), 1.34 (s, 3H, Me-6), 4.40 (q, J=6.6 Hz, 1H, H-5), 4.91 (br s, 1H, OH), 7.27–7.35 (m, 4H, ArH). Signals attributed to minor isomer **12b**: 1.31 (s, Me-6), 4.48 (q, J=6.5 Hz, H-5), 5.10 (br s, OH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 12.5 (C-7), 23.1 (C-6), 81.1 (C-5), 89.3 (C-4), 128.0 (C-9), 129.0 (C-10), 133.1 (C-11), 133.2 (C-8), 156.7 (C-2); MS (70 eV) 241 (M^+, 1), 225 (10), 223 (30), 154

(34), 152 (100), 113 (12), 111 (29), 75 (22). Anal. Calcd for $C_{12}H_{15}NO_3$: C, 54.67; H, 5.01; N, 5.80; Found: C, 54.67; H, 5.40; N, 6.03.

(4*R,5*S**)-4-Hydroxy-4,5-dimethyl-*N*-(*p*-tolyl)-2-oxazolidinone (11c). (4*R**,5*R**)-4-Hydroxy-4,5-dimethyl-*N*-(*p*-tolyl)-2-oxazolidinone (12c).** Using the general procedure with 0.69 g of **3c** gave a mixture of **11c/12c** (77:23), which after recrystallization (hexane/CH_2Cl_2, 1:1) yielded 0.54 g (72%) of **11c** as colorless crystals: R_f 0.57 (hexane/EtOAc, 7:3); mp 110–111°C, IR (KBr) 3325, 2916, 1740, 1626, 1588, 1271, 1223, 1088 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.30 (d, J=6.6 Hz, 3H, Me-7), 1.33 (s, 3H, Me-6), 2.36 (s, 3H, CH_3Ar), 4.41 (q, J=6.6 Hz, 1H, H-5), 4.64 (br s, 1H, OH), 7.13–7.27 (m, 4H, ArH). Signals attributed to minor isomer **12c**: 4.46 (q, J=6.6 Hz, H-5), 5.00 (br s, OH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 12.7 (C-7), 21.1 (C-12), 23.4 (C-6), 80.8 (C-5), 89.1 (C-4), 127.3 (C-9), 129.5 (C-10), 131.9 (C-8), 135.2 (C-11), 156.8 (C-2); MS (70 eV) 221 (M^+, 33), 134 (100), 106 (83), 91 (20), 77 (23). Anal Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.03; H, 6.91; N, 6.48.

(4*R,5*S**)-*N*-(2-Chloroethyl)-4-hydroxy-4,5-dimethyl-2-oxazolidinone (11d). (4*R**,5*R**)-*N*-(2-Chloroethyl)-4-hydroxy-4,5-dimethyl-2-oxazolidinone (12d).** Using the general procedure with 0.55 g of **3e** gave a mixture of **11d/12d** (85:15), which after recrystallization (hexane/CH_2Cl_2, 1:1) yielded 0.46 g (70%) of **11d** as colorless crystals: R_f 0.49 (hexane/EtOAc, 7:3); mp 76–77°C, IR (KBr) 3354, 1735, 1407, 1312, 1216, 1153, 1074, 1021 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.42 (d, J=6.6 Hz, 3H, Me-7), 1.48 (s, 3H, Me-6), 3.45–3.62 (m, 2H, H-8 or H-9), 3.63–3.76 (m, 2H, H-9 or H-8), 4.35 (q, J=6.6 Hz, 1H, H-5), 4.42 (br s, 1H, OH). Signals attributed to minor isomer **12d**: 1.33 (d, J=6.6 Hz, Me-7), 1.48 (s, Me-6), 4.50 (q, J=6.6 Hz, H-5), 4.70 (br s, OH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 12.7 (C-7), 23.5 (C-6), 41.1 (C-8 or C-9), 42.0 (C-9 or C-8), 80.5 (C-5), 87.9 (C-4), 158.0 (C-2); MS (70 eV) 193 (M^+, 2), 178 (19), 144 (14), 121 (12), 106 (4), 86 (3), 72 (47), 43 (100). Anal Calcd for $C_7H_{12}ClNO_3$: C, 43.42; H, 6.25; N, 7.23. Found: C, 43.16; H, 6.41; N, 7.50.

General procedure for the preparation of *N*-substituted 4,5-dimethyl-4-oxazolin-2-ones 10a–10e

A solution of alcohols **11/12** (1.4 mmol) in dry DMSO (5 mL) was heated to reflux for 8 h. The solvent was removed under vacuum, and the residue was purified by column chromatography on silica gel (30 g per gram of crude) (hexane/EtOAc, 8:2).

4,5-Dimethyl-*N*-phenyl-4-oxazolin-2-one (10a). Using the general procedure with 0.30 g of **11a/12a** (76:24) gave 0.25 g (90%) of **10a** as colorless crystals (hexane/CH_2Cl_2, 3:7): R_f 0.60 (hexane/EtOAc, 7:3); mp 79–80°C [lit.[21] 79.5–80.0°C], IR (KBr) 1761, 1708, 1502, 1379, 1250, 1187 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.85 (br s, 3H, Me-6), 2.11 (br s, 3H, Me-7), 7.23–7.48 (m, 5H, PhH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 8.8 (C-6), 10.0 (C-7), 117.8 (C-4), 129.9 (C-9), 128.2 (C-11), 129.4 (C-10), 132.3 (C-5), 133.9 (C-8), 153.8 (C-2); MS (70 eV) 189 (M^+, 44), 144 (33), 130 (100), 119 (9), 103 (34), 91 (9), 77 (71). Anal. Calcd for $C_{11}H_{11}NO_2$: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.90; H, 6.07; N, 7.60.

***N*-(*p*-Chlorophenyl)-4,5-dimethyl-4-oxazolin-2-one (10b).** Using the general procedure with 0.35 g of **11b/12b** (80:20) gave 0.31 g (97%) of **10b** as colorless crystals (hexane/CH_2Cl_2, 1:1): R_f 0.32 (hexane/EtOAc, 7:3); mp 125–126°C, IR (KBr) 1747, 1706, 1495, 1382, 1248, 1186, 1083, 985, 830 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.86 (br s, 3H, Me-6), 2.10 (br s, 3H, Me-7), 7.17–7.28 (m, 2H, ArH), 7.33–7.46 (m, 2H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 8.9 (C-6), 10.1 (C-7), 117.6 (C-4), 128.1 (C-9), 129.7 (C-10), 132.6 (C-5 or C-8), 132.7 (C-8 or C-5), 134.0 (C-11), 154.3 (C-2); MS (70 eV) 225 (M^++2, 16), 223 (M^+, 48), 178 (3), 152 (100), 111 (27), 75 (29). Anal. Calcd for $C_{11}H_{10}ClNO_2$: C, 59.07; H, 4.51; N, 6.26. Found: C, 59.30; H, 4.75; N, 6.50.

4,5-Dimethyl-*N*-(*p*-tolyl)-4-oxazolin-2-one (10c). Using the general procedure with 0.32 g of **11c/12c** (77:23) gave 0.35 g (80%) of **10c** as colorless crystals (hexane/CH_2Cl_2, 3:7): R_f 0.61 (hexane/EtOAc, 7:3); mp 64–65°C, IR (KBr) 1750, 1705, 1517, 1380, 1249, 1180, 1044, 981, 816 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.82 (br s, 3H, Me-6), 2.09 (br s, 3H, Me-7), 2.38 (s, 3H, CH_3Ar), 7.12–7.28 (m, 4H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 8.6 (C-6), 9.9 (C-7), 21.0 (C-12), 117.9 (C-4), 126.7 (C-9), 130.0 (C-10), 131.4 (C-8), 132.0 (C-5), 138.2 (C-11), 154.7 (C-2); MS (70 eV) 203 (M^+, 40), 132 (100), 91 (28), 65 (18). Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.91; H, 6.45; N, 6.89. Found: C, 71.13; H, 6.51; N, 6.86.

***N*-(2-Chloroethyl)-4,5-dimethyl-4-oxazolin-2-one (10d).** Using the general procedure with 0.28 g of **11d/12d** (85:15) gave 0.25 g (98%) of **10d** as colorless crystals (hexane/CH_2Cl_2, 3:7): R_f 0.56 (hexane/EtOAc, 7:3); mp 83–84°C, IR (KBr) 1754, 1708, 1528, 1436, 1380, 1231, 1190, 1123 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.90 (br s, 3H, Me-6), 1.94 (br s, 3H, Me-7), 3.62–3.67 (m, 2H, H-8 or H-9), 3.69–3.74 (m, 2H, H-9 or H-8); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 7.9 (C-6 or C-7), 9.7 (C-7 or C-6), 41.1 (C-8), 43.2 (C-9), 117.3 (C-4), 131.5 (C-5), 155.2 (C-2); MS (70 eV) 177 (M^++2, 11), 175 (M^+, 35), 140 (100), 114 (15), 82 (47), 68 (48). Anal. Calcd for $C_7H_{10}ClNO_2$: C, 47.88; H, 5.74; N, 7.98. Found: C, 47.95; H, 5.53; N, 7.84.

***N*-(*p*-Anisyl)-4,5-dimethyl-4-oxazolin-2-one (10e).** To a solution of 0.320 g (1.45 mmol) of **9d** in dry ethyl ether (15 mL) a drop of conc. H_2SO_4 was added. The mixture was stirred at room temperature for 15 h, diluted with ethyl ether (30 mL), and washed with an aqueous saturated solution of $NaHCO_3$ until neutral. The organic layer was dried (Na_2SO_4), and the solvent was removed under vacuum. The residue was recrystallized (hexane/CH_2Cl_2, 1:1) to give 0.31 (98%) of **10e** as a white solid: R_f 0.40 (hexane/EtOAc, 7:3); mp 76–77°C, IR (KBr) 1749, 1702, 1513, 1329, 1246, 1164, 1031, 979, 831 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.81 (br s, 3H, Me-6), 2.10 (br s, 3H, Me-7), 3.83 (s, 3H, MeOAr), 6.94–7.00 (m, 2H, ArH), 7.17–7.23 (m, 2H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 8.9 (C-6), 10.1 (C-7), 55.6 (MeO), 114.8 (C-10), 118.3 (C-4), 127.0 (C-8), 128.4 (C-9), 131.9

(C-5), 154.2 (C-2), 159.6 (C-11); MS (70 eV) 219 (M^+, 50), 174 (4), 148 (100), 107 (8), 92 (11), 77 (18). Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.78; H, 5.98; N, 6.39. Found: C, 65.90; H, 6.03; N, 6.47.

5-Methyl-4-methylene-5-(3-oxobut-1-yl)-*N*-phenyl-2-oxazolidinone (15). In a screw-cap ACE pressure tube, under an N_2 atmosphere, a mixture of 0.47 g (2.5 mmol) of **10a**, and 0.35 g (5.0 mmol) of **13** in dry xylene (3 mL) was heated to 150°C for 24 h. The solvent was removed under vacuum, and the residue was purified by column chromatography on silica gel (30 g, hexane/EtOAc, 9:1) to give 0.53 g (83%) of **15** as colorless crystals (hexane/CH_2Cl_2, 1:1): R_f 0.50 (hexane/EtOAc, 7:3); mp 94–96°C, IR (KBr) 1766, 1713, 1672, 1655, 1496, 1396, 1067 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.62 (s, 3H, Me), 2.03–2.25 (m, 2H, CH_2), 2.19 (s, 3H, CH_3CO), 2.48–2.74 (m, 2H, CH_2CO), 4.05 (d, J=3.0 Hz, 1H, H-6b), 4.20 (d, J=3.0 Hz, 1H, H-6a), 7.28–7.52 (m, 5H, PhH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 27.0 (Me), 30.1 (CH_3CO), 34.2 (CH_2), 37.4 (CH_2CO), 82.1 (CH_2=), 83.0 (C-5), 127.0, 128.5, 129.7, 133.8, 149.8 (C-4), 154.5 (C-2), 207.2 (CO); MS (70 eV) 259 (M^+, 1), 149 (19), 134 (20), 106 (43), 78 (61), 52 (100). Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.59; H, 6.74; N, 5.43.

2,5-Dimethyl-1-(*p*-nitrobenzoyloxy)-4-phenylaminobenzene (18). 2-Acetyl-6-methyl-5-(*p*-nitrobenzoyloxy)-4*H*-pyran (19).[15] In a screw-cap ACE pressure tube, under an N_2 atmosphere, a mixture of 0.47 g (2.5 mmol) of **10a**, and 1.17 g (5.0 mmol) of **17** in dry xylene (3 mL) was heated to 180°C for 24 h. The solvent was removed under vacuum, and the residue was purified by column chromatography on silica gel (30 g, hexane/EtOAc, 8:2) to give 0.41 g (45%) of **18** as a red powder (hexane/CH_2Cl_2, 1:1), R_f 0.70 (hexane/EtOAc, 7:3); and 0.23 g (61%) of **19** as a white powder, R_f 0.75 (hexane/EtOAc, 7:3). Data of **18**: mp 120–121°C, IR (KBr) 3389, 1737, 1596, 1525, 1496, 1343, 1261, 1179, 1096 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.14 (s, 3H, MeAr), 2.24 (s, 3H, MeAr), 4.20 (br s, 1H, NH), 6.89–6.97 (m, 3H, PhH), 6.99 (br s, 1H, ArH), 7.14 (br s, 1H, ArH), 7.24–7.30 (m, 2H, PhH), 8.37–8.39 (m, 4H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 16.1 (MeAr), 17.6 (MeAr), 117.5, 120.6, 121.4, 123.7, 123.8, 126.9, 128.0, 129.4, 131.3, 135.0, 139.5, 143.6, 144.0, 150.9, 163.5 (CO_2). Anal. Calcd for $C_{21}H_{18}N_2O_4$: C, 69.60; H, 5.01; N, 7.73. Found: C, 69.59; H, 4.76; N, 7.60.

Acknowledgements

We thank Fernando Labarrios for his help in spectrometric measurements. J. T. acknowledges DEPI/IPN (Grant 916510) and CONACYT (Grant 32273E) for financial support. R. M. thanks DEPI/IPN for a graduate fellowship awarded, and the Ludwig K. Hellweg Foundation for a scholarship complement.

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