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# A New Route to 2-Oxazolines, Bis-oxazolines, and 2-Imidazoline-5-ones from Imidates using Solvent-Free Cycloadditions : Synthesis, Chemical Properties, and PM3 MO Calculations.

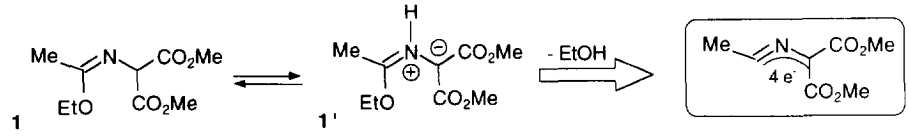
Jean Michel Lerestif[1], Loïc Toupet[2], Sourisak Sinbandhit[3], François Tonnard[4], Jean Pierre Bazureau[1,*] and Jack Hamelin[1]

[1)] *Synthèse et Electrosynthèse Organiques 3, UMR 6510,* [2)] *Groupe Matière Condensée et Matériaux, URA au CNRS N° 804,* [3)] *Centre Régional de Mesures Physiques de l'Ouest, Université de Rennes 1, Campus de Beaulieu, Avenue du Général Leclerc, 35042 Rennes Cédex, France.*
[4)] *Institut Universitaire de Technologie, Département Génie Chimie, Rue du Clos Courtel - BP 1144, 35014 Rennes Cédex, France*

**Abstract** : The 1,3-dipolar cycloadditions between imidate **1**, derived from dimethylaminomalonate and aldehydes **2(a-f)**, phthalaldehyde **2g**, isophthalaldehyde **2h**, 4-chlorophenylisocyanate **9a**, ethoxycarbonylisothiocyanate **9d** as dipolarophiles proceeds regioselectively in good yield using solvent-free conditions. Synthesis of *ortho* - and *meta*-bis-(2'-oxazoline-5'-yl)benzenes **6g, 6h** are also reported. The regiochemistry and the reactivity in these cycloaddition reactions are rationalized by PM3 MO calculations. The stereoselective demethoxycarbonylation of dimethyl 2-oxazoline-4,4-dicarboxylate **4a** is described. The mild hydrolysis of 5-(2-formylphenyl)-2-oxazoline **4g** leads to the formation of a new 3,4-dihydroisoquinoline **8h** in quantitative yield. © 1997 Elsevier Science Ltd.

## INTRODUCTION

2-Oxazolines[1] derivatives are well known to exhibit various properties as therapeutic agents[2], as block copolymers[3], as synthetic precursors[4a] and as protecting group[4b,c] in a wide variety of chemical synthesis. One of the continuing aim of our laboratory is to develop new synthetic ways to five-membered heterocycles[5] using solvent-free conditions, eventually under microwave irradiation[6]. In previous contributions, we described the use of imidates derived from methyl glycinate[7] in 1,3-dipolar cycloaddition. Recently, we have shown[8] that imidate **1** derived from dimethyl aminomalonate is also in equilibrium by thermal 1,2-prototropy[9] with azomethine ylide **1'** which is regarded as the synthetic equivalent of nitrile ylide after elimination of ethanol (Scheme 1).



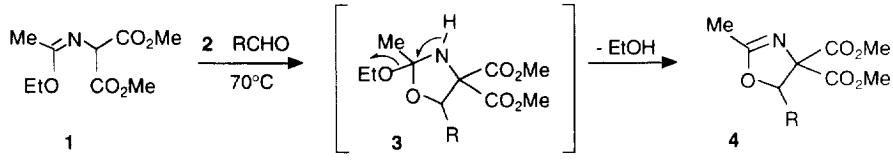

**Scheme 1**

According to the versatility for synthesis associated with 2-oxazolines moieties in medicinal chemistry[10], it appeared that a new and general approach to 2-oxazolines from imidate **1** and aldehydes[11], di-aldehydes (phthalaldehyde, isophthalaldehyde) as dipolarophiles in intermolecular 1,3-dipolar cycloaddition would be interesting. Herein, we wish to report on the synthesis of 2-oxazolines and their chemical reactivities. Preparative procedures including full characterization of these new compounds are reported. Similarly, cycloaddition reactions of imidate **1** with isocyanates and ethoxycarbonylisothiocyanate as dipolarophiles are also examined. Then, the regioselectivity of these cycloadditions is rationalized on the basis of PM3 molecular orbital (MO) calculations using MOPAC program (version 6.0)[12].

* Fax : (33) 02 99 28 63 74; E-mail : Jean-Pierre.Bazureau@univ-rennes1.fr

## RESULTS AND DISCUSSION

*Cycloaddition reaction with aldehydes* ***2(a-f)*** *as dipolarophiles, dealkoxycarbonylation of the 2-oxazoline-4,4-dicarboxylate* ***4a*** - Synthesis of 2-oxazolines **4** was readily achieved according to the following process : a mixture of distilled imidate[7a,13] **1** and freshly distilled aliphatic or aromatic aldehyde was heated to 70°C without solvent with vigorous stirring. This reaction was monitored by $^1$H NMR spectroscopy : the analysis of the crude reaction mixture indicated the formation of the expected compounds **4(a-f)** together with ethanol. After removal of alcohol *in vacuo*, the cycloadducts **4(a-f)** were isolated in good yields (Table 1) after chromatographic purification on silica or by recrystallization (**4d**). In all cases, the formation of a single regioisomer bears testimony of a highly regioselective preceding 1,3-dipolar cycloaddition, but the primary cycloadducts **3** could not be isolated (Scheme 2).

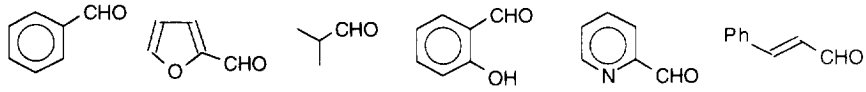



**Scheme 2**

The structure of **4(a-f)** was established on the basis of analytical and spectroscopic data. In the $^1$H NMR spectrum, one of the *gem*-methyl ester groups (C-4) was shielded (**4a** : $\delta$ = 3.13 ppm and the other at 3.86 ppm) by the aromatic group on C-5[14] (except for **4c**); in $^{13}$C NMR analysis, a small coupling constant (**4a** : $^2J$ = 4 Hz) between C-4 and H-5 (**4a** : $\delta_{C\text{-}4}$ = 86.2 ppm) was identified.

**Table 1 :** Synthesis of 2-oxazolines **4(a-f)** from aliphatic and aromatic aldehydes **2(a-f)**

| Aldehyde | R | Reaction time | Compound | Yield (%)[a] |
|---|---|---|---|---|
| **2a** | Phenyl | 2 h | **4a** | (96) 91 |
| **2b** | 2-Furyl | 3 h | **4b** | (93) 89 |
| **2c**[b] | $Me_2CH$ | 8 h | **4c** | (75) 64 |
| **2d** | $(2\text{-OH})C_6H_4$ | 20 min | **4d** | (95) 65 |
| **2e** | 2-Pyridyl | 45 min | **4e** | (95) 86 |
| **2f** | Ph-CH=CH | 5 h | **4f** | (94) 87 |




(a) Yield for crude **4** estimated by $^1$H NMR in parentheses and yield after purification by chromatography on silica gel 60 $F_{254}$ (Merck) or by recrystallization. (b) 3 eq. of isobutyraldehyde **2c** were used.

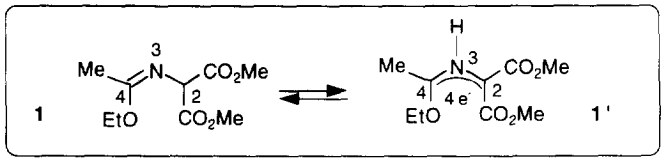
In order to understand the regioselectivity and the chemical reactivity observed in these cycloadditions, PM3 Molecular Orbital (MO) calculations were examined on the assumption that reaction (Scheme 2) would proceed *via* the intermediate **3** (not isolated). In the frontier molecular orbital (FMO) treatment of [3+2] cycloadditions, the relative reactivity of the 1,3-dipole **1'** (Table 2) towards a series of aldehydes **2(a-f)** is estimated primarily by the stabilization afforded by groundstate interactions of the $HOMO_{(1,3\text{-dipole})}$ and the $LUMO_{(dipolarophile)}$ or interactions between

the $LUMO_{(1,3\text{-dipole})}$ and the $HOMO_{(dipolarophile)}$.

Table 2 shows that the favourable interaction of frontier orbitals of **1'** and aldehydes **2(a-f)** as dipolarophiles, is dominated by the interaction $HOMO_{1'}$ - $LUMO_2$ in all cases (see column $\Delta E_1$). Furthermore, it is interesting to notice that for the cycloaddition of **1** with dipolarophiles **2a**, **2b** and **2d**, **2e** the $\Delta E_1$ are very close (**2a** : $\Delta E_1$ = 7.94 eV and **2b** : $\Delta E_1$ = 7.98 eV; **2d** : $\Delta E_1$ = 7.77 eV and **2e** : $\Delta E_1$ = 7.64 eV) and the reaction times are nearly the same (**2a** : 2 h and **2b** : 3 h; **2d** : 20 min and **2e** : 45 min). Then, the long reaction time observed for **2c** (**2c** : 8 h) is due to the high level of its LUMO ($LU_{2c}$ = 0.87 eV, $\Delta E_1$ = 9.29 eV). In fact, the FMO interaction can give an estimate of the reactivities of these dipolarophiles (except for **2f**) in this 1,3-dipolar cycloaddition reaction.

According to the simple FMO theory, the orientation of the addition should be such that the atom with the largest coefficient in the HOMO of imidate **1'** ($coefficient_{(HOMO)}$ = 0.687) becomes bound to the atom with the largest coefficient in the LUMO of the aldehyde **2(a-f)** (C coefficient in all cases) : in table 2, our experimental findings (from the $\pi$ character MO's) agree with this prediction (*i.e.* **2a** : O $coefficient_{(LUMO)}$ = 0.333 and C $coefficient_{(LUMO)}$ = - 0.362).

**Table 2 :** Calculated frontier orbital energies, HOMO and LUMO coefficients, net atomic charges for imidate **1** and aldehydes **2(a-f)**. Frontier orbital (FO) energy differences between **1** and **2(a-f)** with respect to formation of the intermediate **3**.

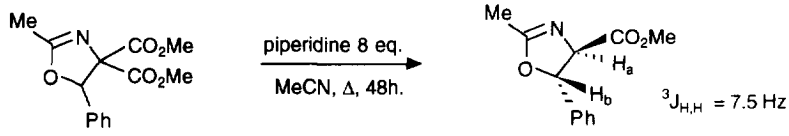



| | HOMO | | | LUMO | | | Net Atomic Charge | |
|---|---|---|---|---|---|---|---|---|
| Compound | (eV) | C-2 | C-4 | (eV) | C-2 | C-4 | C-2 | C-4 |
| **1'** | -8.42 | 0.687 | -0.383 | -0.60 | 0.274 | 0.512 | -0.682 | -0.244 |
| Compound | (eV) | N-3 | C-4 | (eV) | N-3 | C-4 | N-3 | C-4 |
| **1** | -10.29 | -0.342 | -0.416 | 0.33 | 0.502 | -0.594 | -0.155 | 0.090 |

| | HOMO | | | LUMO | | | Net Atomic Charge | | $\Delta E_1$[a] | $\Delta E_2$[b] |
|---|---|---|---|---|---|---|---|---|---|---|
| Aldehyde | (eV) | C= | O | (eV) | C= | O | C= | O | (eV) | (eV) |
| **2a** | -10.50 | -0.005 | -0.129 | -0.48 | -0.362 | 0.333 | 0.39 | -0.32 | 7.94 | 9.45 |
| **2b** | -9.73 | -0.009 | 0.242 | -0.44 | -0.421 | 0.376 | 0.36 | -0.31 | 7.98 | 9.13 |
| **2c** | -10.52 | -0.124 | 0.327 | 0.87 | 0.446 | -0.330 | 0.28 | -0.31 | 9.29 | 9.92 |
| **2d** | -9.35 | -0.034 | 0.135 | -0.65 | 0.421 | -0.351 | 0.36 | -0.36 | 7.77 | 8.75 |
| **2e** | -10.36 | 0.019 | 0.212 | -0.78 | 0.318 | -0.306 | 0.33 | -0.31 | 7.64 | 9.76 |
| **2f** | -10.33 | -0.013 | -0.220 | -0.85 | 0.429 | -0.237 | 0.33 | -0.31 | 7.64 | 8.83 |

(a) $\Delta E_1$ = $HOMO_{1'}$ - $LUMO_2$. (b) $\Delta E_2$ = $HOMO_2$ - $LUMO_{1'}$

In the course of this study, we found it interesting to de-alkoxycarbonylate[15] the 2-oxazoline **4** replacing one of the methoxycarbonyl groups (C-4) by hydrogen. The racemic **4a** (Scheme 3) on treatment with freshly distilled piperidine[16] (8 eq.) in dry acetonitrile (reflux, 48 h) lead to a racemic mixture of **5a**. The selective demethoxycarbonylation on the ester in *cis* position with respect to the phenyl group was confirmed by observation of one singlet only at $\delta$ = 3.81 ppm for the Me ester group on C-4. The *trans* geometry[17] of **5a** can be distinguished by the value of the coupling constant between H-4 and H-5 protons ($^3J$ = 7.5 Hz). In addition, the $^{13}C$ NMR spectrum exhibited a signal at $\delta$ = 52.8 ppm for the Me ester group; for the carbonyl group, we found one peak at $\delta$ = 171.4 ppm.

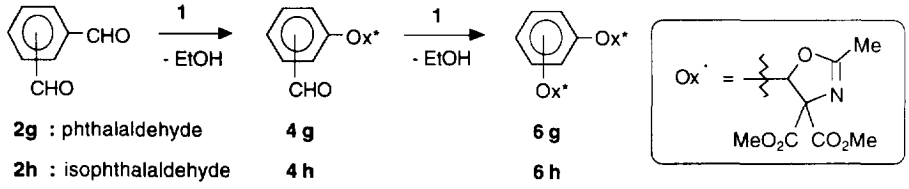



**4a** **5a**

**Scheme 3**

*Cycloaddition reaction with phthalaldehyde **2g** and isophthalaldehyde **2h*** - Similar cycloaddition of imidate **1** with phthalaldehyde **2g** and isophthalaldehyde **2h** as dipolarophiles were also studied. When a mixture of 1 equivalent of imidate **1** and 2 equivalents of **2g** or **2h** was stirred at 70 °C during one hour, the cycloadducts **4g** or **4h** were respectively formed in good yields. $^1$H NMR analysis of the crude reaction mixture exhibited signals which could readily be assigned to **4g** ($\delta_{CHO}$ = 10.26 ppm) or to **4h** ($\delta_{CHO}$ = 10.02 ppm) together with the signals of **2g** or **2h** in excess. The cycloadducts **4g,h** were isolated as pure compounds by chromatography on silica gel. Next, the direct synthesis of 1,2-bis(oxazolinyl)benzene **6g** was easily realized by stirring a mixture of imidate **1** (2 eq.) and **2g** (1 eq.) for an appropriate reaction time at 70 °C (Table 3). When the reaction was monitored by $^1$H NMR, we could follow the formation and disappearence of **4g**. The same reactions conditions were applied to **2h** and after 7.5 hours (ratio **1/2** : 2/1) the 1,3-bis(oxazolinyl)benzene **6h** was formed in 94% yield of crude product. According to the reaction time (Table 3) observed for the preparation of bis(oxazolinyl)benzene **6g,h**, it is noteworthy that the short reaction time for **6g** is probably due to an *ortho* director effect[1b] of the oxazolinyl group of the intermediate **4g** which activates the other formyl group for addition of a second equivalent of **1**. This is confirmed by the longer reaction time for the formation of **6h** in which the oxazolinyl group of **4h** is in *meta* position.

**Table 3 :** Synthesis of 2-oxazolines **4g,h** and bis(oxazolines) **6g,h** from phthalaldehyde **2g** and isophthalaldehyde **2h**.




**2g** : phthalaldehyde **4g** **6g**

**2h** : isophthalaldehyde **4h** **6h**

| Aldehyde | ratio **1/2** | Reaction time (h) | Compound | Yield (%)[a] |
|---|---|---|---|---|
| **2g** | 1 : 2 | 1 | **4g** | (97) 93 |
| **2h** | 1 : 2 | 1 | **4h** | (96) 80 |
| **2g** | 2 : 1 | 4 | **6g** | (90) 86 |
| **2h** | 2 : 1 | 7.5 | **6h** | (94) 83 |

(a) Yield for crude **4** estimated by $^1$H NMR and yield after purification by chromatography on silica gel 60 $F_{254}$ (Merck) or by recrystallization.

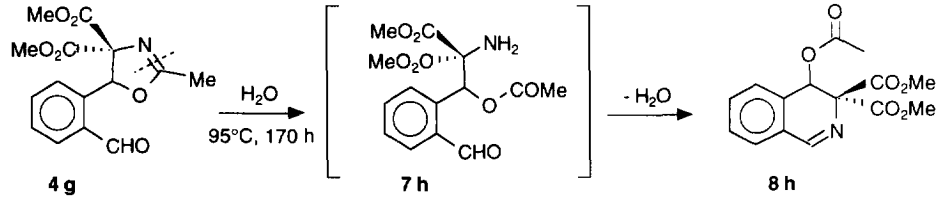
The regiochemistry and the chemical reactivity observed in these 1,3-dipolar cycloaddition reactions are discussed using the PM3 MO calculations. The results (Table 4) show that the orientation of this reaction is in agreement with the simple FMO theory : in all cases, the largest coefficient observed in the LUMO of the aldehydes **2g,h** and **4g,h** is on the C= which becomes bound to the atom with the largest coefficient in the HOMO of **1'**, *i.e.* C-2 with coefficient$_{(HOMO)}$ = 0.687. In the same manner, the favorable frontier orbitals interactions between **1'** and aldehydes **2g,h** and **4g,h** as dipolarophiles are due to the interaction $HOMO_{1'}$ - $LUMO_{\textbf{aldehyde}}$ (see column $\Delta E_1$, Table 4).

**Table 4 :** Calculated frontier orbital energies, HOMO and LUMO coefficients, net atomic charges for aldehydes **2(g,h)** and **4(g,h)**. Frontier orbitals (FO) energy differences between **1** and **2(g,h)**, and **4(g,h)**.

| | HOMO | | | LUMO | | | Net Atomic Charge | | $\Delta E_1$[(a)] | $\Delta E_2$[(b)] |
|---|---|---|---|---|---|---|---|---|---|---|
| Aldehyde | (eV) | C= | O | (eV) | C= | O | C= | O | (eV) | (eV) |
| **2g** | -10.27 | 0.013 | -0.005 | -0.85 | -0.292 | 0.268 | 0.32 | -0.31 | 7.57 | 9.67 |
| **2h** | -10.33 | -0.013 | -0.220 | -0.85 | 0.249 | -0.237 | 0.33 | -0.31 | 7.57 | 9.73 |
| **4g** | -10.13 | 0.002 | -0.064 | -0.69 | 0.306 | -0.288 | 0.31 | -0.30 | 7.73 | 9.53 |
| **4h** | -10.10 | -0.003 | -0.109 | -0.63 | 0.340 | -0.316 | 0.33 | -0.32 | 7.79 | 9.50 |

(a) $\Delta E_1$ = $HOMO_1$' - $LUMO_{aldehyde}$ (b) $\Delta E_2$ = $HOMO_{aldehyde}$ - $LUMO_1$'

Our attention was then focused on the chemical reactivity of **4g**. After long storage in the refrigerator, we have found that pure **4g** is sensible to moisture and leads to a new heterocyclic compound **8h** (Scheme 4).




**Scheme 4**

The chemical structure of this unexpected product **8h** was established by $^1H$ and $^{13}C$ NMR spectroscopic data. For example, **8h** exhibits a singlet at $\delta_{H\text{-}1}$ = 8.64 ppm which can be assigned to the imino hydrogen; another singlet at $\delta_{H\text{-}4}$ = 6.68 ppm and the Me ester groups appear respectively at $\delta$ = 3.66 and 3.89 ppm (for **4g** : $\delta$ = 3.11 and 3.89 ppm). In the $^{13}C$ NMR spectrum of **8h**, the number of carbon atoms and the multiplicity of each peak are similar to that of **4g** but the chemical shifts are quite different : it shows a doublet of doublet at $\delta_{C\text{-}1}$ = 162.4 ppm ($^1J$ = 180 and $^4J$ = 4.8 Hz) and another at $\delta_{C\text{-}4}$ = 67.2 ppm ($^1J$ = 159 and $^4J$ = 3.7 Hz). In the MS analysis, the molecular ion peaks of **4g** and **8h** are similar ($C_{15}H_{15}O_6N$ : 264 uma), but the MS degradation pattern of **8h** exhibits a fragment at *m/z* 43 uma which is in agreement with an acylium ion ($MeCO^+$). Finally, the chemical structure of **8h** has been established from single crystal X-ray diffraction analysis (Figure 1).

The transformation of **4g** into the 3,4-dihydroisoquinoline **8h** is consistent with a mild hydrolysis of the oxazolinyl[18] moiety to give **7h** as an intermediate which then undergoes an intramolecular cyclocondensation to afford the unexpected product **8h** after water elimination. The oxazoline cleavage has been confirmed by the formation of **8h** in quantitative yield after heating **4g** at 95°C during 170 hours. Furthermore, it is interesting to notice that no hydrolysis of **4h** has been detected in the same heating conditions or after long storage.

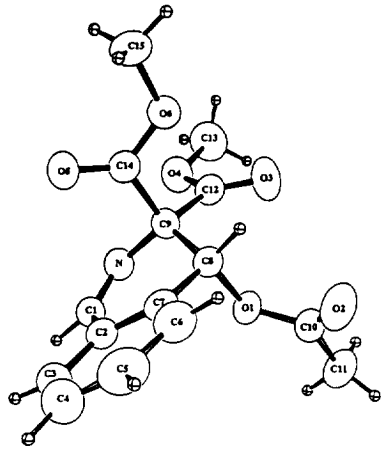
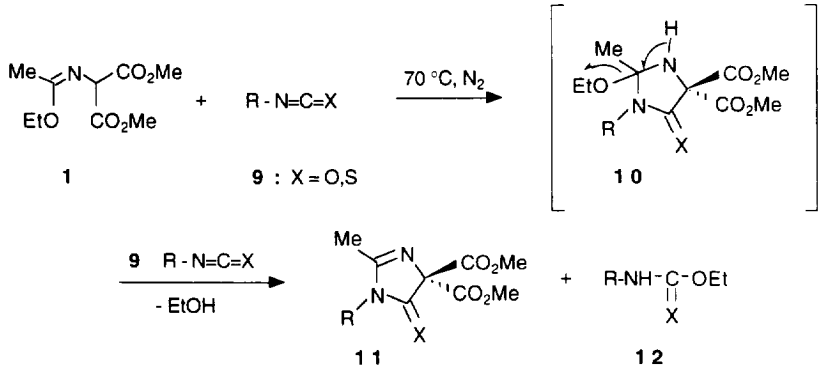


**Figure 1 :** Ortep diagram of the 3,4-dihydroisoquinoline **8h**.

*Cycloadditions with isocyanates 9(a-c) and isothiocyanates 9(d-f)* - Following our investigations of the chemical reactivity of imidate **1** as 1,3-dipole, we used isocyanates[19] **9(a-c)** and isothiocyanates **9(d-f)** as dipolarophiles. Reactions of **1** with **9** were carried out at 70 °C under nitrogen using solvent-free conditions (Scheme 5). This reaction was monitored by $^1$H NMR spectroscopy (see Table 6 for the reaction time).



**Scheme 5**

**Table 6 :** Synthesis of 2-imidazoline-5-ones **11** from isocyanates **9(a-f)**.

| Isocyanate | R | X | Reaction time (h) | Compound | Yield (%)[(a)] |
|---|---|---|---|---|---|
| **9a** | p-$ClC_6H_4$ | O | 40 | **11a** | 35 |
| **9b** | $C_6H_5$ | O | 40 | **11b** | - |
| **9c** | Et | O | 50 | **11c** | - |
| **9d** | $EtO_2C$ | S | 5 | **11d** | 61 |
| **9e** | $C_6H_5$ | S | 50 | **11e** | - |
| **9f** | Me | S | 50 | **11f** | - |

(a) Yield of isolated product.

From the crude reaction mixture, the urea derivatives resulting from the isocyanate were crystallized in acetonitrile and the expected cycloadducts **11** were purified by fractionnated crystallization (**11a**) or by chromatography on silica gel (**11d**). The results summarized in table 6 show that imidate **1** reacts only with 4-chlorophenylisocyanate **9a** in moderate yield (35%) after 40 hours and more rapidly with ethoxycarbonylisothiocyanate **9d** in 61% yield (reaction time : 5 hours).

The regiochemical course of this cycloaddition and the chemical structure of cycloadducts **11a** and **11d** were established by $^{1}H$ and $^{13}C$ NMR data. The $^{1}H$ NMR spectrum of **11a** and **11d** show only one peak (Figure 2) for the *gem*-methyl ester groups (C-4) indicating no vicinal cis relationship with respect to the phenyl group (which is observed in compound **4a** for example). The orientation of the cycloaddition was deduced from the nuclear Overhauser effect (NOE) measurements on compound **11a** : irradiation of the 2-methyl protons ($\delta_{Me}$= 2.19 ppm) caused 7.5% enhancement of the *ortho*-phenyl protons ($\delta$ = 7.45-7.50 ppm). In addition, the $^{14}N$ NMR spectrum of **11a** shows only one signal at $\delta$ = -72 ppm in agreement with an $sp^2$ nitrogen N-3 and in $^{15}N$ NMR, a peak at $\delta$ = -212 ppm for an $sp^3$ nitrogen N-1 according to the litterature[20].

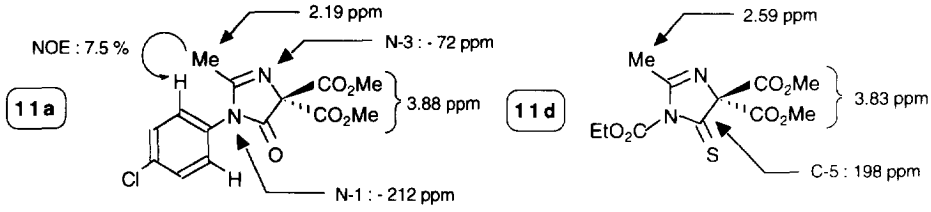



**Figure 2**

In $^{13}C$ NMR, **11a** exhibits two signals at $\delta$ = 163.4 ppm ($^{2}J$ = 5 Hz) and 171.5 ppm which can be assigned to C-2 and C-5 respectively (**11d** : $\delta_{C\text{-}5}$ : 198 ppm for the thiocarbonyl).

Now FMO analysis of the cycloaddition reaction of imidate **1** with isocyanates **9(a-c)** and isothiocyanates **9(d-f)** as dipolarophiles is described. PM3 MO calculations are developed to explain the first step (*via* the intermediate **10**) in scheme 5 according to FMO theory. Calculated properties of compounds **9(a-f)** are given in table 7. The calculated energies of the lower unoccupied molecular orbitals (LUMO) are in the range of -0.24 to 0.05 eV.

**Table 7 :** Calculated frontier orbital energies, HOMO and LUMO coefficients, net atomic charges for isocyanates **9(a-c)** and isothiocyanates **9(d-f)**.

| | HOMO | | | | LUMO | | | | Net Atomic Charge | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Product | (eV) | N | C | X[(a)] | (eV) | N | C | X[(a)] | N | C | X[(a)] |
| **9a** | -9.51 | -0.382 | -0.201 | 0.260 | -0.45 | 0.071 | -0.361 | 0.208 | -0.16 | 0.32 | -0.20 |
| **9b** | -9.17 | -0.191 | -0.096 | 0.130 | -0.18 | -0.040 | 0.161 | -0.091 | -0.16 | 0.32 | -0.21 |
| **9c** | -10.07 | 0.713 | 0.263 | -0.487 | 0.30 | 0.008 | -0.173 | 0.112 | -0.24 | 0.31 | -0.22 |
| **9d** | -9.82 | 0.582 | 0.010 | -0.777 | -1.16 | -0.014 | 0.030 | -0.023 | -0.08 | -0.08 | 0.11 |
| **9e** | -8.85 | 0.485 | 0.122 | -0.679 | -0.77 | 0.238 | -0.470 | 0.281 | 0.05 | -0.15 | 0.03 |
| **9f** | -9.15 | -0.531 | -0.069 | 0.771 | -0.79 | -0.057 | 0.187 | -0.131 | -0.04 | -0.14 | -0.01 |

(a) X = O,S.

The results in table 8 show that the cycloaddition is also controlled by the interaction $HOMO_1$ - $LUMO_{(dipolarophile)}$. According to this model, a reaction should occur with phenylisothiocyanate **9c** ($LUMO_{9c}$ = -0.77 eV) and methylisothiocyanate **9f** ($LUMO_{9f}$ = -0.79 eV), and this shows the limits of the simple FMO analysis. We have also developed calculations of second order pertubation energy $E_2$[21] with four possible approaches (Figure 3).

**Figure 3**
Different possible approaches

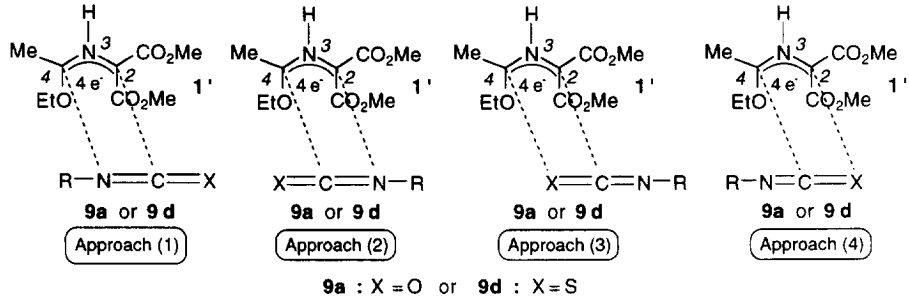



**Table 8 :** Frontier Orbitals (FO) energy differences and second order pertubation energy $E_2$ between imidate **1** and isocyanate **9a**, isothiocyanate **9d**.

| | | $\Delta E_1$[a] | $\Delta E_2$[b] | $E_2(1)$[c] | $E_2(2)$[d] | $E_2(3)$[e] | $E_2(4)$[f] |
|---|---|---|---|---|---|---|---|
| Isocyanate | X | (eV) | | (kcal/mole) | | | |
| **9a** | O | 7.98 | 8.91 | - 0.85 | - 0.47 | -0.67 | -0.38 |
| **9d** | S | 7.26 | 9.22 | - 0.28 | - 0.09 | -0.24 | -0.07 |

(a) $\Delta E_1$ = $HOMO_{1'}$ - $LUMO_9$. (b) $\Delta E_2$ = $HOMO_9$ - $LUMO_1$ (c) $E_2(1)$ = second order pertubation energy according to approach (1) (d) $E_2(2)$ = second order pertubation energy according to approach (2).(e) $E_2(3)$ = second order pertubation energy according to approach (3).(d) $E_2(4)$ = second order pertubation energy according to approach (4)

Values[22] obtained in column $E_2(1)$ show that the favoured orientation results (Table 8) from approach (1) for isocyanate **9a** (X = O, R = p-$ClC_6H_4$), isothiocyanate **9d** (X = S, R = $EtO_2C$), and this is in agreement with the experimental results.

## CONCLUSION

We have shown that [3+2] cycloaddition of imidate **1** derived from dimethyl aminomalonate with a variety of aldehydes as dipolarophiles may be useful for the synthesis of 2-oxazoline derivatives, *ortho* and *meta* bis(2'-oxazoline-5'-yl)benzenes. The simplicity of the experimental procedures using solvent-free conditions and the good yields render this process particularly attractive. We have also analyzed the regioselectivity and the chemical reactivity of this cycloaddition by PM3 MO calculations. Unfortunately, the extension of this methodology to isocyanates and isothiocyanates as dipolarophiles is not general. Further applications of activated imidates in [3+2] cycloadditions are under study in our laboratory.

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## Experimental section

**General.** Thin-layer chromatography (TLC) was accomplished on 0.2-mm precoated plates of silica gel 60 F-254 (Merck). Visualization was made with ultraviolet light (254 and 365 nm) or with a

fluorescence indicator. For preparative column chromatography, silica gel 60F 254 Merck (230-240 Mesh ASTM) was used. Melting points were determined on a Kofler melting point apparatus and are uncorrected.

IR spectra were taken with a PERKIN-ELMER 157G spectrometer. $^{1}H$ NMR spectra were recorded on BRUKER ARX 200 P (200 MHz), BRUKER AC 300 P (300 MHz) spectrometers, $^{13}C$ NMR spectra on BRUKER ARX 200 P (50 MHz), BRUKER AC 300 P (75 MHz) spectrometers. Chemical shifts are expressed in parts per million downfield from tetramethylsilane as an internal standard. $^{14}N$ and $^{15}N$ NMR spectra were recorded on BRUKER AMX 300 (300 MHz) spectrometer with nitromethane as internal standard. The mass spectra (HRMS) were taken on a VARIAN MAT 311 at a ionizing potential of 70 eV in the Centre Régional de Mesures Physiques de l'Ouest (CRMPO, Rennes).

Acetonitrile was distilled over calcium chloride after standing overnight and stored over molecular sieves (3Å). Solvents were evaporated with a BUCHI rotary evaporator.

All reagents were purchased from Acros, Aldrich Chimie, Fluka France and used without further purification. Dimethyl 2-(1-ethoxyethyliden)aminomalonate **1** was synthesized according to our previous method[7a] from commercial ethyl acetimidate hydrochloride and dimethyl aminomalonate hydrochloride.

*Computational Procedures*

Geometry of all aldehydes **2(a-h)**, **4g,h**, isocyanates **9(a-c)**, isothiocyanates **9(d-f)** and imidate **1** were created and roughly optimized by using MM2 force field calculations in CAChe MOPAC version 3.7 (©Copyright 1994, CAChe Scientific Inc., all rights reserved). MO calculations were carried out with PM3 method[12a] using MOPAC program (version 6.0)[12b] on Power Macintosh 7100/80 in the Centre Régional de Mesures Physiques de l'Ouest (CRMPO), Université de Rennes I.

*General procedure for the preparation of dimethyl 2-oxazoline-4,4-dicarboxylate* ***4(a-j)****,* ***4(k,l)****, 1,2-bis and 1,3-bis (2'-oxazolin-5'-yl)benzene* ***4(i,j)***

A mixture of dimethyl 2-(1-ethoxyethylidene)aminomalonate **1** (1.0 g, 4.6 mmol) and freshly distilled aldehyde **2(a-f)** (4.6 mmol) was heated to 70 °C during the appropriate time (monitored by TLC) under magnetic stirring. The reaction mixture was allowed to cool down. After removal of ethanol *in vacuo*, the crude residue was purified* by chromatography on silica gel (60F 254, Merck) with appropriate eluent. Solvent evaporation gave the desired compounds which crystallized on standing.

(*) except for compound **6g** which was recrystallized.

**Dimethyl 2-methyl-5-phenyl-2-oxazoline-4,4-dicarboxylate (4a)**

The crude product was obtained from **1** (1.0 g, 4.6 mmol) and benzaldehyde **2a** (0.49 g, 4.6 mmol) with a reaction time of 2 h. Purification by column chromatography on silica gel ($CH_2Cl_2$/EtOAc : 1/1, $R_f$ 0.58) gave **4a** (1.10 g, 91%) as colourless needles (mp = 67-68 °C); IR (nujol) 2920, 2850, 1760, 1730, 1645 $cm^{-1}$; $^{1}H$ NMR (300 MHz, $CDCl_3$) δ 2.22 (s, 3 H), 3.13 (s, 3 H), 3.86 (s, 3 H), 6.26 (s, 1 H), 7.31 (m, 5 H, Ar); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 14.24 (q, $J$ = 130 Hz), 52.29 (q, $J$ = 148 Hz), 53.61 (q, $J$ = 148 Hz), 85.08 (d, $J$ = 159 Hz, C-5), 86.22 (sd, $J$ = 3 Hz, C-4), 126.39, 128.04, 128.18, 128.82, 135.03 (Ar), 166.91 (C-2), 168.81 (s, C=O), 169.16 (s, C=O); HRMS, *m/z* : 218.0812 found for $M^+$ -$CO_2Me$ (calc for $C_{14}H_{15}NO_5$ -$CO_2Me$ : 218.0828). Anal. Calcd for $C_{14}H_{15}NO_5$ : C, 60.65; H, 5.41; N, 5.05; O, 28.89. Found : C, 60.32; H, 5.61; N, 5.07; O, 29.00.

**Dimethyl 5-(2-furyl)-2-methyl-2-oxazoline-4,4-dicarboxylate (4b)**

The crude product was obtained from **1** (1.0 g, 4.6 mmol) and 2-furaldehyde **2b** (0.44 g, 4.6 mmol) with a reaction time of 4 h. Purification by column chromatography on silica gel ($CH_2Cl_2$/EtOAc : 8/2, $R_f$ 0.50) gave **4b** (1.09 g, 89%) as brown needles (mp = 76-77 °C); IR (nujol) 3100, 2920, 2860, 1760, 1735, 1655 $cm^{-1}$; $^{1}H$ NMR (300 MHz, $CDCl_3$) δ 2.16 (s, 3 H), 3.51 (s, 3 H), 3.84 (s, 3 H), 6.28 (s, 1 H), 6.36 (sdd, 1 H, $J$ = 3.3, 1.84 Hz), 6.45 (sd, 1 H, $J$ = 3.2 Hz), 7.39 (sd, 1 H, $J$ = 1.3 Hz); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 14.20 (q, $J$ = 131 Hz), 52.99 (q, $J$ = 148 Hz), 53.80 (q, $J$ = 149 Hz), 78.75 (d, $J$ = 156 Hz, C-5), 84.02 (sd, $J$ = 3 Hz, C-4), 110.73 (d, $J$ = 176 Hz), 110.76

(d, $J$ = 176 Hz), 143.66 (ddd, $J$ = 204, 10.5, 7.5 Hz), 147.89 (s), 167.13 (s, C-2), 168.16 (s, C=O), 168.69 (s, C=O); HRMS, $m/z$ : 208.0623 found for $M^+$-$CO_2Me$ (calc for $C_{10}H_{10}NO_4$ - $CO_2Me$ : 208.0610). Anal. Calcd for $C_{12}H_{13}NO_6$ : C, 53.93; H, 4.87; N, 5.24; O, 35.95. Found : C, 53.81; H, 4.83; N, 5.19; O, 36.17.

**Dimethyl 2-methyl-5-methylethyl-2-oxazoline-4,4-dicarboxylate (4c)**
The crude product was obtained from **1** (1.0 g, 4.6 mmol) and 2-methyl propionaldehyde **2c** (0.99 g, 13.8 mmol) with a reaction time of 8 h at 55 °C. Purification by column chromatography on silica gel ($CH_2Cl_2$/EtOAc : 1/1, $R_f$ 0.43) gave **4c** (1.11 g, 64%) as colourless needles (mp = 84-85 °C); IR (nujol) 2920, 2850, 1760, 1730, 1650 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 0.93 (d, 3 H, $J$ = 6.5 Hz), 1.00 (d, 3 H, $J$ = 6.5 Hz), 1.91 (m, 1 H, $J$ = 6.2 Hz), 2.06 (s, 3 H), 3.78 (s, 3 H), 3.81 (s, 3 H), 4.89 (d, 1 H, $J$ = 6.6 Hz); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 14.09 (q, $J$ = 130 Hz), 17.90 (q, $J$ = 127 Hz), 19.87 (q, $J$ = 127 Hz), 29.36 (d, $J$ = 128 Hz), 52.84 (q, $J$ = 148 Hz), 53.42 (q, $J$ = 148 Hz), 82.83 (s, C-4), 89.25 (d, $J$ = 160 Hz, C-5), 168.20 (s, C-2), 168.82 (s, C=O), 169.26 (s, C=O); HRMS, $m/z$ : 243.1119 found for $M^+$ (calc for $C_{11}H_{17}NO_5$ : 243.1107). Anal. Calcd for $C_{11}H_{17}NO_5$ : C, 54.32; H, 6.99; N, 5.76; O, 32.92. Found : C, 54.36; H, 7.11; N, 5.84; O, 32.69.

**Dimethyl 5-(2-hydroxyphenyl)-2-methyl-2-oxazoline-4,4-dicarboxylate (4d)**
The crude product was obtained from **1** (1.0 g, 4.6 mmol) and 2-hydroxybenzaldehyde **2a** (0.56 g, 4.6 mmol) with a reaction time of 20 min. Purification by column chromatography on silica gel ($CH_2Cl_2$/Petroleum ether, boiling range 40-65 °C : 9/1, $R_f$ 0.41) gave **4d** (1.35 g, 65%) as colourless needles (mp = 184-185 °C/MeCN); IR (nujol) 3100, 2920, 2850, 1755, 1730, 1640, 1595 $cm^{-1}$;$^1H$ NMR (200 MHz, $CDCl_3$/$d^6$ DMSO (1/1)) δ 2.18 (s, 3 H), 3.17 (s, 3 H), 3.81 (s, 3 H), 6.67 (s, 1 H), 6.72-7.14 (m, 4 H, Ar), 12.15 (broad s, 1 H, OH); $^{13}C$ NMR (50 MHz, $CDCl_3$/$d^6$ DMSO (1/1)) δ 14.00 (q, $J$ = 130 Hz), 51.88 (q, $J$ = 148 Hz), 53.28 (q, $J$ = 148 Hz), 80.38 (d, $J$ = 162 Hz, C-5), 85.58 (sd, $J$ = 2.5 Hz, C-4), 115.48, 118.83, 121.88, 126.94, 129.70 (Ar), 163.91 (s, C-2', Ar), 167.14 (s, C-2) ; 168.46 (s, C=O) ; 168.77 (s, C=O); IR (nujol, $cm^{-1}$) 3100 (broad), 2920, 2850, 1755, 1730, 1640, 1595; HRMS, $m/z$ : 293.0899 found for $M^+$ (calc for $C_{14}H_{15}NO_6$ : 293.0899). Anal. Calcd for $C_{14}H_{15}NO_6$ : C, 57.34; H, 5.12; N, 4.78; O, 32.76. Found : C, 57.23; H, 5.17; N, 4.91; O, 32.69.

**Dimethyl 2-methyl-5-(2-pyridyl)-2-oxazoline-4,4-dicarboxylate (4e)**
The crude product was obtained from **1** (1.0 g, 4.6 mmol) and 2-pyridine carboxaldehyde **2e** (0.49 g, 4.6 mmol) with a reaction time of 1 h. Purification by column chromatography on silica gel ($CH_2Cl_2$/MeCN : 6/4, $R_f$ 0.40) gave **4e** (1.28 g, 86%) as white needles (mp = 73-74 °C); IR (nujol) 2920, 2830, 1750, 1725, 1650, 1580 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 2.25 (s, 3 H), 3.21 (s, 3 H), 3.89 (s, 3 H), 6.29 (s, 1 H), 7.26-7.32 (m, 1 H, Pyr), 7.62-7.66 (m, 1 H, Pyr), 8.55-8.65 (m, 2 H, Pyr); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 14.16 (q, $J$ = 131 Hz), 52.56 (q, $J$ = 149 Hz), 53.74 (q, $J$ = 149 Hz), 83.05 (d, $J$ = 158 Hz, C-5), 86.26 (sd, $J$ = 2.7 Hz, C-4), 123.07, 130.96, 133.91, 147.97, 150.16 (Pyr), 166,61 (s, C-2), 168.49 (s, C=O), 169.10 (s, C=O); HRMS, $m/z$ : 208.0776 found for $M^+$-$CO_2Me$ (calc for $C_{11}H_{11}N_2O_3$ -$CO_2Me$ : 219.0769). Anal. Calcd for $C_{13}H_{14}N_2O_5$ : C, 56.11; H, 5.03; N, 10.07; O, 28.77. Found : C, 56.65; H, 5.24; N, 9.78; O, 29.33.

**Dimethyl 2-methyl-5-[(*1E*)-2-phenylethenyl)]-2-oxazoline-4,4-dicarboxylate (4f)**
The crude product was obtained from **1** (1.0 g, 4.6 mmol) and *trans*-cinnamaldehyde **2f** (0.61 g, 4.6 mmol) with a reaction time of 5 h. Purification by column chromatography on silica gel (EtOAc/Petroleum ether, boiling range 40-65 °C : 7/3, $R_f$ 0.45) gave **4f** (1.37 g, 87%) as pale brownish needles (mp = 60-61 °C); IR (nujol) 2920, 2850, 1730, 1650 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 2.14 (s, 3 H), 3.63 (s, 3 H), 3.84 (s, 3 H), 5.81 (dd, 1 H, $J$ = 7.8, 0.9 Hz), 6.05 (dd, 1 H, $J$ = 16, 7.8 Hz), 6.75 (dd, 1 H, $J$ = 16, 0.9 Hz), 7.23 - 7.36 (m, 5 H, Ar); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 14.26 (q, $J$ = 130 Hz), 52.91 (q, $J$ = 148 Hz), 53.53 (q, $J$ = 148 Hz), 84.17 (d, $J$ = 160 Hz, C-5), 84.81 (sd, $J$ = 3 Hz, C-4), 121.72 (d, $J$ = 160 Hz, CH=), 126.74, 128.55, 128.70, 135.52 (Ar), 135.06 (d, $J$ = 154 Hz, CH=), 167.36 (s, C-2), 168.52 (s, C=O), 169.03 (s, C=O); HRMS, $m/z$ : 303.1107 found for $M^+$ (calc for $C_{16}H_{17}NO_5$ : 303.1106). Anal. Calcd for $C_{16}H_{17}NO_5$ : C, 63.37; H, 5.61; N, 4.62; O, 26.40. Found : C, 63.10; H, 5.76; N, 4.59; O, 26.55.

**Dimethyl 5-(2-formylphenyl)-2-methyl-2-oxazoline-4,4-dicarboxylate (4g)**
The crude product was obtained from **1** (1.0 g, 4.6 mmol) and 1,2-phthalic dicarboxaldehyde **2g** (1.23 g, 9.2 mmol) with a reaction time of 1 hour. Purification by column chromatography on silica gel (EtOAc/Petroleum ether, boiling range 40-65 °C : 7/3, $R_f$ 0.45) gave **4g** (1.30 g, 93%) as white needles (mp = 81-82 °C); IR (nujol) 2920, 2850, 1750, 1725, 1650, 1680 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 2.27 (s, 3 H), 3.11 (s, 3 H), 3.89 (s, 3 H), 7.24 (s, 1 H), 7.37-7.63 (m, 3 H, Ar), 7.88-7.91 (m, 2 H, Ar), 10.26 (s, 1 H, CHO); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 14.08 (q, $J$ = 131 Hz), 52.12 (q, $J$ = 148 Hz), 53.80 (q, $J$ = 149 Hz), 80.80 (dd, $J$ = 163, 3.6 Hz, C-5), 86.45 (sd, $J$ = 3 Hz, C-4), 126.65, 129.12, 131.06, 133.63, 133.77, 136.94 (Ar), 166.69 (s, C-2), 168.18 (s, C=O) ; 168,89 (s, C= O), 191.01 (d, J = 5.5 Hz, CHO); HRMS, *m/z* : 305.0914 found for $M^+$ (calc for $C_{15}H_{15}NO_6$ : 305,0899). Anal. Calcd for $C_{15}H_{15}NO_6$ : C, 59.01; H, 4.92; N, 4.59; O, 31.47. Found : C, 58.94; H, 4.94; N, 4.51; O, 31.61.

**Dimethyl 5-(3-formylphenyl)-2-methyl-2-oxazoline-4,4-dicarboxylate (4h)**
The crude product was obtained from **1** (1.0 g, 4.6 mmol) and 1,3-phthalic dicarboxaldehyde **2h** (1.23 g, 9.2 mmol) with a reaction time of 1 h. Purification by column chromatography on silica gel (EtOAc, $R_f$ 0.60) gave **4h** (1.12 g, 80%) as colourless needles (mp = 80-81 °C); IR (nujol) 2920, 2850, 1730, 1680, 1645 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 2.27 (s, 3 H), 3.15 (s, 3 H), 3.89 (s, 3 H), 6.34 (s, 1 H), 7.48-7.64 (m, 2 H, Ar), 7.84-7.89 (m, 2 H, Ar), 10.02 (s, 1 H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 14.21 (q, $J$ = 131 Hz), 52.44 (q, $J$ = 149 Hz), 53.72 (q, $J$ = 149 Hz), 84.39 (d, $J$ = 163 Hz, C-5), 86.34 (sd, $J$ = 2.7 Hz, C-4), 127.73, 129.01, 129.79, 132.32, 136.39 (Ar), 166.67 (s, C-2), 168.66 (s, C=O), 169.17 (s, C=O), 191.62 (d, J = 5.5 Hz, CHO); HRMS, *m/z* : 246.0759 found for $M^+$-$CO_2Me$ (calc for $C_{13}H_{13}NO_4$ -$CO_2Me$ : 246.0766). Anal. Calcd for $C_{15}H_{15}NO_6$ : C, 59.01; H, 4.92; N, 4.59; O, 31.47. Found : C, 58.98; H, 4.91; N, 4.57; O, 31.54.

**Methyl 2-methyl-5-phenyl-2-oxazoline-4-carboxylate (5a)**
A mixture of dimethyl 2-methyl-5-phenyl-2-oxazoline-4,4-dicarboxylate **4a** (1.0 g, 3.61 mmol) and freshly distilled piperidine (2.17 g, 25.53 mmol) in dry acetonitrile (30 mL) was heated at 81 °C during 48 h (monitored by TLC, eluent : AcOEt, $R_f$ 0.62), under magnetic stirring. Then, the reaction mixture was allowed to cool down. After elimination of solvent and excess of piperidine *in vacuo*, the crude reaction mixture was purified by chromatography on silica gel (60F 254, Merck) with ethyl acetate as eluent. Removal of solvent gave **5a** in 80% yield as pure colourless crystals (mp = 67-68 °C). IR (nujol) 2920, 2850, 1750, 1725, 1650, 1680 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) δ 2.05 (sd, 3 H, $J$ = 1.2 Hz), 2.68 (s, 3 H), 3.67 (s, 3 H), 4.35 (dd, 1 H, $J$ = 6.9, 1.2 Hz), 4.72 (d, 1 H, $J$ = 6.9 Hz), 7.24-7.40 (m, 5 H, Ar); $^{13}C$ NMR (50 MHz, $CDCl_3$) δ 14.53 (q, $J$ = 129 Hz), 31.93 (q, $J$ = 139 Hz), 52.39 (q, $J$ = 147 Hz), 70.34 (d, $J$ = 136 Hz), 75.50 (d, $J$ = 140 Hz), 127.12-128.12-128.92-140.34 (Ar), 165.33 (s, C-2), 172.60 (s, CO); HRMS, *m/z* : 232.1197 found for $M^+$ (calc. for $C_{13}H_{14}N_2O_3$ : 232.1212), 173.1071 found for $M^+$ -$CO_2Me$ (calc. for $C_{13}H_{14}N_2O_3$ -$CO_2Me$ : 173.1078).

**1,2-Bis(4',4'-dimethyloxycarbonyl-2'-methyl-2'-oxazoline-5'-yl)benzene (6g)**
The crude product was obtained from **1** (1.0 g, 4.6 mmol) and 1,2-phthalic dicarboxaldehyde **2g** (0.31 g, 2.3 mmol) with a reaction time of 4 h. Recrystallization from $Et_2O$ gave **6g** (0.56 g, 80%) as colourless needles (mp = 210-211 °C); IR (nujol) 2920, 2850, 1760, 1735, 1650, 1290, 1200 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 2.26 (s, 6 H), 3.14 (s, 6 H), 3.91 (s, 6 H), 6.83 (s, 2 H), 7.10-7.13 (m, 2 H, Ar), 7.27-7.30 (m, 2 H, Ar); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 14.23 (q, $J$ = 130 Hz), 52.45 (q, $J$ = 149 Hz), 53.94 (q, $J$ = 149 Hz), 81.21 (dd, $J$ = 160, 3.5 Hz, C-5'), 86.97 (sd, $J$ = 2.2 Hz, C-4'), 125.74, 128.76, 133.94 (Ar), 166.84 (s, C-2'), 168.29 (s, C=O), 169.09 (s, C=O); HRMS, *m/z* : 476.1476 found for $M^+$ (calc for $C_{22}H_{24}N_2O_{10}$ : 476.1431). Anal. Calcd for $C_{22}H_{24}N_2O_{10}$ : C, 55.46; H, 5.04; N, 5.88; O, 33.61. Found : C, 55.02; H, 5.02; N, 6.16; O, 33.80.

**1,3-Bis(4',4'-dimethyloxycarbonyl-2'-methyl-2'-oxazoline-5'-yl)benzene (6h)**
The crude product was obtained from **1** (1.0 g, 4.6 mmol) and 1,3-phthalic dicarboxaldehyde **2h** (0.31 g, 2.3 mmol) with a reaction time of 7.5 h. Purification by column chromatography on silica gel (EtOAc, $R_f$ 0.24) gave **6h** (0.58 g, 83%) as colourless needles (mp = 72-74 °C); IR (nujol) 2920, 2850, 1720, 1650, 1300, 1225 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 2.23 (s, 3 H), 2.24 (s, 3 H), 3.22 (s, 3 H), 3.25 (s, 3 H), 3.87 (s, 6 H), 6.22 (s, 1 H), 6.23 (s, 1 H), 7.23-7.35 (m, 4 H, Ar); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 14.25 (q, $J$ = 131 Hz), 53.48 (q, $J$ = 144 Hz), 53.53 (q, $J$ = 149 Hz), 53.66 (q, $J$ = 149 Hz), 84.72 (d, $J$ = 158 Hz, C-5'), 84.96 (d, $J$ = 160 Hz, C-5'), 86.06 (sd, $J$ = 2.8 Hz, C-4'), 86.14 (sd, $J$ = 2.6 Hz, C-4'), 124.79, 124.83, 126.83, 127.23, 128.20, 128.29, 135.35, 135.37 (Ar), 166.75 (s, C-2'), 166.81 (s, C=O), 168.68 (s, C=O), 169.10 (s, C=O), 169.13 (s, C=O); HRMS, *m/z* : 476.1406 found for $M^+$ (calc for $C_{22}H_{24}N_2O_{10}$ : 476.1431). Anal. Calcd for $C_{22}H_{24}N_2O_{10}$ : C, 55.46; H, 5.04; N, 5.88; O, 33.61. Found : C, 55.41; H, 5.34; N, 5.42; O, 33.83.

**Dimethyl 4-ethanoyloxy-3,4-dihydroisoquinoline-3,3-dicarboxylate (8h)**
**4g** heated at 95°C during 170 h is quantitatively transformed in **8h** (mp = 98-99 °C); $^1H$ NMR (300 MHz, $CDCl_3$) δ 1.93 (s, 3 H), 3.66 (s, 3 H), 3.89 (s, 3 H), 6.68 (s, 1 H, H-4), 7.46-7.59 (m, 4 H, Ar), 8.64 (s, 1 H, H-1); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 20.78 (q, $J$ = 130 Hz), 53.49 (q, $J$ = 148 Hz), 53.62 (q, $J$ = 148 Hz), 67.21 (dd, $J$ = 159, 3.7 Hz, C-4), 73.95 (sd, $J$ = 1.4 Hz, C-3), 126.18-128;40-128.83-130.39-131.05-133.04 (Ar), 162.40 (dd, $J$ = 180, 4.8 Hz, C-1), 165.39 (sm, CO), 167.38 (sm, CO), 169.34 (sm, CO); HRMS, *m/z* : 305.0915 found for $M^+$ (calc for $C_{15}H_{15}NO_6$ : 305.0899).

**X-Ray Crystallographic data for 8h : $C_{15}H_{15}O_6N$**
Crystal data for $C_{15}H_{15}O_6N$ **(8h)**, Mr = 267.28, triclinic, P-1, a = 8.239(8), b = 8.391(4), c = 11.825(9)Å, α = 102.91(5), β = 105.28(8), γ = 104.49(6)°, V = 726(1)$Å^{-3}$, Z = 2, $D_x$ = 1.396 $Mg.m^{-3}$, λ(MoKα) = 0.70926Å, μ = 1.021 $cm^{-1}$, F(000) = 320, T = 293 K, final R = 0.042 for 1690 observations. The sample (0.20*0.20*0.35 mm) was studied on an automatic diffractometer CAD4 ENRAF-NONIUS with graphite monochromatized MoKα radiation. The cell parameters were obtained by fitting a set of 25 high-theta reflections. The data collection ($2\theta_{max}$ = 50°, scan $\omega/2\theta$ = 1, $t_{max}$ = 60 s, range HKL : H 0,9 K -10,10 L -14,14, intensity controls without appreciable decay (0.2%) gave 2726 reflections from which 1690 were independent ($R_{int}$ = 0.021) with $I>3\sigma(I)$. After Lorenz and polarization corrections the structure was solved with Direct Method which revealled all the non-hydrogen atoms of the structure. After isotropic (R = 0.115), then anisotropic refinement (R = 0.082), all the hydrogen atoms were found with a Fourier Difference between 1.17 and 0.54 $e.Å^{-3}$. The whole structure was refined by the full-matrix least-square techniques (use of F magnitude ; x, y, z, $\beta_{ij}$ for N, O and C atoms and x, y, z for H atoms ; 245 variables and 1690 observations ; $w = 1/\sigma(F_o)^2=[\sigma^2(I) + (0.04F_o^2)^2]^{-1/2}$) with the resulting R = 0.043, $R_w$ = 0.042 and $S_w$ = 0.715 (residual $\Delta\rho \leq 0.41$ e $Å^{-3}$). Atomic scattering factors from International Tables for X-ray Crystallography (1974)[23]. All the calculations were performed on a Digital MicroVAX3100 computer with the MOLEN package[24]. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.

**Dimethyl 1-(4-chlorophenyl)-2-methyl-5-oxo-2-imidazoline-4,4-dicarboxylate (11a)**
A mixture of dimethyl 2-(1-ethoxyethylidene)aminomalonate **1** (1.0 g, 4.6 mmol) and freshly distilled 4-chlorophenyl isocyanate **9a** (1.48 g, 9.66 mmol) was stirred vigorously at 70 °C under nitrogen during 40 h. After elimination of ethanol in a rotary evaporator, diethyl ether (30 mL) was added to the crude residue and the suspension was filtered. Removal of the solvent *in vacuo* gave an oil which crystallized on standing. Recrystallization from acetonitrile gave **11a** (0.54 g, 36%) as colourless needles (mp = 161-162 °C); IR (nujol) 2920, 2840, 1755, 1730, 1710, 1480 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) δ 2.19 (s, 3 H), 3.88 (s, 6 H), 7.17-7.21 (d, 2 H, Ar), 7.45-7.50 (d, 2 H, Ar); $^{13}C$ NMR (50 MHz, $CDCl_3$) δ 16.81 (q, $J$ = 131 Hz), 54.03 (q, $J$ = 149 Hz), 80.69 (s, C-4),

128.76, 130.14, 130.99, 135.60 (Ar), 163.36 (sq, $J$ = 5 Hz, C-2), 165.87 (sq, $J$ = 7 Hz, CO), 171.53 (s, C-5); $^{14}$N NMR (300 MHz, $MeNO_2$) δ - 72 (N-3); $^{15}$N NMR (300 MHz, $MeNO_2$) δ - 212 (N-1), HRMS, *m/z* : 324.5118 found for $M^+$ (calc for $C_{14}H_{13}N_2O_5Cl$ : 324.5120). Anal. Calcd for $C_{14}H_{13}N_2O_5Cl$ : C, 51.78; H, 4.00; N, 8.63; O, 24.66; Cl, 10.92. Found : C, 51.95; H, 4.11; N, 8.71; O, 24.17; Cl, 11.06.

**Dimethyl 1-ethoxycarbonyl-2-methyl-5-thioxo-2-imidazoline-4,4-dicarboxylate (11d)**

This compound was prepared according to the method described for the synthesis of **11a** with a reaction time of 1.75 h, from dimethyl 2-(1-ethoxyethylidene)aminomalonate **1** (1.0 g, 4.6 mmol) and ethoxycarbonyl isothiocyanate **9d** (1.27 g, 9.66 mmol). Purification by chromatography on silica gel (eluent, $R_f$ 0.43) gave **11d** (0.85 g, 61%) as pale yellow viscous oil which crystallized on standing (mp = 57-58 °C); IR (nujol) 2930, 2835, 1765, 1740, 1715, 1490 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) δ 1.43 (t, 3 H, $J$ = 7.1 Hz), 2.59 (s, 3 H), 3.83 (s, 6 H), 4.72 (q, 2 H, $J$ = 7.1 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 13.91 (qt, $J$ = 128, 2.6 Hz), 18.16 (q, $J$ = 132 Hz), 54.13 (q, $J$ = 149 Hz), 65.23 (tq, $J$ = 150, 4.3 Hz), 92.07 (s, C-4), 149.33 (st, $J$ = 3.1 Hz, CO), 162.95 (sq, $J$ = 4.3 Hz, C-2), 164.17 (sq, $J$ = 7.7 Hz, CO); 198.02 (s, C=S, C-5); HRMS, *m/z* : 302.0608 found for $M^+$ (calc for $C_{11}H_{14}N_2O_6S$ : 302.0573). Anal. Calcd for $C_{11}H_{14}N_2O_6S$ : C, 43.71; H, 4.64; N, 9.27; O, 31.79; S, 10.60. Found : C, 43.68; H, 4.73; N, 9.36; O, 32.02; S, 10.21.

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