Stereocontrolled formation of substituted imidazolidines in the reaction between *N*-metallated azomethine ylides and isocyanates

Edurne Erkizia,[a,1] Eneko Aldaba,[a] Yosu Vara,[a] Ana Arrieta,[a] Heinz Gornitzka,[b] and Fernando P. Cossío [a,*]

[a] *Kimika Fakultatea, Universidad del País Vasco – Euskal Herriko Unibertsitatea P. K. 1072, 20080 San Sebastián – Donostia, Spain*
[b] *Laboratoire Hétérochimie Fondamentale et Appliquée, Université Paul Sabatier 118 rue de Narbonne, 31062 Toulouse Cedex 4, France*
E-mail: fp.cossio@sq.ehu.es

Dedicated to Professors José Elguero and Pedro Molina on the occasion of their 70th and 60th birthdays, respectively

(received 14 Dec 04; accepted 18 Mar 05; published on the web 25 Mar 05)

Abstract

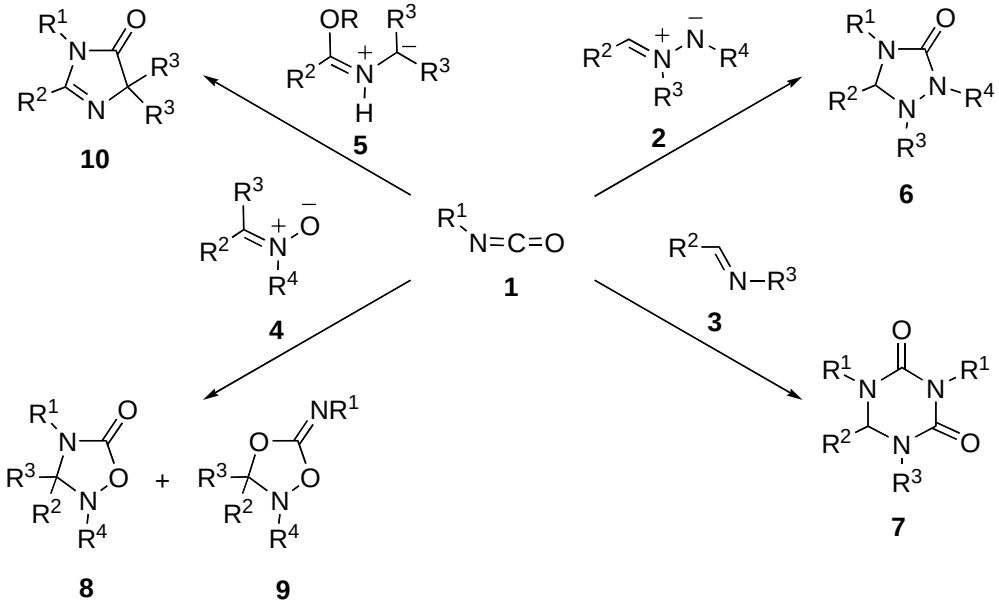
Substituted imidazolidines (and not imidazolidin-4-ones) are the unexpected cycloadducts obtained in the reaction between imines and isocyanates. The reaction is shown to take place via stepwise [3+2] cycloaddition between the *N*-metallated azomethine ylide formed *in situ* and the starting imine, followed by nucleophilic addition of the resulting imidazolidine on the *sp*-hybridized carbon atom of the isocyanate. Density-Functional Theory calculations provide a model for the mechanism of this unusual reaction and for the origins of the observed regio- and stereoselectivity.

Keywords: Azomethine ylides, imines, isocyanates, imidazolidines, cycloadditions

Introduction

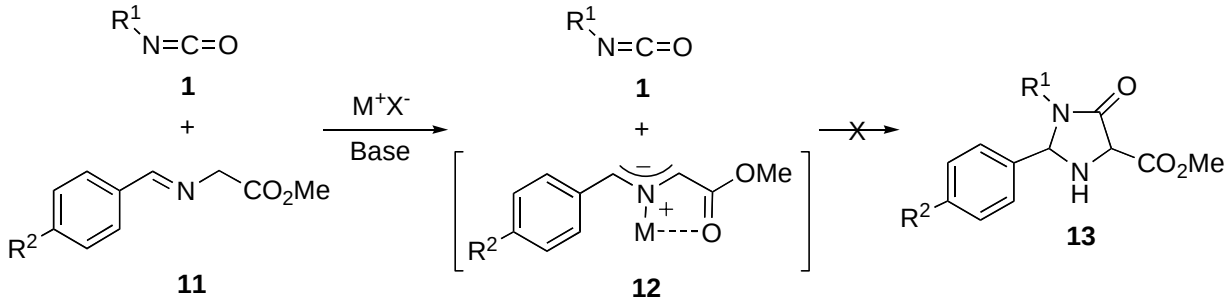
It is well-known that cumulenes, in particular ketenes and isocyanates, can participate in 1,3-dipolar reactions to yield different cycloadducts (Scheme 1).[2] For example, isocyanates **1** can react with azomethine imines **2** to form 1,2,4-triazolidin-3-ones **6**.[3] In contrast, imines **3** react with isocyanates to yield 1,3,5-triazenane-2,4-diones **7** as [2+2+2] cycloadducts.[4] The reaction between nitrones **4** and isocyanates has also been described.[5,6] In this case, both the C=N [5] and C=O [6] bonds of the isocyanate can participate in the [3+2] cycloaddition to yield 1,2,4-oxazolidin-5-ones **8** and 1,2,4-dioxazolidines **9**, respectively. It is noteworthy that the cycloadducts **9** have been found as transient species only when chlorosulfonyl isocyanate is used

as dipolarophile. Finally, it has been reported that stabilized *NH*-azomethine ylides **5** derived from imidates react with isocyanates via the C=N bond to yield 1*H*-imidazol-5(4*H*)-ones **10** as the corresponding [3+2] cycloadducts.[7]



Scheme 1. [2+2+2] and [3+2] cycloadditions between isocyanates and imines and 1,3-dipoles.

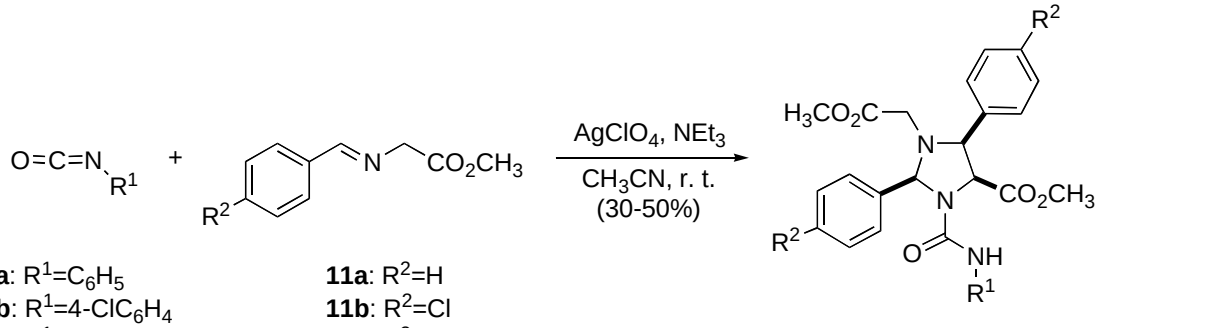
Within this context, and as part of our studies on the reactivity of *N*-metallated azomethine ylides toward diverse dipolarophiles,[8] we decided to explore the reaction between these 1,3-dipoles and isocyanates, as shown in Scheme 2, in order to extend the scope of reactions shown in Scheme 1. However, the outcome of this reaction was found to be completely different.



Scheme 2. The expected (but not obtained) cycloadducts **13** resulting from the formal [3+2] cycloaddition between *N*-metallated azomethine ylides **12** and isocyanates **1**.

Results and Discussion

We first studied the reaction in acetonitrile between imine **11a** and phenyl isocyanate **1a** (Scheme 3) using $AgClO_4$ as metal source and triethylamine as base. The product obtained showed a ^{1}H-NMR spectrum incompatible with the corresponding imidazolidin-4-one **13** shown in Scheme 2. Thus, two doublets at δ 3.24 and 3.09 ppm were observed, with a coupling constant of 17.4 Hz. The remaining spectroscopic and analytical data indicated that the structure of cycloadduct **14a** was that indicated in Scheme 3. In addition, Molecular Mechanics simulations suggested that the large value of the coupling constant between the methine protons at C4 and C5 indicated a *cis*- (4*S**,5*S**) configuration for these carbon atoms.



1a: R^1=C_6H_5
1b: R^1=4-ClC_6H_4
1c: R^1=$CH_2C_6H_5$

11a: R^2=H
11b: R^2=Cl
11c: R^2=Br

14a: R^1=C_6H_5, R^2=H **14d**: R^1=4-ClC_6H_4, R^2=H
14b: R^1=C_6H_5, R^2=Cl **14e**: R^1=$CH_2C_6H_5$, R^2=Cl
14c: R^1=C_6H_5, R^2=Br **14f**: R^1=4-ClC_6H_4, R^2=Cl

Scheme 3. Imidazolidines **14a–f** obtained in the reaction between imines **11a–c** and isocyanates **1a–c**.

After this first experiment, we performed several analogous reactions using two equivalents of imines **11a–c**. In all cases only one regio- and stereoisomer was obtained in low to moderate yields. The relative all- *cis* (2*S**,3*S**,4*S**) stereochemistry was assigned from the respective ^{1}H-NMR spectra (*vide supra*) and on the basis of the X-ray diffraction analysis[9] on compound **14b** (Figure 1). Experiments conducted with salts such as $Mg(ClO_4)_2$, $MgBr_2.OEt_2$ or $ZnBr_2$ did not improve the yields above those obtained with $AgClO_4$.

In order to elucidate the sequence of events in this cycloaddition we studied the reaction of two equivalents of imine **11b** in the presence of one equivalent of $AgClO_4$ and triethylamine (Scheme 4). Under these conditions, the imidazolidine **15a** was obtained in 33% yield. Subsequent reaction with one equivalent of phenyl isocyanate **1a** led to the previously obtained compound **14b** in good yield (Scheme 4). This result is compatible with a mechanism involving formation of the silver azomethine ylides derived from imines **11** followed by [3+2] autocyclization with another equivalent of the starting imine. Finally, nucleophilic addition of the *N*-metallated imidazolidines with isocyanates **1** should lead to the corresponding carbamoyl derivatives **14**. This mechanism is compatible with the findings of Grigg's group[10] on the reaction between imines in the presence of metallic salts.

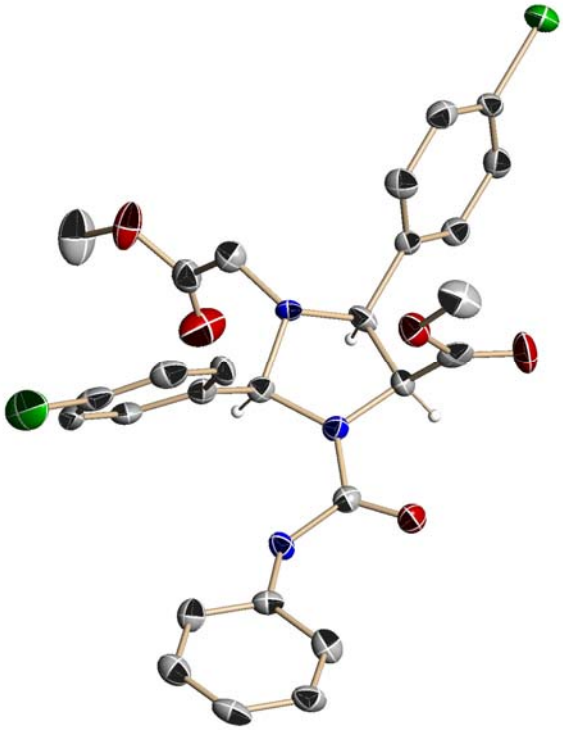
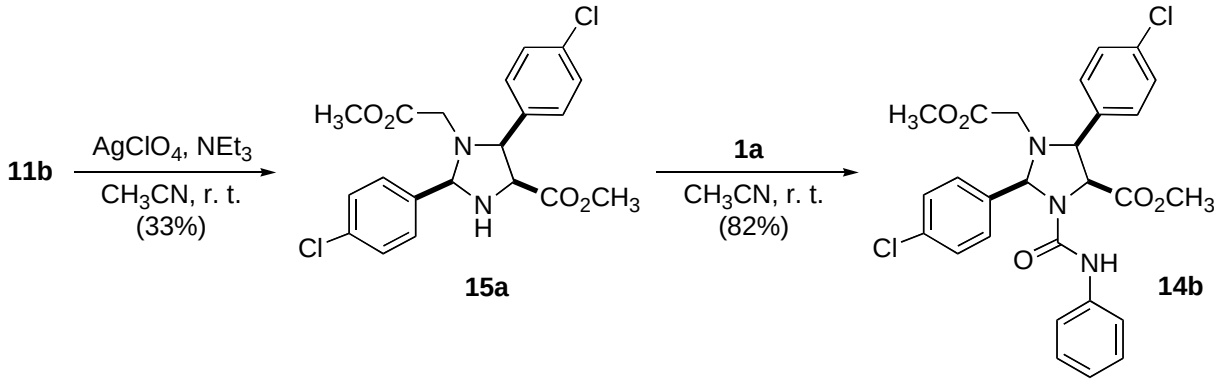


Figure 1. *ORTEP* diagram (50% probability ellipsoids) of compound **14b** according to the X-ray diffraction analysis. Only the stereochemically relevant hydrogen atoms are shown.



Scheme 4. Autocyclization of imine **11b** and subsequent formation of derivative **14b** in the presence of the isocyanate **1a**.

In view of these experimental results, we carried out a computational study using the Density Functional Theory[11] on the model reaction indicated in Scheme 5 in order to understand the nature of this unusual [3+2] autocyclization. According to our computational results, the reaction mechanism is not concerted, but is stepwise. The main geometric and energetic features of the stationary points (reaction intermediates and transition structures) located and characterized for this model reaction are shown in Figure 2.

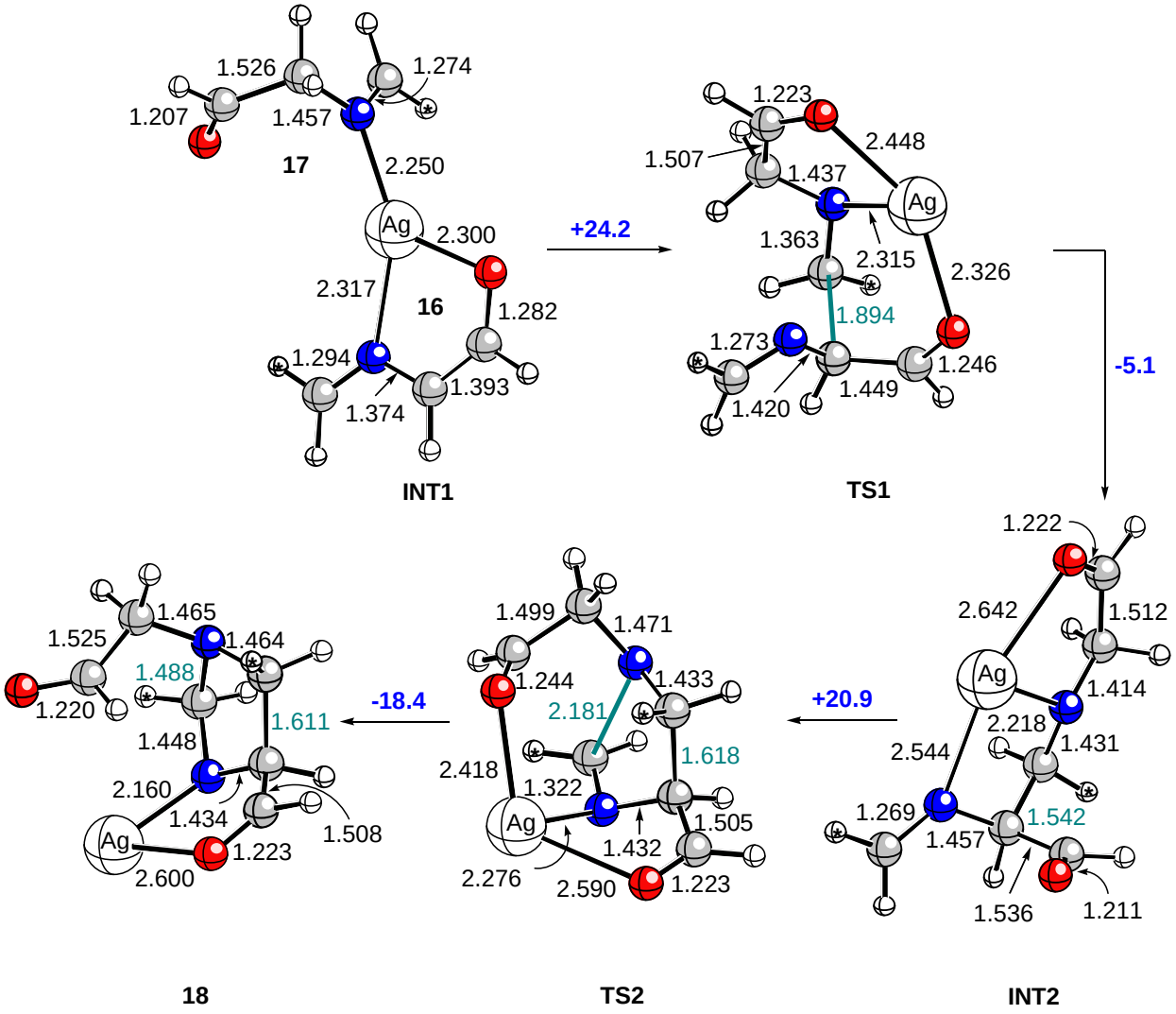
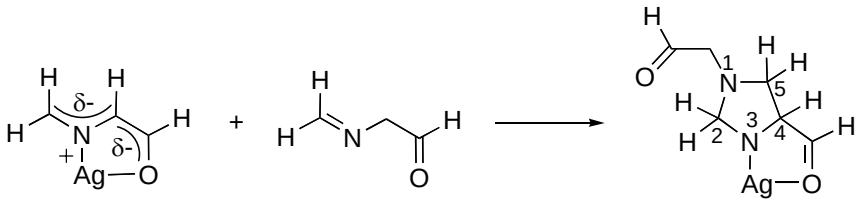


Figure 2. Stationary points (B3LYP/6-31G*&LANL2DZ level of theory) associated with the reaction shown in Scheme 5. Bond distances are given in Å. Bonds and bond distances corresponding to formation of new sigma bonds are shown in green. Numbers marked in blue are the relative energies (in kcal/mol, B3LYP/6-31G*&LANL2DZ+ΔZPVE level of theory) and are shown on the arrows connecting the corresponding stationary points. Unless otherwise stated, hydrogen-, carbon-, nitrogen- and oxygen atoms are represented in white, gray, blue and red, respectively. The asterisks on several hydrogen atoms indicate the position of aryl substituents in substituted (*E*-) imines of type **11**.



16 **17** **18**

Scheme 5. Model [3+2] cycloaddition between silver azomethine ylide **16** and imine **17** to form *N*-metallated imidazolidine **18**.

First, we located the intermediate **INT1** in which the 1,3-dipole **16** is coordinated to the silver cation through the nitrogen and the oxygen atoms, whereas the imine sub-unit **17** is coordinated only by means of the nitrogen atom. The alternative intermediate in which the coordination of the imine **17** takes place via the oxygen atom was calculated to be 5.5 kcal/mol less stable than **INT1**. Formation of the C4–C5 bond takes place via **TS1**, which was found to lie 24.2 kcal/mol above **INT1**. This cyclic transition structure has a sofa conformation and shows the geometric features that would be expected for an aldol-like transition state. The next reaction intermediate found in our computed reaction coordinate was **INT2**, in which the C4–C5 bond is already formed. This intermediate was calculated to lie 5.1 kcal/mol below **TS1** and shows the same coordination pattern as this latter saddle point. Finally, formation of the N1–C2 bond was found to take place via **TS2**, the calculated activation energy for this second step being *ca.* 3.3 kcal/mol lower than that associated with formation of the C4–C5 bond. This transition structure connects **INT2** with the *N*-metallated imidazolidine **18**. This latter intermediate leads to the corresponding NH- imidazolidine analogous to **15a** or could alternatively perform the nucleophilic attack on the *sp*- hybridized carbon atom of the isocyanate **1** to yield the corresponding ureas of type **14**. It is noteworthy that, according to our computational results, the coordination patterns along the reaction coordinate and the (*E*)-stereochemistry of the starting imines lead to the preferential formation of the all- *cis*- (2*S**,4*S**,5*S**) cycloadducts, in good agreement with our experimental results (Figure 2).

Conclusions

In this Paper we report an unusual [3+2] cyclization in the reaction between imines and isocyanates. The proposed mechanism consists of the formation of *N*-metallated azomethine ylides whose stepwise aldol-type reaction with another equivalent of the imine yields the corresponding (2*S**,4*S**,5*S**)-imidazolidines. Nucleophilic addition of these cycloadducts on isocyanates leads to the corresponding carbamoyl derivatives. This transformation adds a novel reaction pathway to the well-known [2+2] cycloadditions between cumulenes and imines.[2b,12]

Computational Methods

All the calculations reported in this paper were performed within the Density Functional Theory,[11] using the hybrid three-parameter functional customarily denoted as B3LYP.[13] The standard 6-31G* basis set [14] as implemented in the GAUSSIAN 98 [15] suite of programs was used to describe hydrogen, carbon, nitrogen and oxygen atoms. Silver atoms were described by the Hay–Wadt effective core potential.[16] This computational treatment is denoted as B3LYP/6-31G*&LANL2DZ. Harmonic analysis on reaction intermediates and transition structures showed that local minima **INT1**, **INT2** and **18** had positive definite Hessian matrices, whereas both saddle-points **TS1** and **TS2** had only one imaginary frequency, associated with nuclear motion along the reaction coordinate associated with formation of the C4–C5 and N1–C2 bonds, respectively. Reported differences in energy include zero-point vibration energy corrections, denoted as ΔZPVE. The connection between transition structures and local minima was confirmed by Intrinsic Reaction Coordinate (IRC) analysis.[17]

Experimental Section

General Procedures. Imines **11a–c** were prepared as previously reported.[8a,b] All commercially available compounds were used without further purification (CAUTION: Perchlorates are potentially explosive materials. Under the experimental conditions described below, $AgClO_4$ can be used safely). Acetonitrile was purified according to standard procedures.[18] Melting points were determined on a Büchi B-540 apparatus and are uncorrected. IR spectra were registered on a Nicolet Magna 560 FTIR spectrophotometer; $\nu_{max.}$ (cm^{-1}) is given for the main absorption bands. ^{1}H- NMR and ^{13}C- NMR spectra were recorded on Bruker Advance 300 and 500 spectrometers, using TMS (δ_H 0.0 ppm) and $CDCl_3$ (δ_C 76.9 ppm) as internal references. Elemental analyses were determined on a Leco CHNS 932 apparatus. All compounds described in this Section are racemic.

General procedure for the preparation of compounds 14a–f

The imine **11** (10 mmol) was dissolved in CH_3CN (50 mL) and then NEt_3 (0.7 mL, 5 mmol), $AgClO_4$ (1.04 g, 5 mmol) and the isocyanate **1** (5 mmol) were added. The resulting mixture was stirred under argon overnight and then Cl_2CH_2 (50 mL) was added and the resulting mixture was filtered through a Celite pad. The filtrate was washed with saturated aqueous NH_4Cl solution (2 x 20 mL) and water (4 x 10 mL). The organic extract was dried with Na_2SO_4 and the organic solvent was evaporated under reduced pressure. The resulting residue was triturated and crystallized in Et_2O–hexanes to yield the corresponding adduct **14**.

(2*S,4*S**,5*S**)- Methyl 1-(methoxycarbonyl)methyl-3-(phenylcarbamoyl)-2,5-diphenyl-imidazolidine-4-carboxylate (14a).** Obtained from imine **11a** (1.77 g, 10 mmol) and phenyl isocyanate **1a** (0.60 g, 5 mmol). Yield 42 %. M.p. 135–137 ºC. IR (ν, cm^{-1}): 3400, 1748, 1664,

1532, 1442, 1207. ^{1}H NMR ($CDCl_3$, δ ppm): 8.08–6.90 (m, 15H); 6.03 (s, 1H); 5.61 (s, 1H); 5.02 (s, 2H): 3.59 (s, 3H): 3.24 (d, *J* = 17.4 Hz, 1H); 3.18 (s, 3H); 3.09 (d, *J* = 17.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, δ ppm): 170.86, 170.44, 152.80, 138.46, 134.90, 130.77, 129.78, 129.67, 128.89, 128.79, 128.74, 128.46, 123.16, 119.36, 77.84, 64.97, 63.72, 51.66, 45.58. Anal. Calcd. for $C_{27}H_{27}N_3O_5$: C, 68.50; H, 5.71; N, 8.88. Found: C, 68.13; H, 5.72; N, 9.00 %.

(2*S,4*S**,5*S**)- Methyl 1-((methoxycarbonyl)methyl)-3-(phenylcarbamoyl)-2,5-bis-(4-chlorophenyl)imidazolidine-4-carboxylate (14b).** Obtained from imine **11b** (2.11 g, 10 mmol) and phenyl isocyanate **1a** (0.60 g, 5 mmol). Yield: 43 %. M.p. 170–171 ºC. IR (ν, cm^{-1}): 3400, 3332, 1750, 1735, 1639, 1523, 1440, 1198, 1174. ^{1}H NMR ($CDCl_3$, δ ppm): 8.01 (d, *J* = 8.2 Hz, 2H); 7.52 (d, *J* = 8.2 Hz, 2H); 7.35–6.96 (m, 9H); 5.94 (s, 1H); 5.61 (s, 1H); 5.01 (s, 2H); 3.62 (s, 3H); 3.25 (s, 3H); 3.18 (d, *J* = 17.9 Hz, 1H); 3.06 (d, *J* = 17.9 Hz, 1H). ^{13}C-NMR ($CDCl_3$, δ ppm): 170.78, 170.16, 152.59, 138.08, 136.94, 134.86, 133.22, 130.93, 130.05, 129.76, 129.07, 128.96, 123.55, 119.50, 76.52, 64.27, 63.50, 51.95, 45.29. Anal. Calcd. for $C_{27}H_{25}N_3O_5Cl_2$: C, 59.78; H, 4.61; N, 7.75. Found: C, 59.72; H, 4.67; N, 7.84 %.

(2*S,4*S**,5*S**)-Methyl 1-(methoxycarbonyl)methyl)-3-(phenylcarbamoyl)-2,5-bis-(4-bromophenyl)imidazolidine-4-carboxylate (14c).** Obtained from imine **11c** (2.57 g, 10 mmol) and phenyl isocyanate **1a** (0.60 g, 5 mmol). Yield: 50 %. M.p. 184–185 ºC. IR (ν, cm^{-1}): 3372, 1748, 1740, 1649, 1527, 1442. ^{1}H NMR ($CDCl_3$, δ ppm): 7.94 (d, *J* = 8.2 Hz, 2H), 7.68 (d, *J* = 8.2 Hz, 2H), 7.49 (d, *J* = 8.1, 2H), 7.25–6.93 (m, 7H); 5.92 (s, 1H), 5.59 (s, 1H); 5.02 (d, *J* = 8.4 Hz, 1H); 4.97 (d, *J* = 8.4 Hz, 1H); 3.62 (s, 3H), 3.26 (s, 3H), 3.18 (d, *J* = 17.8 Hz, 1H), 3.06 (d, *J* = 17.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, δ ppm) 170.75, 170.14, 152.58, 138.06, 137.46, 133.74, 133.02, 132.03, 131.19, 130.07, 128.95, 125.07, 123.56, 123.01, 119.52, 77.07, 64.34, 63.45, 51.96, 51.74, 45.28. Anal. Calcd. for $C_{27}H_{25}N_3O_5Br_2$: C 51.36, H 3.96, N, 6.66. Found C 50.64, H 3.97, N 6.63 %.

(2*S,4*S**,5*S**)-Methyl 3-(4-chlorophenylcarbamoyl)-1-((methoxycarbonyl)methyl)-2,5-diphenylimidazolidine-4-carboxylate (14d).** Obtained from imine **11a** (1.77 g, 10 mmol) and 4-chlorophenyl isocyanate **1b** (0.77 g, 5 mmol). Yield: 30 %. M.p. 136–137 ºC. IR (ν, cm^{-1}): 3409, 1748, 1734, 1668, 1518, 1212. ^{1}H NMR ($CDCl_3$, δ ppm): 8.06 (d, *J* = 6.9 Hz, 2H); 7.57–7.53 (m, 3H); 7.37-7.32 (m, 5H); 7.08 (d, *J* = 8.8 Hz, 2H); 6.86 (d, *J* = 8.8 Hz, 2H); 6.02 (s, 1H); 5.62 (s, 1H); 5.02 (d, *J* = 8.8 Hz, 1H); 5.01 (d, *J* = 8.8 Hz, 1H); 3.60 (s, 3H); 3.25 (d, *J* = 17.7 Hz, 1H); 3.19 (s, 3H); 3.10 (d, *J* = 17.7 Hz, 1H). ^{13}C NMR ($CDCl_3$, δ ppm): 170.77, 170.42, 152.59, 138.32, 137.07, 134.78, 130.89, 129.85, 129.65, 128.96, 128.78, 128.45, 128.08, 120.49, 77.78, 64.94, 63.72, 51.72, 51.53, 45.51. Anal. Calcd. for $C_{27}H_{26}N_3O_5Cl$: C 63.84, H 5.12, N, 8.23. Found C 63.22, H 5.20, N 8.10 %.

(2*S,4*S**,5*S**)-Methyl 3-(benzylcarbamoyl)-1-((methoxycarbonyl)methyl)-2,5-bis(4-chlorophenyl)imidazolidine-4-carboxylate (14e).** Obtained from imine **11b** (2.11 g, 10 mmol) and benzyl isocyanate **1c** (0.65 g, 5 mmol). Yield: 47 %. M.p. 185–187 ºC. IR (ν, cm^{-1}): 3436, 3339, 1752, 1726, 1629, 1532, 1491, 1209. ^{1}H NMR ($CDCl_3$, δ ppm): 7.88 (d, *J* = 8.3 Hz, 2H); 7.39 (d, *J* = 8.3 Hz, 2H); 7.32 (d, *J* = 8.3 Hz, 2H); 7.28 (d, *J* = 8.3 Hz, 2H); 7.25–7.20 (m, 3H); 6.86 (d_b, *J* = 5.9 Hz, 2H); 5.44 (s, 1H); 4.95 (d, *J* = 8.4 Hz, 1H); 4.91 (d, *J* = 8.4 Hz, 1H); 4.28 (dd, *J* = 13.8

Hz, J'=5.0 Hz, 1H); 4.18–4.12 (m, 2H); 3.59 (s, 3H); 3.24 (s, 3H); 3.13 (d, *J* = 17.8 Hz, 1H); 3.03 (d, *J* = 17.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, δ ppm): 171.02, 170.20, 155.04, 138.526, 137.35, 136.24, 134,79, 133.46, 130.77, 129.78, 129.70, 129.01, 128.63, 127.35, 127.16, 77.58, 64.52, 63.68, 51.80, 51.61, 45.43, 44.72. Anal. Calcd. for $C_{28}H_{27}N_3O_5Cl_2$: C 60.43, H 4.86, N 7.55. Found C, 60.10, H 4.92, N, 7.63 %.

(2*S,4*S**,5*S**)-Methyl 3-(4-chlorophenylcarbamoyl)-1-((methoxycarbonyl)methyl)-2,5-bis-(4-chlorophenyl)imidazolidine-4-carboxylate (14f).** Obtained from imine **11b** (2.11 g, 10 mmol) and 4-chlorophenyl isocyanate **1b** (0.77 g, 5 mmol). Yield: 31 %. M.p. 170–172 ºC. IR (ν, cm^{-1}): 3391, 3325, 1749, 1739, 1640, 1522, 1485, 1202, 1169, 1085, 1014. ^{1}H-NMR ($CDCl_3$, δ ppm): 8.01 (d, *J* = 7.4 Hz, 2H); 7.53 (d, *J* = 7.4 Hz, 2H); 7.34 (d, *J* = 7.6 Hz, 2H); 7.30 (d, *J* = 7.6 Hz, 2H); 7.11 (d, *J* = 8.3 Hz, 2H); 6.92 (d, *J* = 8.3 Hz, 2H); 5.93 (s, 1H); 5.61 (s, 1H); 5.0 (d, *J* = 8.9 Hz, 1H); 4.99 (d, *J* = 8.9 Hz, 1H); 3.62 (s, 3H); 3.25 (s, 3H); 3.18 (d, *J* = 18.0 Hz, 1H); 3.06 (d, *J* = 18.0 Hz, 1H). ^{13}C-NMR ($CDCl_3$, δ ppm): 170.64, 170.10, 152.40, 136.89, 136.82, 136.75, 134.93, 133.13, 130.91, 130.08, 129.75, 129.08, 128.91, 128.47, 77.06, 64.33, 63.51, 51.94, 51.70, 45.31. Anal. Calcd. for $C_{27}H_{24}N_3O_5Cl_3$: C 56.20, H 4.16, N 7.28. Found: C 55.95, H 4.20, N, 7.33 %.

(2*R,4*S**,5*S**)-Methyl 1-(methoxycarbonyl)methyl)-2,5-bis(4-chlorophenyl)imidazolidine-4-carboxylate (15a).** The imine **11a** (1.76g, 10 mmol) was dissolved in CH_3CN (50 mL) and then NEt_3 (0.7 mL, 5 mmol) and $AgClO_4$ (1.04 g, 5 mmol) were added. The resulting mixture was stirred under argon overnight and then Cl_2CH_2 (50 mL) was added and the resulting mixture was filtered through a Celite pad. The filtrate was washed with saturated aqueous NH_4Cl solution (2 x 20 mL) and water (4 x 10 mL). The organic extract was dried with Na_2SO_4 and the organic solvent was evaporated under reduced pressure. The resulting oily residue was purified by flash chromatography (Silica gel 70–230 mesh, 1:5 mixture of AcOEt–hexanes as eluent) to yield the corresponding the title product. Yield: 33 %. Colorless oil. IR (ν, cm^{-1}): 3296, 1738, 1487, 1437, 1211, 1176, 1095, 1020. ^{1}H-NMR ($CDCl_3$, δ ppm): 7.58 (d, *J* = 8.2 Hz, 2H); 7.40 (d, *J* = 8.2 Hz, 2H); 7.32–7.25 (m, 4H); 5.03, (s, 1H); 4.63 (d, *J* = 9.3 Hz, 1H); 4.32 (d, *J* = 9.3 Hz, 1H); 3.54 (s, 3H); 3.26 (d, *J* = 17.3 Hz, 1H); 3.20 (s, 3H); 3.17 (d, *J* = 17.3 Hz, 1H); 2.95 (s_b, 1H). ^{13}C-NMR ($CDCl_3$, δ ppm): 171.49, 170.68, 137.24, 136.88, 135.08, 133.88, 129.53, 129.47, 129.22, 128.47, 79.26, 66.75, 64.65, 51.90, 51.47, 47.60. The title compound **15a** (2.11 g, 5 mmol) was transformed into a solid derivative by means of reaction with phenyl isocyanate **1a** (0.60 g, 5 mmol) in CH_3CN (50 mL) overnight at room temperature and under argon atmosphere. The above-described workup and crystallization in Et_2O–hexanes gave a product (Yield: 82 %) whose analytical properties were identical to those found for compound **14b**.

Acknowledgements

This work has been supported by the Universidad del País Vasco – Euskal Herriko Unibertsitatea, by the Gobierno Vasco – Eusko Jaurlaritza (Grant 9/UPV00170.215-13548/2001), by Dominion Pharmakine Ltd. and by the Spanish Ministerio de Educación y Ciencia (Project BQU2001-0904). E. E. and E. A. thank the Gobierno Vasco – Eusko Jaurlaritza for their respective postdoctoral and predoctoral fellowships. Y. V. also thanks the Ministerio de Educación y Ciencia for his predoctoral fellowship.

References and Notes

1. Present address: *Labein Fundazioa, Parque Tecnológico de Bizkaia, Edificio 700, 48160 Derio (Vizcaya), Spain.*
2. (a) Huisgen, R. *Angew. Chem., Int. Ed.* **1963**, *2*, 565. (b) Tidwell, T. T. *Ketenes*; Wiley: New York, 1995; pp 536–544.
3. (a) Bedel, O.; Urban, D.; Langlois, Y. *Tetrahedron Lett.* **2002**, *43*, 607. (b) Bast, K.; Behrens, M.; Durst, T.; Grashey, R.; Huisgen, R.; Schiffer, R.; Temme, R. *Eur. J. Org. Chem.* **1998**, 379.
4. (a) Tietz, H.; Rademacher, O.; Zahn, G. *Eur. J. Org. Chem.* **2000**, 2105. (b) Giesecke, H.; Hocker, J. *Synthesis* **1977**, 806. (c) Richter, R.; Ulrich, H. *J. Org. Chem*. **1971**, *36*, 2005.
5. (a) Matsuoka, T.; Harano, K. *Tetrahedron* **1995**, *51*, 6451. (b) van der Broek, L. A. G. M. *Tetrahedron* **1996**, *52*, 4467.
6. (a) Joseph, S. P.; Dhar, D. N. *Tetrahedron* **1986**, *42*, 5979. (b) Joseph, S. P.; Dhar, D. N. *Tetrahedron* **1988**, *44*, 5209.
7. Lerestif, J. M.; Toupet, L.; Sinbandhit, S.; Tonnard, F.; Bazureau, J. P.; Hamelin, J. *Tetrahedron* **1997**, *53*, 6351.
8. (a) Vivanco, S.; Lecea, B.; Arrieta, A.; Prieto, P.; Morao, I.; Linden, A.; Cossío, F. P. *J. Am. Chem. Soc.* **2000**, *122*, 6078. (b) Ayerbe, M.; Arrieta, A.; Cossío, F. P.; Linden, A. *J. Org. Chem.* **1998**, *63*, 1795. (c) Zubia, A.; Mendoza, L.; Vivanco, S.; Aldaba, E.; Carrascal, T.; Lecea, B.; Arrieta, A.; Vidal-Vanaclocha, F. Cossío, F. P. *Angew. Chem., Int. Ed.* In press.
9. Crystal data for **14b**: $C_{27}H_{25}Cl_2N_3O_5$, M = 542.40, triclinic, *P1*, a = 10.266(1) Å, b = 10.351(1) Å, c = 13.038(1) Å, α = 97.610(2)°, β = 110.104(2)°, γ = 90.809(2)°, V = 1287.0(2) Å^3, Z = 2. 5765 reflections (4635 independent, R_{int} = 0.0322) were collected at low temperatures (T = 173(2) K) using an oil-coated shock-cooled crystal on a Bruker-AXS CCD 1000 diffractometer with MoKα radiation (λ = 0.71073 Å). The structure was solved by direct methods (*SHELXS-97*)[19] and all non hydrogen atoms were refined anisotropically using the least-squares method on F^2.[20] Largest electron density residue: 0.228 e Å^{-3}, R_1 (for $I>2\sigma(I)$) = 0.0446 and wR_2 = 0.0900 (all data) with $R_1 = \Sigma||F_o|-|F_c||/\Sigma|F_o|$ and $wR_2 = (\Sigma w(F_o^2-F_c^2)^2/\Sigma w(F_o^2)^2)^{0.5}$. The absolute structure parameter refines to a value of 0.06(7).[21]

CCDC 258275 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/data_request/cif, by emailing to data_request@ccdc.cam.ac.uk or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

10. Amornraksa, K.; Barr, D.; Donegan, G.; Grigg, R.; Ratananukul, P.; Sridharan, V. *Tetrahedron* **1989**, *45*, 4649. For another recent example of [3+2] dimerization of imines see: Pearson, W. H.; Walters, M. A.; Rosen, M. K.; Harter, W. G. *ARKIVOC,* **2002**, *(viii)*, 91.
11. Parr, R. G.; Yang, W. *Density-Functional Theory of Atoms and Molecules*; Oxford University Press: New York, 1989.
12. Ghosez, L.; Marchand-Brynaert, J. In *Comprehensive Organic Chemistry*, Trost, B. M.; Fleming, L., Eds; Pergamon Press: Oxford, 1991; Vol. 5, pp 86-89.
13. (a) Kohn, W.; Becke, A. D.; Parr, R. G.; *J. Phys. Chem.* **1996**, *100*, 12974. (b) Becke, A. D. *J. Chem. Soc.* **1993**, *98*, 5648. (c) Becke, A. D. *Phys. Rev. A* **1988**, *38*, 3098.
14. Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; Wiley: New York, 1986; pp. 76–87 and references therein.
15. *Gaussian 98, Revision A.5*, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, Jr., J. A.; Stratmann, R. E; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A., Gaussian, Inc., Pittsburgh PA, 1998.
16. Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, *82*, 299.
17. (a) Fukui, K. *Acc. Chem. Res.* **1981**, *14*, 363. (b) Gonzalez, C.; Schlegel, H. B. *J. Chem. Phys.* **1989**, *90*, 2154. (c) Gonzalez, C.; Schlegel, H. B. *J. Phys. Chem*. **1990**, *94*, 5523.
18. Armarego, W. L. F.; Perrin, D. D. *Purification of Laboratory Chemicals,* 4th Ed.; Butterworth-Heinemann: Oxford, 1996.
19. Sheldrick, G. M. *Acta Crystallogr.* **1990**, *A46*, 467.
20. *SHELXL-97, Program for Crystal Structure Refinement*, Sheldrick, G. M., University of Göttingen, 1997.
21. Flack, H. D. *Acta Crystallogr. Sect. A.* **1983**, *39*, 876.