NJC

PAPER

View Article Online
View Journal

Cite this: DOI: 10.1039/c9nj00022d

Chiral arylideneaminoimidazolidin-4-ones: green synthesis and isomerisation mechanism in solution†

Nadia Bouzayani,[a] Sylvain Marque,*[b] Yakdhane Kacem,*[a] Jamil Kraïem,[c] Flavien Bourdreux,[b] Jérôme Marrot[b] and Béchir Ben Hassine[a]

Received 2nd January 2019,
Accepted 19th February 2019

DOI: 10.1039/c9nj00022d

rsc.li/njc

A green and eco-friendly synthetic approach of pure 2,5-disubstituted 3-arylideneaminoimidazolidin-4-ones is developed using water as the solvent. These new chiral arylideneaminoimidazolidin-4-one derivatives were obtained diastereoselectively in high overall yields and with high atom economy *via* the cyclocondensation of various aromatic aldehydes and α-amino acid hydrazides. Solid state studies were complemented by the behavior in solution investigated by NMR experiments and DFT quantum chemical calculations. The transformation from the kinetic arylideneaminoimidazolidin-4-one to the thermodynamic form is explained by a ring opening mechanism and by kinetic observations highlighting the important role played by the electronic richness of the substituents.

Introduction

One of the main objectives of organic and medicinal chemistry is the synthesis and production of compounds having value as human therapeutic targets. Heterocyclic structures have attracted the attention of many scientists in recent decades, as an important class of compounds with proven utility in medicinal chemistry.[1] Particularly, nitrogenated compounds with five membered rings containing two heteroatoms (*e.g.* imidazolidinone) are an important scaffold known to be associated with various biological activities. Cyclocondensation is a simple and efficient reaction leading to a nitrogenated core associated with various biological activities of drugs, pharmaceutical intermediates and agrochemicals.[2–4] *N*-Aminoimidazolidin-4-one derivatives[5] belong to the family of heterocyclic compounds, which exhibit a wide range of biological properties such as antibacterial,[6] antifungal[7] and anticonvulsant activities.[8] For example, *Nitrofurantoin* **I** is a potent antibiotic, which is a famous example derived from the family of aminohydantoins (Fig. 1).[9] Among bioactive molecules, *Azimilide* **II** is an antiarrhythmic drug that has been developed to treat supraventricular and ventricular tachyarrhythmias.[10] The synthesis of *N*-aminoimidazolidin-4-ones can be generally prepared through the cyclocondensation of amino amides with carbonyl compounds.[11] The traditional protocol for these compounds requires the use of solvents, catalysts and heating.[12] According to solvent selection guides described by chemical companies,[13] the major drawback of such reactions in terms of green chemistry is the use of toxic or non-ecofriendly solvents. However, most of these protocols generate undesirable waste in stoichiometric amounts. The search for simple chemical processes as well as the decrease of waste and the use of non-toxic solvents is a primary goal for human development.[14] As a continuation of our studies on the development of environmentally-safe conditions,[15–17] we describe herein a green and eco-friendly route to reach new analogues of chiral arylideneaminoimidazolidin-4-ones using water as the solvent (Scheme 1). Moreover, the objective is to get

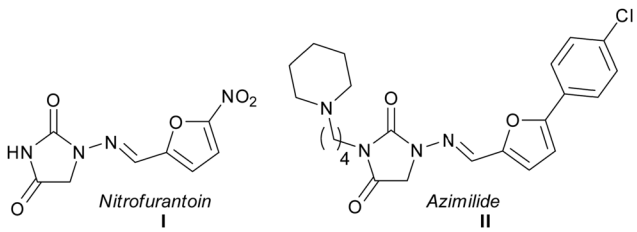


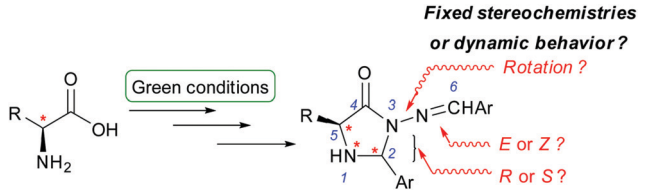
Fig. 1 Bioactive molecules containing an alkyl-arylideneaminoimidazolidin-4-one.

[a] Laboratoire de Synthèse Organique Asymétrique et Catalyse Homogène, (UR 11ES56) Université de Monastir, Faculté des Sciences de Monastir, avenue de l'environnement, Monastir 5000, Tunisia. E-mail: kacem.yakdhane@fphm.rnu.tn; Fax: +216 73 500 278; Tel: +216 73 500 275

[b] Université de Versailles, Saint-Quentin-en-Yvelines, Institut Lavoisier de Versailles (ILV), UMR CNRS 8180, 45 avenue des Etats-Unis, 78035 Versailles Cedex, France. E-mail: sylvain.marque@uvsq.fr

[c] Laboratoire de Développement Chimique, Galénique et Pharmacologique des Médicaments, Faculté de Pharmacie de Monastir, Université de Monastir, Rue Avicenne, 5000 Monastir, Tunisia

† Electronic supplementary information (ESI) available: Crystallographic data, cartesian coordinates and energies of species **5b** and **5f**, 1D & 2D NMR spectra of **5a–m** and dynamic behaviors from NMR spectra. CCDC 1829442. See DOI: 10.1039/c9nj00022d



Scheme 1 Objectives of this work.

control of the stereochemistry and to investigate its potential change.

Results and discussion

Green synthesis

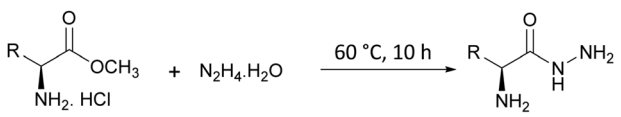
The chiral (L)-α-amino acid hydrazides **3a–e** were used as the starting materials. These compounds were prepared from commercially available (L)-α-amino acid ester hydrochlorides **1a–e** and hydrazine monohydrate **2**, under solvent-free conditions,[18,19] to afford the corresponding hydrazides in good to excellent yields (Table 1).

Following our investigations on developing synthetically useful cyclocondensation reactions with α-amino acid derivatives as chiral pool substrates,[20–25] a novel series of chiral arylideneaminoimidazolidin-4-ones have been synthesized using green conditions. At first, the reaction was screened with EtOH as the solvent under different temperatures and reaction times (Table 2). An investigation of the optimum reaction conditions for the synthesis of compounds **5a–m** was undertaken. A model reaction was chosen using (L)-methionine hydrazide **3d** with 4-methoxybenzaldehyde **4c**. When the reaction was run in EtOH by heating at 55 °C (entries 1 and 2), low yields were obtained and again the yield was much less with the increase of the reaction time. This may be due to the instability of the targeted compounds. Indeed, we tried the reaction at room temperature (entry 3) and the reaction led to the formation of solid arylideneaminoimidazolidin-4-ones in good yields, which were isolated by simple filtration, with complete consumption of the starting materials in a reasonable time (20 h). As mentioned before, one of the principles of green chemistry to develop safer and environmentally-benign alternatives is the choice of green and non-toxic solvents such as water. Furthermore, water is considered to be the greenest solvent despite its high boiling temperature. It is non-hazardous to health and a non-flammable solvent. The efficient conversion of reagents into arylideneaminoimidazolidin-4-ones described above inspired us to explore the possibility of the coupling of (L)-α-amino acid hydrazides with different aldehydes "in water".

Generally, very low amounts of by-products (mainly the reaction intermediates) were observed in water compared with the same reaction performed in organic solvents.

In order to find the optimized conditions for the synthesis of the chiral arylideneaminomidazolidin-4-ones starting from (L)-α-amino acid hydrazides, the same model reaction (Table 2) was chosen for our continuing studies. Firstly, the reaction was screened in water at room temperature without any catalyst (Table 3, entries 1–3). On the other hand, the reaction was performed under the same conditions using SDS (sodium dodecyl sulfate), with different proportions (Table 3, entries 4–9), as a surfactant to ensure the solubility of the starting materials in water. This choice is based on the fact that most organic compounds have poor solubility in water. However, the optimization studies revealed that the reaction works well without using SDS. In the absence of SDS, the reaction medium is homogenous with the naked eye in water at rt, in any event, with the stoichiometric ratio and the concentrations used. Considering this and the organic–water interface, the observed reaction would be more an "in water" than an "on water" process.[26] When the amount of SDS was increased (5%, 10%, and 15%), the reaction was

Table 1 Synthesis of α-amino acid hydrazides **3a–e**



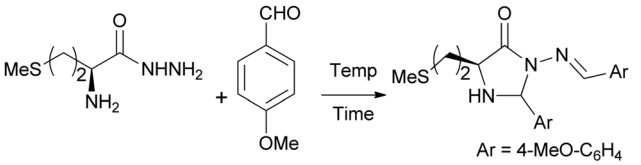
1a-e **2** **3a-e**

R= *i*-Bu, Ph, Bn, $(CH_2)_2SMe$, Trp

Entry	Product	R	Yield[a] (%)	mp (°C)
1	**3a**	i-Bu	92	59–61
2	**3b**	Ph	88	81–83
3	**3c**	Bn	85	85–87
4	**3d**	$(CH_2)_2SMe$	90	55–57
5	**3e**	Trp[b]	83	77–79

[a] Yield of the isolated product. [b] Trp: tryptophan(1*H*-indol-3-yl)methyl moiety.

Table 2 Optimization of the reaction conditions in ethanol[a]



3d **4c** **5g**

Entry	Temp. (°C)	Time (h)	Yields[b] (%)
1	55	12	40
2	55	24	23
3	rt	20	84

[a] Conditions: 4-methoxybenzaldehyde **4** (20 mmol, 2 eq.), (L)-methionine hydrazide **3d** (10 mmol, 1 eq.), ethanol (5 mL). [b] Yield of the isolated product.

Table 3 Optimization of the reaction conditions in water[a]

Entry	Additive (mol%)	Time (h)	Yields[b] (%)
1	—	3	54
2	—	5	60
3	—	11	86
4	SDS (5)	5	48
5	SDS (5)	11	76
6	SDS (10)	5	42
7	SDS (10)	11	71
8	SDS (15)	5	39
9	SDS (15)	11	65

[a] Conditions: 4-methoxybenzaldehyde **4c** (20 mmol, 2 eq.), (L)-methionine hydrazide **3d** (10 mmol, 1 eq.), water (5 mL), rt. [b] Yield of the isolated product.

Table 4 Products of the coupling of the aldehydes **4** and α-amino acid hydrazides **3a–e**[a]

Entry	Product	Yield in EtOH[b] (%)	Yield in H_2O[c] (%)
1	**5a**	78	82
2	**5b**	75	81
3	**5c**	71	81
4	**5d**	78	80
5	**5e**	80	88
6	**5f**	79	86
7	**5g**	84	86
8	**5h**	80	83
9	**5i**	87	90
10	**5j**	81	84
11	**5k**	76	88
12	**5l**	75	81
13	**5m**	77	80

[a] General conditions: aldehyde (20 mmol, 2 eq.), α-amino acid hydrazide (10 mmol, 1 eq.), ethanol (5 mL), 20 h. [b] Yield of the isolated product: in ethanol (5 mL), 20 h. [c] Yield of the isolated product: in water (5 mL), 11 h.

accompanied by a development of yellow coloration with a yield reduction of the product **5**. On the other hand, the starting hydrazides as well as the aldehydes are soluble in water, therefore we continued to work in water without SDS. We kept working at room temperature, increasing the reaction time to total conversion into the desired product, which was obtained after 11 h of stirring (entry 3).

This clean method produced quantitatively pure arylideneaminomidazolidin-4-ones **5** (Table 4) by simple filtration and washing with water without the need for supplementary purification (neither column chromatography nor recrystallization). It is interesting to note that the reaction occurred in ethanol with a slightly prolonged reaction time (20 h). The synthesis of arylideneaminomidazolidin-4-ones in water was extended using various aldehydes such as 4-methoxybenzaldehyde, thiophene-2-carbaldehyde and furan-2-carbaldehyde (Scheme 2).

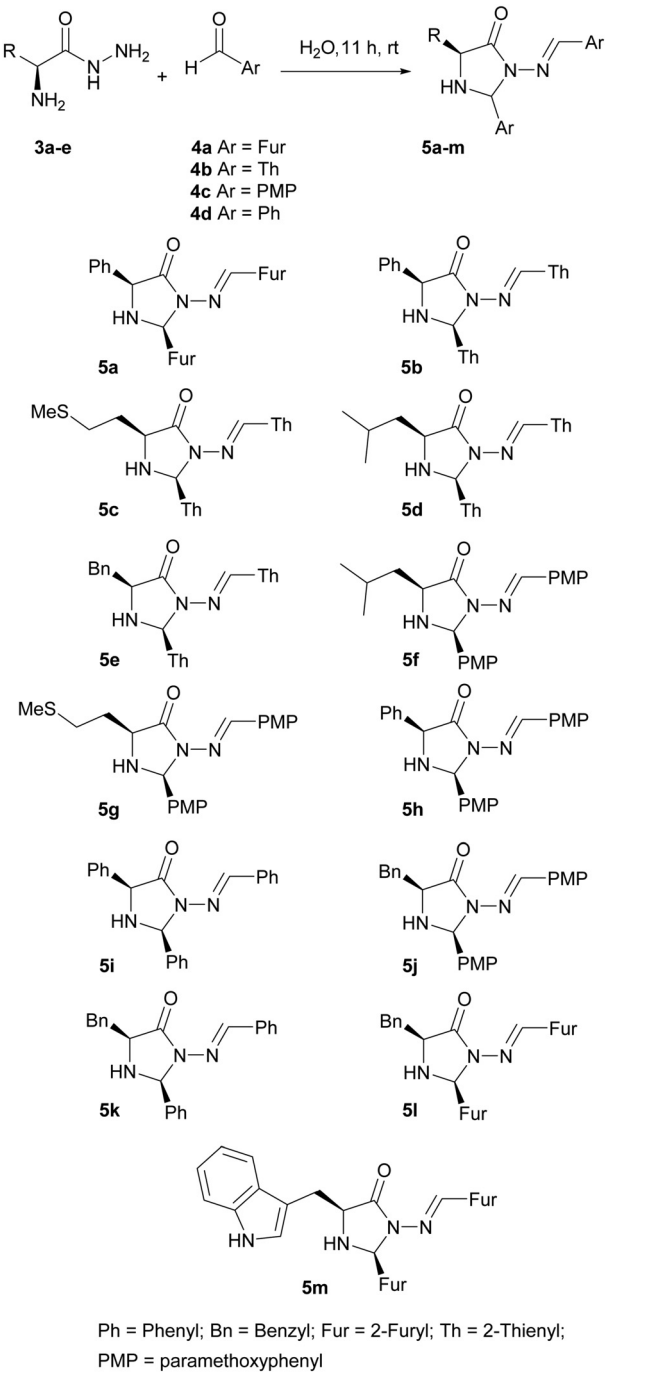
In order to demonstrate the applicability of our green method (water as the solvent), we have synthesized a novel series of chiral arylideneaminomidazolidin-4-ones **5a–m** in good to excellent yields by comparing it with the classical method (EtOH as the solvent); these results are summarized in Table 4. From an ecological point of view, new indicators of the efficiency of green processes have been introduced, such as the atom economy and environmental factor. The atom economy[27] (AE) is the quantity defined as the weighted ratio of the molar mass of the desired product to the sum of the molar masses of the reactants:

$$\mathrm{AE} = \frac{M(\mathrm{product})}{\sum_i M(\mathrm{reactant}_i)} \times 100$$

We define, also, the environmental factor (*E*-factor) introduced by Roger Sheldon.[28] It is the ratio of the total mass of waste to the mass of product:

$$E = \frac{\sum_j M(\mathrm{waste}_j)}{M(\mathrm{product})}$$

The environmental factor *E* highlights the importance of the mass of waste generated during a synthesis. Its ideal value must be as low as possible, tending towards zero. As a conclusion, the closer the atomic use is to 100% and the *E*-factor to zero, the more efficient the method is in obtaining the desired product. In our case, the green method (water as the solvent) is very profitable with a very high atom economy (91.7%) and an excellent *E*-factor (0.09), since only water is left as waste, which is already green.



Scheme 2 Synthesis of the chiral arylideneaminoimidazolidin-4-ones **5a–m**.

Stereochemistry and mechanism

The arylideneaminoimidazolidin-4-ones present several sources of stereochemistry (Fig. 2): three asymmetric centers of which

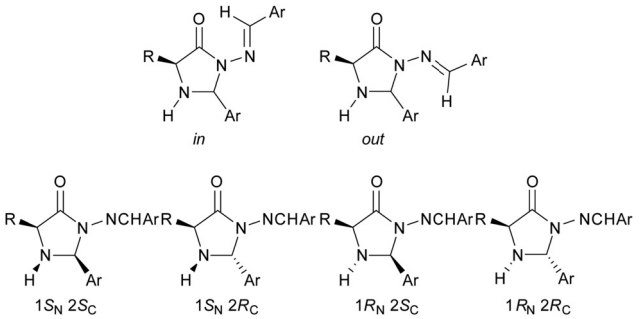


Fig. 2 Notation of configurations and conformations of the arylidene group.

one is nitrogen, a N=C double bond and the possibility to take into account a rotation of the N–N bond (or an inversion of the doublet of the nitrogen), defining two particular conformations in and out according to the position of the hydrogen *vis-à-vis* that of the carbonyl as depicted in Fig. 2. Data of the NMR spectroscopies, X-ray diffraction and theoretical values found by quantum chemical calculations were compared to have a better understanding of the structures and their behaviors.

Static approach. All products **5a–m** were obtained in the form of a white solid. We have noticed that they are stable in the solid state, but reactivity in solution was observed, inducing a development, often a partial isomerization and in rare cases a very limited amount of hydrolysis, of the arylidene moiety, leading to the heterocycle with a primary hydrazide function **3** and the remarkable starting aldehyde **4**. The structures of **5a–m** were elucidated by IR, NMR spectroscopies in benzene-d_6 (^{1}H, ^{13}C, ^{1}H–^{13}C HSQC and HMBC, COSY and NOESY) and mass spectrometric methods. Each proton and carbon could be assigned. The structures of the arylideneaminomidazolidin-4-ones were confirmed by HMBC ^{1}H–^{15}N analysis. The crystallographic analysis of the monocrystal[25] of the stereoisomer **5f** (Fig. 3), obtained after filtration with ethanol and drying in the open air, makes it possible to establish the absolute configuration of the asymmetric centers ($1R_N$,$2S_C$,$5S_C$). It is worth noting that the carbon 5 retains the configuration *S* of the starting amino acid since it has been worked under mild conditions (rt); this is already proved in the course of our work in the literature.[24,29] The first observation is that the hydrazide function is coplanar with the nitrogenated cycle with values of dihedral angles of −4.5° for N(6)–N(3)–C(4)–O and +1.3° for C(2)–N(3)–C(4)–C(5). So, there is very little possibility for conformational flexibility of the central cycle. Although the *cis* stereorelationship exists between H(2) and H(5), the interatomic distance of 3.671 Å is important and NOE interactions remain difficult to see by NMR experiments.

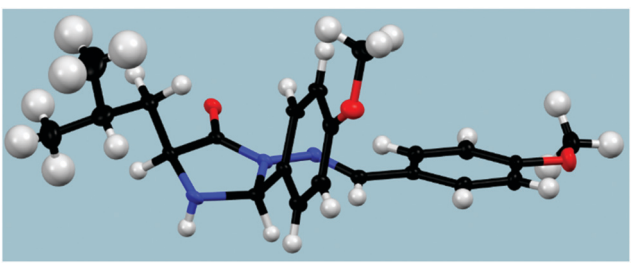


Fig. 3 Structure of the **5f** stereoisomer by X-ray diffraction at a 30% probability level.

Method of calculations and basis sets. The restraint free geometry optimization of species was performed using the Gaussian 09 software[30] with standard parameters and tight criteria of convergence. The determination of structures in benzene solution was carried out using the self-consistent reaction field (SCRF) method. Calculations were performed at the BMK[31]/6-31++G(df,pd)[32] level using the conductor-polarizable continuum model (CPCM)[33] with the Universal Force Field (UFF). Final predicted energies included the zero-point vibrational and thermal energy corrections at 298.15 K (see the ESI†), giving the Gibbs free energy in solution for minima of the electrostatic potential surface. NMR shielding tensors were computed with the Gauge-Independent Atomic Orbital method (GIAO).[34]

Dynamic behavior and mechanism. The molecule **5b** has been chosen as a model. The stereochemistry of C(5) was fixed as a (*S*) absolute configuration and then all combinations of absolute configurations of N(1) and C(2) atoms and the relative configuration of the C(6)–N(3) bond were tested (Table 5). Several singular conformations of the nitrogenated pendant arms were obtained revealing, *vis-a-vis* the imidazolidin-4-one core, coplanar positions (in or out) on the one hand and perpendicular positions on the other hand. The chemical shift of the carbon 6 allows us to clearly differentiate the conformations of the nitrogenated pendant arm. This is an expected result since the chemical environment around this carbon (oxygen of the carbonyl) strongly impacts its magnetic environment. In fact, the C(6) signal for the calculated out conformations is between 148.3 and 149.3 ppm, for in it is between 156.0 and 159.0 ppm and for the others (*i.e.* perpendicular) it is between 161.3 and 164.4 ppm (Table 5). The change of the experimental spectrum shows that the clean initial signal at

Table 5 Privileged stereoisomers of **5b** at BMK/6-31++G(df,pd) in benzene CPCM–UFF[a]

Entry	Configuration	H(6) position[b]	δ^c (ppm)	$G_{rel}{}^d$ (kJ mol^{-1})
1	$1R_N{\cdot}2R_C{\cdot}E$	*Out*	149.66	−28.97
2	$\mathbf{1R_N{\cdot}2R_C{\cdot}E}$	***In***	**159.05**	**−33.77**
3	$1R_N{\cdot}2R_C{\cdot}Z$	—	163.04	−12.25
4	$\mathbf{1R_N{\cdot}2S_C{\cdot}E}$	***Out***	**149.37**	**−32.46**
5	$1R_N{\cdot}2S_C{\cdot}Z$	—	162.79	−5.33
6	$1R_N{\cdot}2S_C{\cdot}Z$	—	163.99	−5.77
7	$1S_N{\cdot}2R_C{\cdot}E$	*Out*	148.32	−25.22
8	$1S_N{\cdot}2R_C{\cdot}E$	*In*	156.02	−28.34
9	$1S_N{\cdot}2R_C{\cdot}Z$	—	161.31	−9.68
10	$1S_N{\cdot}2S_C{\cdot}E$	*Out*	149.26	−18.03
11	$1S_N{\cdot}2S_C{\cdot}Z$	—	164.40	0
12	$1S_N{\cdot}2S_C{\cdot}Z$	—	162.17	−19.60

[a] Experimental NMR result gives the iminic carbon C(6) signal of **5b** at 149.62 ppm in benzene-d_6 at rt, referenced to the TMS signal at 0 ppm. [b] If nothing is specified H(6) and arylidene moieties are in a conformation perpendicular to the medium plane defined by the imidazolidin-4-one cycle (see pictures in the ESI). [c] The chemical shift is given by the difference: calculated nuclear isotropic magnetic shielding of the carbon C(6) – calculated nuclear isotropic magnetic shielding of the carbon in TMS. [d] Relative Gibbs free energy compared to entry 11 at T = 298.15 K and P = 1 atm.

149.62 ppm of C(6) decreases for the benefit to the emergence of a second signal at 156.0 ppm involving **5b** is evolving from an *out* conformation to an *in* one. This result is surprising with the absence of the N–N bond rotation, which is expected since this has been estimated about 117 kJ mol^{-1} in a similar system.[35] It suggests that the development of **5b** does not simply involve the sole rotation of the N–N bond, but is also concomitant with another phenomenon, maybe a ring opening. Moreover, slight but clear correlations for **5b** between H(2) and H(5) and then H(1) and H(5) are shown by the ^{1}H–^{1}H NOESY NMR spectrum and these interactions are absent in the newly isomerized product, confirming that the change concerns a different stereochemistry problem, attributed to an epimerization of the C(2) or N(1) atoms.

The interpretation of all of the data allows us to ascribe the stereochemistry: the compound **5b** very slowly evolves from the isomer 1R_N,2S_C,*E-out* (entry 4) to 1R_N,2R_C,*E-in* (entry 2) in benzene-d$_6$. It is interesting to note that the final isomer is the more stable (Table 5, entry 2), involving a thermodynamic behavior for the transformation, with a low gap of 1.2 kJ mol^{-1} between both isomers. The compounds **5a–m** showed the same stereochemistry links, with an *S* absolute configuration for C(2) of the isolated products. This is in agreement with the crystallographic data of **5f**. The behavior of **5f** was also investigated in benzene-d$_6$, where a weak interaction between H(2) and H(5) in the NOESY spectrum was observed; on the contrary the interaction is absent in the newly formed product. Once more, it is likely due to the epimerization of C(2), from the (1R_N,2S_C,*E*) kinetic product (Table 6, entry 2) to the (1R_N,2R_C,*E*) thermodynamic one (entry 1). The relative Gibbs energies are in concordance with the adequate route for the isomerization with a gap of about 11.5 kJ mol^{-1} between both isomers.

The partial transformation of **5a–m** can be very fast (less than 1 min) or slower (1 h) in $CDCl_3$ or in dichloromethane, but significantly slowed down in benzene-d$_6$ to between 1 h and more than 48 h (see Table 7 and the ESI† for details).

Table 7 shows that the more pronounced the electron donor character (Fur < Ph ≈ Th < PMP) for the Ar group (Fig. 2), the more the kinetic form is stable and the thermodynamic transformation is slowed down. In a more nuanced way, the influence of the amino acid residue (R) is less. Thus, with a well-marked aromatic character (Ar = Ph, Th, PMP), the amino acid residue has poor influence (entries 2–11) on the stability, but a significant effect when Ar = Fur (entries 1, 12 and 13). In these last cases, the steric hindrance of the amino acid residue goes hand-in-hand with the isomerization. It is worth noting that this observation is in agreement with a development process by a ring opening, otherwise the epimerization would not proceed with similar rates for all amino acid residues with Ar = Th (entries 2–5) or else with Ar = PMP (entries 7, 8 and 10). Moreover, arylideneaminoimidazolidin-4-ones from valine (R = i-Pr) presented very low solubility (results not reported here) suggesting that carbonyl and amine moieties require a close environment with non bulky groups for solvation. This explanation is coherent with the ionic writing of the hydrazide function (Scheme 3).

Table 6 Privileged stereoisomers of **5f** at BMK/6-31++G(df,pd) in benzene CPCM–UFF[a]

Entry	Configuration	H(6) position	δ^b (ppm)	$G_{rel}{}^c$ (kJ mol^{-1})
1	**1R_N·2R_C·*E***	***Out***	**153.50**	**−11.53**
2	**1R_N·2S_C·*E***	***Out***	**153.52**	**0**
3	1S_N·2R_C·*E*	*Out*	153.32	−7.14
4	1S_N·2S_C·*E*	*Out*	153.97	−8.50

[a] Experimental NMR result gives the iminic carbon C(6) signal of **5f** at 151.94 ppm in benzene-d$_6$ at rt, referenced to the TMS signal at 0 ppm. [b] The chemical shift is given by the difference: calculated nuclear isotropic magnetic shielding of the carbon C(6) – nuclear isotropic magnetic shielding of the carbon in TMS. [c] Relative Gibbs free energy compared to entry 2 at T = 298.15 K and P = 1 atm.

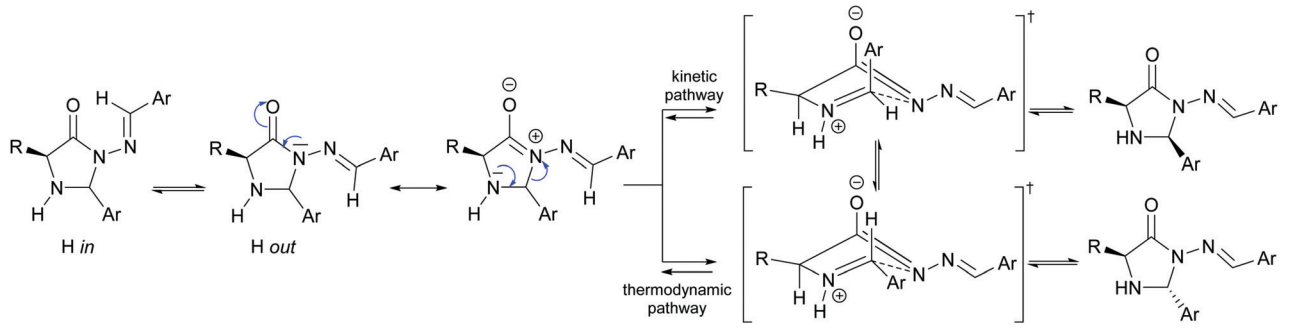
Table 7 Kinetic behavior of **5a–m** in C_6D_6[a]

Entry	Product	R from **3**	Ar from **4**	Stability[b]	Ratio
1	**5a**	Ph	Fur	24 h	88 : 12
2	**5b**	Ph	Th	48 h	
3	**5c**	$(CH_2)_2SMe$	Th	≈16 h	
4	**5d**	i-Bu	Th	≈16 h	
5	**5e**	Bn	Th	≈16 h	
6	**5f**	i-Bu	PMP	>48 h	
7	**5g**	$(CH_2)_2SMe$	PMP	>48 h	
8	**5h**	Ph	PMP	>48 h	
9	**5i**	Ph	Ph	≈16 h	
10	**5j**	Bn	PMP	≈16 h	
11	**5k**	Bn	Ph	≈16 h	
12	**5l**	Bn	Fur	6 h	1 : 1
13	**5m**	Trp	Fur	4 h[c]	+4 in 18 h

[a] All spectra were initially recorded with all products freshly placed in solution to check the isomeric purity and showed the obtaining of a pure isomer form. [b] The given stability indicates the time to get the corresponding ratio; if no ratio is reported, it gives an idea of time up to the NMR recording at which it is possible to get a clean spectrum. [c] Time in neat C_6D_6; if some drops of CD_3CN were added due to the poor solubility of **5m** in C_6D_6, the time was less than 1 h.

The fine stereochemistry determination, the kinetic change, the quantum chemical calculations results, and the relationship between the structure and the behavior allow us to present a detailed and proved mechanism for the development of the arylideneaminoimidazolidin-4-ones (Scheme 3). The **5a–m** compounds are isolated with total diastereoselectivity for the (1R_N,2S_C,*E*) configuration in the solid state. In solution, whatever the solvent is, compounds evolve to acyclic forms having an iminium function, where C–N and N–N bond rotations can take place. In benzene this change is sufficiently slowed down to be followed by NMR spectroscopy. In agreement with the electronic effects, an electron donor moiety on the C(2) position decreases the ring opening rate and allows a longer half-life time of the kinetic product.

With a prolonged analysis time, the equilibrium is governed by thermodynamic control: the trend of the pseudo axial Ar group to situate in the equatorial position leads to the (1R_N,2R_C,*E*) configuration with the aim of avoiding electrostatic repulsion with the anionic oxygen. However in the thermodynamic transition state there may exist also interactions between both Ar groups, according to the conformations of the aminoarylidene pendant arm, which is why the transformation is not complete and the compounds **5a–m** evolve to reach their corresponding thermodynamic ratios.



Scheme 3 Proposed mechanism for the development of the arylideneaminoimidazolidin-4-ones.

Conclusions

In summary, the efficient and eco-friendly process described in this paper has enabled us to prepare a new series of chiral arylideneaminomidazolidin-4-ones from the chiral pool using water as the solvent with a high atom economy (AE = 91.7%) and an excellent *E*-factor (0.09). NMR spectroscopies and crystallographic data have undoubtedly established the unique configuration of the asymmetric centers ($1R_N$,$2S_C$,$5S_C$), which shows the total diastereoselectivity of the reaction. Further experimental investigations in solution aided by DFT calculations at the BMK/6-311++G(df,pd) level of theory have allowed us to explain the change of the stereochemistry. This is under thermodynamic control; the transformation is rapid in chloroform and very slowed down in benzene. An electron donor group on the C(2) position allows the kinetic isomer to be preserved longer in an apolar solvent. All of these data are in full concordance with a ring opening mechanism leading to the isomerization of the heterocycles in solution.

Experimental

General comments

All reactions are carried out under an argon atmosphere in round-bottomed flasks equipped with magnetic stirring. The cyclizations to get **5a–m** compounds were performed under argon or under air; no difference was observed. All solvents were freshly distilled before use. Melting points were determined on a Buchi 510 capillary apparatus. NMR spectra were recorded on Bruker Avance 1 300 MHz and Bruker Avance 1 400 MHz spectrometers [300 MHz (^{1}H), 400 MHz (^{1}H), and 75 MHz (^{13}C)] using $CDCl_3$ and C_6D_6 as solvents. Signals due to the solvent served as the internal standard ($CHCl_3$: δ 7.26 for ^{1}H, δ 77.16 for ^{13}C; C_6D_6: δ 7.16 for ^{1}H, δ 128.38 for ^{13}C). IR spectra were recorded on a Nicolet 6700 FT-IR, ATR, with an accuracy of 1 cm^{-1} (Diamond support). Electrospray ionisation (ESI) mass spectroscopy data of compounds **5a–m** were recorded on an UPLC Waters device (in positive mode); for the voltages of the mass spectroscopies, the following abbreviations are used: C Capillary (kV), SC Sampling Cone, EC Extraction Cone. Calibration was performed with sodium formate (in the range from 100 to 1000 g mol^{-1}) and the lockspray (lock mass leucine enkephalin 556.2771 g mol^{-1}) was used without collision energy; the relative intensity of peaks is given in brackets. Optical rotations were measured by using a PerkinElmer Polarimeter (Model 341) using a mercury lamp (578 nm) at ambient temperature.

General procedures

General procedure for the synthesis of (L)-α-amino acid hydrazides 3a–j. Monohydrate hydrazine (30 mmol, 3 eq.) and (L)-α-amino acid methyl ester hydrochloride (10 mmol, 1 eq.) were mixed in a flask fitted with a condenser and a magnetic stirring bar. The mixture was stirred at 60 °C for 10 h under an inert atmosphere. It was allowed to cool to room temperature. Then, 100 mL of EtOAc, 6 g of Na_2CO_3 and 3 mL of H_2O were added. The mixture was vigorously stirred for 3 h. After filtration, the solvent was concentrated *in vacuo* to obtain the corresponding pure L-α-amino acid hydrazides.

Synthesis of arylideneaminomidazolidin-4-ones in ethanol. A mixture of the corresponding aldehyde (20 mmol, 2 eq.) and α-amino acid hydrazide (10 mmol, 1 eq.) in ethanol (5 mL) was stirred at room temperature for 20 h. The white colored precipitate was filtered, washed with ethanol and dried in air to obtain the corresponding arylideneaminoimidazolidin-4-one.

Synthesis of arylideneaminomidazolidin-4-ones in water. A mixture of the corresponding aldehyde (20 mmol, 2 eq.) and α-amino acid hydrazide (10 mmol, 1 eq.) in water (5 mL) was stirred at room temperature for 11 h. The white colored precipitate was filtered, washed with water and dried in air to obtain the corresponding arylideneaminoimidazolidin-4-one.

Characterization of organic compounds

(L)-Leucine hydrazide (3a). Yield 92%. White solid; mp 59–61 °C; $[\alpha]_{578}$ = +24 ± 1 (MeOH, C = 0.768 ± 0.004) (lit. 36: $[\alpha]_D$ = +29.5 (MeOH, C = 1)). FT-IR (neat, cm^{-1}): 3294, 3240, 3208, 3028, 2954, 1617, 1521; ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.37 (d, 3H, J = 6.24 Hz), 1.40 (d, 3H, J = 6.6 Hz), 1.60 (br s, 2H), 1.77–1.86 (m, 1H), 2.07–2.22 (m, 2H), 3.15 (br s, 2H), 3.87 (dd, 1H, ^1J = 9.7 Hz, ^2J = 4.3 Hz), 9.01 (br s, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 21.31, 23.32, 24.68, 44.03, 52.68, 175.89; ESI(+)-MS CH_3CN [C = 0.5, SC = 30, EC = 3] m/z (rel. int.): 168 (100, $[M + Na]^+$), HRMS ES$^+$ for $C_6H_{15}N_3ONa$ m/z: $[M + Na]^+$ calc. 168.1113, found: 168.1118.

(L)-Phenylglycine hydrazide (3b). Yield 88%. White solid; mp 81–83 °C; $[\alpha]_{578}$ = +79 ± 3 (MeOH, C = 1.280 ± 0.037). FT-IR

(neat, cm^{-1}): 3301, 3215, 3147, 3059, 3024, 1664, 1493; ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.89 (br s, 2H), 3.88 (br s, 2H), 4.59 (s, 1H), 7.30–7.48 (m, 5H), 8.17 (br s, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 59.03, 126.59, 128.19, 128.96, 140.48, 173.38; ESI(+)-MS CH_3CN [*C* = 0.5, SC = 30, EC = 3] *m*/*z* (rel. int.): 188 (100, $[M + Na]^+$), HRMS ES$^+$ for $C_8H_{11}N_3ONa$ *m*/*z*: $[M + Na]^+$ calc. 188.0800, found: 188.0796.

L-Phenylalanine hydrazide (3c). Yield 85%. White solid; mp 85–87 °C; (lit. 18: mp 85–87 °C); $[\alpha]_{578}$ = +49 ± 1 (MeOH, *C* = 0.800 ± 0.004) (lit. 18: $[\alpha]_D$ = +33 ± 1 (MeOH, *C* = 1)). FT-IR (neat, cm^{-1}): 3347, 3175, 2947, 2925, 1662; ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.39 (br s, 2H), 2.74 (dd, 1H, ^1J = 13.5 Hz, ^2J = 9.2 Hz), 3.28 (dd, 1H, ^1J = 13.5 Hz, ^2J = 3.9 Hz), 3.67 (dd, 1H, ^1J = 9.2 Hz, ^2J = 3.9 Hz), 7.22–7.37 (m, 5H), 8.32 (br s, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 41.10, 55.90, 126.84, 128.78, 129.16, 137.58, 174.38; ESI(+)-MS CH_3CN [*C* = 0.5, SC = 30, EC = 3] *m*/*z* (rel. int.): 180 (100, $[M + H]^+$), HRMS ES$^+$ for $C_9H_{14}N_3O$ *m*/*z*: $[M + H]^+$ calc. 180.1137, found: 180.1136.

L-Methionine hydrazide (3d). Yield 90%. White solid; mp 55–57 °C; $[\alpha]_{578}$ = −37 ± 2 (MeOH, *C* = 0.140 ± 0.004). FT-IR (neat, cm^{-1}): 3289, 3175, 3078, 2915, 2660, 1611; ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.57–1.64 (m, 1H), 1.66–1.93 (m, 1H), 1.87 (s, 3H), 2.40–2.45 (m, 2H), 2.77 (br s, 2H), 3.32–3.37 (m, 1H), 8.61 (br s, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 15.26, 30.37, 34.12, 53.21, 175.00; ESI(+)-MS CH_3CN [*C* = 0.5, SC = 30, EC = 3] *m*/*z* (rel. int.): 164 (100, $[M + H]^+$), HRMS ES$^+$ for $C_5H_{14}N_3OS$ *m*/*z*: $[M + H]^+$ calc. 164.0858, found: 164.0857.

L-Tryptophane hydrazide (3e). Yield 83%. White solid; mp 77–79 °C; $[\alpha]_{578}$ = +46 ± 2 (MeOH, *C* = 0.254 ± 0.005). FT-IR (neat, cm^{-1}): 3251, 3047, 2914, 1616; ^{1}H-NMR (300 MHz, CD_3OD): δ = 2.97 (dd, 1H, ^1J = 14.1 Hz, ^2J = 6.9 Hz), 3.15 (dd, 1H, ^1J = 14.1 Hz, ^2J = 6.3 Hz), 3.54–3.58 (m, 1H), 7.00–7.13 (m, 3H), 7.35 (d, 1H, *J* = 7.8 Hz), 7.60 (d, 1H, *J* = 7.5 Hz); ^{13}C-NMR (75 MHz, CD_3OD): δ = 32.37, 55.88, 111.28, 112.54, 119.48, 119.98, 122.96, 124.86, 128.86, 138.14, 176.27; ESI(+)-MS CH_3CN [*C* = 0.5, SC = 30, EC = 3] *m*/*z* (rel. int.): 219 (100, $[M + H]^+$), HRMS ES$^+$ for $C_{11}H_{15}N_4O$ *m*/*z*: $[M + H]^+$ calc. 219.1246, found: 219.1237.

(2*S*,3*E*,5*S*)-2-((Furan-2-yl)-3-(furan-2-yl)methyleneamino)-5-phenylimidazolidin-4-one (5a). Yield 82%. White solid; mp 131–133 °C; R_f 0.60 (EtOAc/*c*-C_6H_{12} = 40/60); $[\alpha]_{578}$ = −9 ± 2 (C_6H_6, *C* = 0.096 ± 0.004). FT-IR (neat, cm^{-1}): 3313, 3129, 3026, 1705, 1480; ^{1}H-NMR (300 MHz, benzene-d_6): δ = 2.12 (s, 1H), 4.26 (s, 1H), 5.59 (s, 1H), 5.83–5.84 (m, 1H), 5.95–5.96 (m, 1H), 6.24 (d, 2H, *J* = 2.7 Hz), 6.87 (d, 1H, *J* = 1.2 Hz), 6.98 (d, 1H, *J* = 0.9 Hz), 7.08–7.11 (m, 1H), 7.16–7.20 (m, 2H), 7.59 (d, 1H, *J* = 5.7 Hz), 9.39 (s, 1H); ^{13}C-NMR (75 MHz, benzene-d_6): δ = 62.78, 71.69, 110.03, 110.65, 111.82, 114.02, 127.99, 128.29, 128.76, 128.81, 138.63, 143.13, 143.60, 144.63, 150.51, 152.21, 169.59; DEPT 135 (75 MHz, benzene-d_6): δ = 62.78 (up), 71.69 (up), 110.03 (up), 110.65 (up), 111.82 (up), 114.02 (up), 127.99 (up), 128.29 (up), 128.76 (up), 143.13 (up), 143.60 (up), 144.63 (up); ESI(+)-MS CH_3CN [*C* = 0.5, SC = 30, EC = 3] *m*/*z* (rel. int.): 322 (100, $[M + H]^+$), HRMS ES$^+$ for $C_{18}H_{15}N_3O_3$ *m*/*z*: $[M + H]^+$ calc. 322.1192, found: 322.1192.

(2*S*,3*E*,5*S*)-5-Phenyl-2-(thiophen-2-yl)-3-(thiophen-2-yl)methyleneaminoimidazolidin-4-one (5b). Yield 81%. White solid; mp 141–143 °C; R_f 0.62 (EtOAc/*c*-C_6H_{12} = 40/60); $[\alpha]_{578}$ = −6 ± 2 (C_6H_6, *C* = 0.126 ± 0.004) FT-IR (neat, cm^{-1}): 3104, 3077, 3026, 1719, 1588; ^{1}H-NMR (300 MHz, benzene-d_6): δ = 1.93 (s, 1H), 4.18 (s, 1H), 5.61 (s, 1H), 6.46–6.49 (m, 1H), 6.63–6.65 (m, 1H), 6.70–6.75 (m, 2H), 6.89–6.91 (m, 1H), 7.09–7.14 (m, 1H), 7.16–7.28 (m, 3H), 7.67 (d, 1H, *J* = 7.5 Hz), 9.43 (s, 1H); ^{13}C-NMR (75 MHz, benzene-d_6): δ = 62.57, 72.77, 126.58, 127.00, 127.54, 128.14, 128.37, 128.61, 128.73, 131.35, 138.83, 140.29, 145.09, 149.62, 168.58; DEPT 135 (75 MHz, benzene-d_6): δ = 62.57 (up), 72.77 (up), 126.58 (up), 127.00 (up), 127.54 (up), 128.14 (up), 128.37 (up), 128.61 (up), 128.73 (up), 131.35 (up), 149.62 (up); ESI(+)-MS CH_3CN [*C* = 0.5, SC = 30, EC = 3] *m*/*z* (rel. int.): 354 (100, $[M + H]^+$), HRMS ES$^+$ for $C_{18}H_{16}N_3OS_2$ *m*/*z*: $[M + H]^+$ calc. 354.0735, found: 354.0742.

(2*S*,3*E*,5*S*)-5-((2-(Methylthio)ethyl)-2-(thiophen-2-yl)-3-(thiophen-2-yl)methylene)aminoimidazolidin-4-one (5c). Yield 81%. White solid; mp 123–125 °C; R_f 0.84 (EtOAc/*c*-C_6H_{12} = 40/60); $[\alpha]_{578}$ = −51 ± 3 (C_6H_6, *C* = 0.108 ± 0.004). FT-IR (neat, cm^{-1}): 3272, 3085, 2902, 1696, 1594; ^{1}H-NMR (400 MHz, benzene-d_6): δ = 1.58–1.62 (m, 1H), 1.74 (s, 3H), 1.77 (s, 1H), 1.96–2.01 (m, 1H), 2.39–2.43 (m, 2H), 3.63 (q, 1H, *J* = 3.9 Hz), 5.81 (s, 1H), 6.63 (t, 1H, *J* = 4.2 Hz), 6.76–6.79 (m, 1H), 6.82 (d, 1H, *J* = 4.8 Hz), 6.87 (d, 1H, *J* = 3.3 Hz), 6.94 (d, 1H, *J* = 4.8 Hz), 7.15 (d, 1H, *J* = 3.6 Hz), 9.88 (s, 1H); ^{13}C-NMR (75 MHz, benzene-d_6): δ = 15.01, 30.45, 31.11, 57.57, 73.72, 126.09, 126.17, 127.22, 127.60, 128.38, 128.72, 131.20, 140.49, 143.87, 147.85, 171.42; DEPT 135 (75 MHz, benzene-d_6): δ = 15.01 (up), 30.45 (down), 31.11 (down), 57.57 (up), 73.72 (up), 126.09 (up), 126.17 (up), 127.22 (up), 127.60 (up), 128.38 (up), 128.72 (up), 131.20 (up), 147.85 (up); ESI(+)-MS CH_3CN [*C* = 0.5, SC = 30, EC = 3] *m*/*z* (rel. int.): 352 (100, $[M + H]^+$), HRMS ES$^+$ for $C_{15}H_{18}N_3OS_3$ *m*/*z*: $[M + H]^+$ calc. 352.0612, found: 352.0603.

(2*S*,3*E*,5*S*)-5-Isobutyl-2-(thiophen-2-yl)-3-(thiophen-2-yl)methyleneaminoimidazolidin-4-one (5d). Yield 80%. White solid; mp 134–136 °C; R_f 0.63 (EtOAc/*c*-C_6H_{12} = 40/60); $[\alpha]_{578}$ = −114 ± 4 (C_6H_6, *C* = 0.740 ± 0.027). FT-IR (neat), ν_{max} (cm^{-1}): 3307, 3076, 2952, 2932, 1690, 1593; ^{1}H-NMR (300 MHz, benzene-d_6): δ = 0.81 (d, 3H, *J* = 6.3 Hz), 0.86 (d, 3H, *J* = 6.3 Hz), 1.49–1.51 (m, 1H), 1.59 (br s, 1H), 1.69–1.90 (m, 2H), 3.21 (dd, 1H, ^1J = 11.7 Hz, ^2J = 3.3 Hz), 5.58 (s, 1H), 6.51 (dd, 2H, ^1J = 4.8 Hz, ^2J = 3.6 Hz), 6.69–6.77 (m, 3H), 6.86 (dd, 1H, ^1J = 5.1 Hz, ^2J = 0.09 Hz), 7.18 (d, 1H, *J* = 3.3 Hz), 9.73 (s, 1H); ^{13}C-NMR (75 MHz, benzene-d_6): δ = 20.34, 21.99, 23.18, 40.59, 56.29, 72.16, 124.85, 125.13, 125.63, 126.26, 126.54, 127.05, 127.54, 128.35, 128.50, 131.09, 139.37, 143.40, 147.18, 170.57; DEPT 135 (75 MHz, benzene-d_6): δ = 15.01 (up), 20.34 (up), 21.99 (up), 23.18 (up), 40.59 (down), 56.29 (up), 72.16 (up), 126.26 (up), 126.54 (up), 127.05 (up), 127.54 (up), 128.35 (up), 128.50 (up), 131.09 (up), 147.18 (up); ESI(+)-MS CH_3CN [*C* = 0.5, SC = 30, EC = 3] *m*/*z* (rel. int.): 356 (100, $[M + Na]^+$), HRMS ES$^+$ for $C_{16}H_{19}N_3OS_2Na$ *m*/*z*: $[M + Na]^+$ calc. 356.0867, found: 356.0867.

(2*S*,3*E*,5*S*)-5-Benzyl-2-(thiophen-2-yl)-3-(thiophen-2-yl)methyleneaminoimidazolidin-4-one (5e). Yield 88%. White solid; mp 151–153 °C; R_f 0.66 (EtOAc/*c*-C_6H_{12} = 40/60); $[\alpha]_{578}$ = −381 ± 3 (MeCN, *C* = 0.546 ± 0.004). FT-IR (neat, cm^{-1}): 3319, 3298, 3075, 3028, 2927, 1695, 1591; ^{1}H-NMR (300 MHz, benzene-d_6): δ = 1.75 (br s, 1H), 3.10 (dd, 1H, ^1J = 12.9 Hz, ^2J = 8.1 Hz), 3.25 (dd, 1H, ^1J = 13.8 Hz, ^2J = 3.3 Hz), 3.51–3.56

(m, 1H), 5.58 (s, 1H), 6.60 (dd, 1H, ^1J = 4.8 Hz, ^2J = 3.9 Hz), 6.76–6.81 (m, 3H), 6.91 (dd, 1H, ^1J = 4.8 Hz, ^2J = 1.2 Hz), 7.17–7.25 (m, 3H), 7.28–7.31 (m, 3H), 9.79 (s, 1H); ^{13}C-NMR (75 MHz, benzene-d_6): δ = 38.55, 60.45, 73.31, 126.26, 126.48, 126.79, 126.96, 127.49, 128.36, 128.56, 128.85, 130.03, 131.16, 137.96, 140.43, 144.80, 148.88, 170.11; DEPT 135 (75 MHz, benzene-d_6): δ = 38.55 (down), 60.45 (up), 73.31 (up), 126.48 (up), 126.79 (up), 126.96 (up), 127.49 (up), 128.36 (up), 128.56 (up), 128.85 (up), 130.03 (up), 131.16 (up), 148.88 (up); ESI(+)-MS CH_3CN [C = 0.5, SC = 30, EC = 3] m/z (rel. int.): 368 (100, $[M + H]^+$), HRMS ES$^+$ for $C_{19}H_{18}N_3OS_2$ m/z: $[M + H]^+$ calc. 368.0891, found: 368.0895.

(2*S*,3*E*,5*S*)-5-Isobutyl-3-(4-methoxybenzylideneamino)-2-(4-methoxyphenyl)imidazolidin-4-one (5f). Yield 86%. White solid; mp 136–138 °C; R_f 0.56 (EtOAc/c-C_6H_{12} = 40/60); $[\alpha]_{578}$ = −112 ± 8 (C_6H_6, C = 0.290 ± 0.021). FT-IR (neat), ν_{max} (cm^{-1}): 3310, 2950, 2865, 1700, 1606; ^{1}H-NMR (300 MHz, benzene-d_6): δ = 0.96 (d, 3H, J = 4.5 Hz), 0.98 (d, 3H, J = 5.1 Hz), 1.46–1.55 (m, 3H), 1.81–1.91 (m, 1H), 2.13–2.22 (m, 1H), 3.23 (s, 3H), 3.35 (s, 3H), 3.52 (dd, 1H, ^1J = 9.6 Hz, ^2J = 3.9 Hz), 5.64 (s, 1H), 6.69 (d, 2H, J = 8.7 Hz), 6.87 (d, 2H, J = 8.7 Hz), 7.43 (d, 2H, J = 8.7 Hz), 7.65 (d, 2H, J = 8.7 Hz), 9.61 (s, 1H); ^{13}C-NMR (75 MHz, benzene-d_6): δ = 21.74, 23.37, 25.53, 41.97, 54.65, 54.73, 58.05, 77.79, 114.29, 114.37, 128.35, 128.86, 128.93, 129.34, 129.40, 132.31, 153.27, 160.53, 161.80, 173.08; DEPT 135 (75 MHz, benzene-d_6): δ = 21.74 (up), 23.37 (up), 25.53 (up), 41.97 (down), 54.65 (up), 54.73 (up), 58.05 (up), 77.79 (up), 114.29 (up), 114.37 (up), 128.35 (up), 128.93 (up), 129.40 (up), 153.27 (up); ESI(+)-MS CH_3CN [C = 0.5, SC = 30, EC = 3] m/z (rel. int.): 382 (100, $[M + H]^+$), HRMS ES$^+$ for $C_{22}H_{28}N_3O_3$ m/z: $[M + H]^+$ calc. 382.2131, found: 382.2108.

(2*S*,3*E*,5*S*)-3-(4-Methoxybenzylideneamino)-2-(4-methoxyphenyl)-5-(2-(methylthio)ethyl)imidazolidin-4-one (5g). Yield 86%. White solid; mp 140–142 °C; R_f 0.39 (EtOAc/c-C_6H_{12} = 40/60); $[\alpha]_{578}$ = −55 ± 1 (C_6H_6, C = 0.322 ± 0.004). FT-IR (neat, cm^{-1}): 3312, 3300, 2930, 2839, 1693, 1512; ^{1}H-NMR (300 MHz, benzene-d_6): δ = 1.49–1.63 (m, 1H), 1.78 (s, 3H), 1.81–1.89 (m, 1H), 2.18–2.34 (m, 1H), 2.48–2.53 (m, 2H), 3.12 (s, 3H), 3.59 (s, 3H), 5.42 (s, 1H), 6.56 (d, 2H, J = 8.7 Hz), 6.77 (d, 2H, J = 8.7 Hz), 7.32 (d, 2H, J = 8.7 Hz), 7.51 (d, 2H, J = 8.7 Hz), 9.47 (s, 1H); ^{13}C-NMR (75 MHz, benzene-d_6): δ = 15.03, 30.60, 31.93, 54.71, 54.79, 58.25, 77.45, 114.32, 114.34, 114.35, 128.27, 129.07, 129.31, 132.36, 153.28, 160.61, 161.89, 171.75; DEPT 135 (75 MHz, benzene-d_6): δ = 15.03 (up), 30.60 (down), 25.53 (down), 31.93 (down), 54.79 (up), 58.25 (up), 77.45 (up), 114.25 (up), 128.27 (up), 129.07 (up), 129.31 (up), 153.28 (up); ESI(+)-MS CH_3CN [C = 0.5, SC = 30, EC = 3] m/z (rel. int.): 400 (100, $[M + H]^+$), HRMS ES$^+$ for $C_{21}H_{26}N_3O_3S$ m/z: $[M + H]^+$ calc. 400.1695, found: 400.1689.

(2*S*,3*E*,5*S*)-3-(4-Methoxybenzylideneamino)-2-(4-methoxyphenyl)-5-phenylimidazolidin-4-one (5h). Yield 83%. White solid; mp 129–131 °C; R_f 0.68 (EtOAc/c-C_6H_{12} = 40/60); $[\alpha]_{578}$ = −156 ± 5 (MeCN, C = 0.700 ± 0.022). FT-IR (neat, cm^{-1}): 3311, 3062, 3030, 2834, 1696, 1512; ^{1}H-NMR (300 MHz, benzene-d_6): δ = 1.82 (s, 1H), 3.12 (s, 3H), 3.24 (s, 3H), 4.40 (s, 1H), 5.51 (s, 1H), 6.55 (d, 2H, J = 8.4 Hz), 6.76 (d, 2H, J = 8.4 Hz), 7.21–7.26 (m, 2H), 7.37 (d, 2H, J = 8.1 Hz), 7.50 (d, 2H, J = 8.4 Hz), 7.66 (d, 2H, J = 7.2 Hz), 9.40 (s, 1H); ^{13}C-NMR (75 MHz, benzene-d_6): δ = 54.70, 54.77, 62.98, 77.11, 114.34, 128.14, 128.25, 128.35, 128.80, 129.25, 129.46, 132.41, 138.88, 154.07, 161.91, 169.88; DEPT 135 (75 MHz, benzene-d_6): δ = 54.70 (up), 54.77 (up), 62.98 (up), 77.11 (up), 114.34 (up), 128.14 (up), 128.25 (up), 128.35 (up), 128.80 (up), 129.25 (up), 129.46 (up), 154.07 (up); ESI(+)-MS CH_3CN [C = 0.5, SC = 30, EC = 3] m/z (rel. int.): 402 (100, $[M + H]^+$), HRMS ES$^+$ for $C_{24}H_{23}N_3O_3$ m/z: $[M + H]^+$ calc. 402.1818, found: 402.1809.

(2*S*,3*E*,5*S*)-3-(Benzylideneamino)-2,5-diphenylimidazolidin-4-one (5i). Yield 90%. White solid; mp 137–139 °C; R_f 0.64 (EtOAc/c-C_6H_{12} = 40/60); $[\alpha]_{578}$ = −4 ± 2 (C_6H_6, C = 0.104 ± 0.004). FT-IR (neat, cm^{-1}): 3351, 3060, 3033, 2886, 1709, 1397; ^{1}H-NMR (300 MHz, benzene-d_6): δ = 1.90 (s, 1H), 4.45 (s, 1H), 5.57 (s, 1H), 7.03–7.05 (m, 3H), 7.18–7.24 (m, 3H), 7.30–7.35 (m, 3H), 7.50 (d, 2H, J = 7.2 Hz), 7.58–7.61 (m, 2H), 7.70 (d, 2H, J = 7.5 Hz), 9.47 (s, 1H); ^{13}C-NMR (75 MHz, benzene-d_6): δ = 62.91, 77.37, 127.81, 127.93, 128.07, 128.35, 128.75, 128.81, 128.88, 129.16, 130.45, 135.15, 138.51, 140.24, 154.00, 170.04; DEPT 135 (75 MHz, benzene-d_6): δ = 62.91 (up), 77.37 (up), 127.81 (up), 127.93 (up), 128.07 (up), 128.35 (up), 128.75 (up), 128.81 (up), 128.88 (up), 129.16 (up), 130.45 (up), 154.00 (up); ESI(+)-MS CH_3CN [C = 0.5, SC = 30, EC = 3] m/z (rel. int.): 342 (100, $[M + H]^+$), HRMS ES$^+$ for $C_{22}H_{20}N_3O$ m/z: $[M + H]^+$ calc. 342.1606, found: 342.1614.

(2*S*,3*E*,5*S*)-5-Benzyl-3-(4-methoxybenzylideneamino)-2-(4-methoxyphenyl)imidazolidin-4-one (5j). Yield 84%. White solid; mp 132–134 °C; R_f 0.54 (EtOAc/c-C_6H_{12} = 40/60); $[\alpha]_{578}$ = −330 ± 2 (C_6H_6, C = 0.620 ± 0.041). FT-IR (neat, cm^{-1}): 3307, 3080, 2837, 1712, 1513, 1250; ^{1}H-NMR (300 MHz, benzene-d_6): δ = 1.66 (br s, 1H), 3.05 (dd, 1H, ^1J = 10.4 Hz, ^2J = 3.2 Hz), 3.11 (s, 3H), 3.18 (s, 3H), 3.23 (dd, 1H, ^1J = 10.4 Hz, ^2J = 4.5 Hz), 3.63-3.70 (m, 1H), 5.44 (s, 1H), 6.53 (d, 2H, J = 6.6 Hz), 6.65 (d, 2H, J = 6.6 Hz), 6.98 (d, 2H, J = 6.5 Hz), 7.03–7.20 (m, 5H), 7.48 (d, 2H, J = 6.5 Hz), 9.43 (s, 1H); ^{13}C-NMR (75 MHz, benzene-d_6): δ = 37.38, 54.71, 60.47, 77.81, 114.30, 114.35, 127.02, 128.35, 128.92, 128.97, 129.41, 130.25, 132.32, 137.47, 153.41, 160.58, 161.87, 171.28; DEPT 135 (75 MHz, benzene-d_6): δ = 37.38 (down), 54.71 (up), 60.47 (up), 77.81 (up), 114.30 (up), 114.35 (up), 127.02 (up), 128.35 (up), 128.92 (up), 128.97 (up), 129.41 (up), 130.25 (up), 153.41 (up); ESI(+)-MS CH_3CN [C = 0.5, SC = 30, EC = 3] m/z (rel. int.): 416 (100, $[M + H]^+$), HRMS ES$^+$ for $C_{25}H_{26}N_3O_3$ m/z: $[M + H]^+$ calc. 416.1974, found: 416.1947.

(2*S*,3*E*,5*S*)-5-Benzyl-3-(benzylideneamino)-2-phenylimidazolidin-4-one (5k). Yield 88%. White solid; mp 152–154 °C; R_f 0.61 (EtOAc/c-C_6H_{12} = 40/60); $[\alpha]_{578}$ = −388 ± 15 (C_6H_6, C = 0.108 ± 0.004). FT-IR (neat, cm^{-1}): 3309, 3058, 3024, 2936, 1713, 1393; ^{1}H-NMR (300 MHz, benzene-d_6): δ = 3.13 (dd, 1H, ^1J = 14.4 Hz, ^2J = 4.2 Hz), 3.27 (dd, 1H, ^1J = 14.4 Hz, ^2J = 6.3 Hz), 3.72 (t, 1H, J = 5.4 Hz), 5.47 (s, 1H), 7.01–7.04 (m, 3H), 7.12–7.18 (m, 8H), 7.23 (d, 2H, J = 1.5 Hz), 7.56–7.59 (m, 2H), 9.53 (s, 1H); ^{13}C-NMR (75 MHz, benzene-d_6): δ = 37.43, 60.47, 78.02, 127.03, 127.63, 127.76, 128.35, 128.69, 128.87, 128.96, 129.11, 130.16, 130.37, 135.18, 137.36, 140.16, 153.31, 171.41; DEPT 135 (75 MHz, benzene-d_6): δ = 37.43 (down), 60.47 (up), 78.02 (up), 127.03 (up), 127.63 (up), 127.76 (up), 128.35 (up), 128.69 (up), 128.87 (up), 128.96 (up), 129.11 (up), 130.16 (up), 130.37 (up), 153.31 (up); ESI(+)-MS CH_3CN [C = 0.5, SC = 30, EC = 3] m/z (rel. int.):

356 (100, $[M + H]^+$), HRMS ES^+ for $C_{23}H_{22}N_3O$ *m/z*: $[M + H]^+$ calc. 356.1763, found: 356.1757.

(2*S*,3*E*,5*S*)-5-Benzyl-2-(furan-2-yl)-3-(furan-2-yl)methyleneaminoimidazolidin-4-one (5l). Yield 81%. White solid; mp 132–134 °C; R_f 0.59 (EtOAc/*c*-C_6H_{12} = 40/60); $[\alpha]_{578} = -341 \pm 19$ (C_6H_6, $C = 0.070 \pm 0.004$). FT-IR (neat, cm^{-1}): 3314, 3113, 3021, 1699, 1327; ^{1}H-NMR (400 MHz, benzene-d_6): δ = 1.88 (s, 1H), 3.02 (dd, 1H, ^1J = 14.4 Hz, ^2J = 7.6 Hz), 3.12 (dd, 1H, ^1J = 14.4 Hz, ^2J = 4.0 Hz), 3.44–3.49 (m, 1H), 5.45 (d, 1H, J = 8.0 Hz), 5.83 (dd, 1H, ^1J = 3.2 Hz, ^2J = 1.6 Hz), 5.91 (dd, 1H, ^1J = 2.8 Hz, ^2J = 1.6 Hz), 7.09 (d, 1H, J = 2.8 Hz), 7.26 (d, 1H, J = 3.2 Hz), 6.86 (s, 1H), 6.90 (s, 1H), 7.02–7.14 (m, 5H), 9.49 (s, 1H); ^{13}C-NMR (75 MHz, benzene-d_6): δ = 36.54, 59.44, 70.67, 108.34, 109.28, 110.44, 112.41, 125.54, 126.32, 127.42, 128.52, 136.61, 141.70, 143.60, 149.54, 150.60, 169.47; DEPT 135 (75 MHz, benzene-d_6): δ = 36.54 (down), 59.44 (up), 70.67 (up), 109.28 (up), 110.44 (up), 112.41 (up), 125.54 (up), 126.32 (up), 127.42 (up), 128.52 (up), 129.94 (up), 143.60 (up); ESI(+)-MS CH_3CN [C = 0.5, SC = 30, EC = 3] *m/z* (rel. int.): 336 (100, $[M + H]^+$), HRMS ES^+ for $C_{19}H_{18}N_3O_3$ *m/z*: $[M + H]^+$ calc. 336.1348, found: 336.1347.

(2*S*,3*E*,5*S*)-5-((1*H*-Indol-3-yl)methyl)-2-(furan-2-yl)-3-(furan-2-yl)methyleneaminoimidazolidin-4-one (5m). Yield 80%. White solid; mp 135–137 °C; R_f 0.19 (EtOAc/*c*-C_6H_{12} = 40/60); $[\alpha]_{578} = -268 \pm 4$ (C_6H_6/MeCN (1 : 1), $C = 0.290 \pm 0.004$). FT-IR (neat, cm^{-1}): 3329, 3319, 1698, 1625; ^{1}H-NMR (400 MHz, benzene-d_6): δ = 2.15 (s, 1H), 3.21 (dd, 1H, ^1J = 14.8 Hz, ^2J = 4.4 Hz), 3.27 (dd, 1H, ^1J = 14.8 Hz, ^2J = 4.8 Hz), 3.95–3.99 (m, 1H), 5.00 (s, 1H), 5.84–5.86 (m, 2H), 5.96 (d, 2H, J = 3.2 Hz), 6.30 (d, 1H, J = 3.2 Hz), 6.74–6.77 (m, 1H), 6.86 (s, 1H), 7.00–7.03 (m, 1H), 7.17–7.21 (m, 2H), 7.34 (s, 1H), 7.78–7.81 (m, 1H), 9.16 (s, 1H); ^{13}C-NMR (75 MHz, benzene-d_6 + CD_3CN): δ = 26.66, 59.15, 70.07, 108.95, 110.25, 110.62, 111.69, 112.14, 114.05, 114.89, 119.23, 119.60, 122.10, 124.21, 128.34, 136.89, 139.61, 142.45, 143.11, 144.93, 150.17, 156.03, 157.91, 177.70; DEPT 135 (75 MHz, benzene-d_6): δ = 36.54 (down), 59.44 (up), 70.67 (up), 108.95 (up), 110.25 (up), 110.62 (up), 111.69 (up), 112.14 (up), 114.05 (up), 114.89 (up), 119.23 (up), 119.60 (up), 122.10 (up), 124.21 (up), 128.34 (up), 139.61 (up) 142.45 (up), 143.11 (up), 144.93 (up); ESI(+)-MS CH_3CN [C = 0.5, SC = 30, EC = 3] *m/z* (rel. int.): 375 (100, $[M + H]^+$), HRMS ES^+ for $C_{21}H_{19}N_4O_3$ *m/z*: $[M + H]^+$ calc. 375.1457, found: 375.1462.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

Authors thank the DGRST (Direction Générale de la Recherche Scientifique et de la Technologie) of the Tunisian Ministry of Higher Education and Scientific research and Technology for financial support of this research.

Notes and references

1 (*a*) D. A. Horton, G. T. Bourne and M. L. Smyth, *Chem. Rev.*, 2003, **103**, 893–930; (*b*) A. Patel, S. Bari, G. Telele, J. Patel and M. Sarangapani, *Iran. J. Pharm. Sci.*, 2006, **4**, 249–254; (*c*) P. Caroline and D. L. William, *Pept. Sci.*, 2013, **102**, 7–15; (*d*) D. Ngoc-Duc, H. Robert and D. L. William, *Org. Lett.*, 2014, **16**, 2232–2235.

2 (*a*) S. N. H. Pandeya, D. Sriram, G. Nath and E. De Clercq, *Eur. J. Med. Chem.*, 2000, **35**, 249–255; (*b*) H. Joshi, P. Upadhyay, D. Karia and A. Baxi, *Eur. J. Med. Chem.*, 2003, **38**, 837–840.

3 K. Jat Rakesh, *Pharmacophore*, 2010, **1**, 167–177.

4 A. R. Al-Horani and U. Desai, *Tetrahedron*, 2012, **68**, 2027–2040.

5 (*a*) S. Liang-Quan, X. Hua-Jie, D. Na-Na and J. Xue-Yue, *Acta Crystallogr.*, 2010, **66**, 1601; (*b*) P. Caroline and D. L. William, *Pept. Sci.*, 2013, **102**, 7–15.

6 B. Shipra, C. Sumitra, P. Hemali and R. Paras, *Int. J. Pharm., Chem. Biol. Sci.*, 2015, **5**, 196–202.

7 P. Vicini, M. Incerti, I. A. Doytchinova, P. Colla, B. Busonera and R. Loddo, *Eur. J. Med. Chem.*, 2006, **41**, 624–632.

8 S. Rollas and S. G. Kucukguzel, *Molecules*, 2007, **12**, 1910–1939.

9 P. Swati, B. B. Goswami and D. K. Dube, *Biochem. J.*, 1980, **186**, 323–325.

10 J. Mao, Y. Wang, B. Wan, A. P. Kozikowski and S. G. Franzblau, *Chem. Med. Chem.*, 2007, **2**, 1624–1630.

11 J. Dumčiūtė, V. Martynaitis, W. Holzer, S. Mangelinckx, N. De Kimpe and A. Šačkus, *Tetrahedron*, 2006, **62**, 3309–3319.

12 (*a*) R. Milcent, G. Barbier, B. Yver and F. Mazouz, *J. Heterocycl. Chem.*, 1991, **28**, 1511–1516; (*b*) C. Florac, P. Le Grel, M. Baudy-Floc'h and A. Robe, *J. Chem. Soc., Perkin Trans. 1*, 1991, (5), 1143–1146.

13 (*a*) K. Alfonsi, J. Colberg, P. J. Dunn, T. Fevig, S. Jennings, T. A. Johnson, H. P. Kleine, C. Knight, M. A. Nagy, D. A. Perry and M. Stefaniak, *Green Chem.*, 2008, **10**, 31–36; (*b*) C. Capello, U. Fischer and K. Hungerbuhler, *Green Chem.*, 2007, **9**, 927–934; (*c*) R. K. Henderson, C. Jimenez-Gonzalez, D. J. C. Constable, S. R. Alston, G. G. A. Inglis, G. Fisher, J. Sherwood, S. P. Binks and A. D. Curzons, *Green Chem.*, 2011, **13**, 854–862.

14 J. Kraiem and T. Ollevier, *Green Chem.*, 2017, **19**, 1263–1267.

15 N. Bouzayani, S. Marque, B. Djelassi, Y. Kacem, J. Marrot and B. Ben Hassine, *New J. Chem.*, 2018, **42**, 6389–6398.

16 N. Bouzayani, W. Talbi, S. Marque, Y. Kacem and B. Ben Hassine, *ARKIVOC*, 2018, **3**, 229–239.

17 N. Bouzayani, J. Kraïem, S. Marque, Y. Kacem, A. Carlin-Sinclair, J. Marrot and B. Ben Hassine, *Beilstein J. Org. Chem.*, 2018, **14**, 2923–2930.

18 A. Kudelko, W. Zielinski and K. Jasiak, *Tetrahedron Lett.*, 2013, **54**, 4637–4640.

19 W. Zielinski, A. Kudelko and W. Czardybon, *J. Heterocycl. Chem.*, 2005, **42**, 1393–1398.

20 Y. Kacem, J. Kraiem, E. Kerkani, A. Bouraoui and B. Ben Hassine, *Eur. J. Pharm. Sci.*, 2002, **16**, 221–228.

21 A. O. Aliyenne, J. E. Khiari, J. Kraiem, Y. Kacem and B. Ben Hassine, *Tetrahedron Lett.*, 2006, **47**, 6405–6408.

22 A. O. Aliyenne, J. Kraiem, Y. Kacem and B. Ben Hassine, *Tetrahedron Lett.*, 2008, **49**, 1473–1475.

23 N. Tka, J. Kraiem, Y. Kacem, A. Hajri and B. Ben Hassine, *C. R. Chim.*, 2009, **12**, 1066–1071.

24 Y. Kacem and B. Ben Hassine, *Tetrahedron Lett.*, 2012, **53**, 5608–5610.

25 (*a*) C.-J. Li and L. Chen, *Chem. Soc. Rev.*, 2006, **35**, 68–82; (*b*) R. N. Butler and A. G. Coyne, *J. Org. Chem.*, 2015, **80**, 1809–1817; (*c*) M. De Rosa, P. La Manna, C. Talotta, A. Soriente, C. Gaeta and P. Neri, *Front. Chem.*, 2018, **6**, 84–99; (*d*) S. S. Panda and S. C. Jain, *Mini-Rev. Org. Chem.*, 2011, **8**, 455–464; (*e*) G. Dilauro, M. Dell'Aera, P. Vitale, V. Capriati and F. M. Perna, *Angew. Chem., Int. Ed.*, 2017, **56**, 10200–10203; (*f*) L. Cicco, S. Sblendorio, R. Mansueto, F. M. Perna, A. Salomone, S. Florio and V. Caprati, *Chem. Sci.*, 2016, **7**, 1192–1199.

26 (*a*) B. Trost and B. M. Trost, *Science*, 1991, **254**, 1471–1477; (*b*) B. M. Trost, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 259–281.

27 (*a*) R. A. Sheldon, *CHEMTECH*, 1994, **24**, 38–46; (*b*) R. A. Sheldon, *Green Chem.*, 2007, **9**, 1273–1283.

28 (*a*) G. M. Sheldrick, *SADABS, program for scaling and correction of area detector data*, University of Göttingen, Germany, 1997; (*b*) R. Blessing, *Acta Crystallogr., Sect. A: Found. Crystallogr.*, 1995, **51**, 33–38; (*c*) G. M. Sheldrick, *Acta Crystallogr., Sect. A: Found. Crystallogr.*, 1990, **46**, 467–473; (*d*) G. M. Sheldrick, *SHELX-TL version 5.03, Software Package for the Crystal Structure Determination*, Siemens Analytical X-ray Instrument Division, Madison, WI USA, 1994; (*e*) $C_{22}H_{27}N_3O_3$, M_w = 381.46, monoclinic, space group *P*21; dimensions: a = 13.957(2) Å, b = 5.4550(9) Å, c = 14.7103(19) Å, β = 107.844(9), V = 1066.1(3) Å^3; Z = 2; D_x = 1.188 Mg m^{-3}; μ = 0.08 mm^{-1}; 17176 reflections measured at 200 K; independent reflections: 3545 [2449 $F_o > 4\sigma(F_o)$]; data were collected up to a $2\Theta_{max}$ value of 50.326° (97.0% coverage). Number of variables: 261; R_1 = 0.0666, wR_2 = 0.1579, S = 1.074; highest residual electron density 0.23 e Å^{-3}; CCDC = 1829442†; (*f*) C. F. Macrae, I. J. Bruno, J. A. Chisholm, P. R. Edgington, P. Mc Cabe, E. Pidcock, L. Rodriguez-Monge, R. Taylor, J. van de Streek and P. A. Wood, *J. Appl. Cryst.*, 2008, **41**, 466–470.

29 Y. Kacem and B. Ben Hassine, *Heterocycles*, 2014, **89**, 197–207.

30 M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, J. J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski and D. J. Fox, *Gaussian 09, Revision D.01*, Gaussian, Inc., Wallingford CT, 2009.

31 A. D. Boese and J. M. L. Martin, *J. Chem. Phys.*, 2004, **121**, 3405–3416.

32 Some attempts with the 6-31++G(2df,2pd) basis set gave a double computational time without improvement in the results.

33 (*a*) V. Barone and M. Cossi, *J. Phys. Chem. A*, 1998, **102**, 1995–2001; (*b*) M. Cossi, N. Rega, G. Scalmani and V. Barone, *J. Comput. Chem.*, 2003, **24**, 669–681.

34 (*a*) F. London, *J. Phys. Radium*, 1937, **8**, 397–409; (*b*) R. McWeeny, *Phys. Rev.*, 1962, **126**, 1028–1034; (*c*) R. Ditchfield, *Mol. Phys.*, 1974, **27**, 789–807; (*d*) K. Wolinski, J. F. Hilton and P. Pulay, *J. Am. Chem. Soc.*, 1990, **112**, 8251–8260; (*e*) J. R. Cheeseman, G. W. Trucks, T. A. Keith and M. J. Frisch, *J. Chem. Phys.*, 1996, **104**, 5497–5509.

35 A. Srivastava, V. Srivastava and S. M. Verma, *J. Org. Chem.*, 1994, **59**, 3560–3563.

36 E. A. Zeller, L. A. Blanksma and J. A. Carbon, *Helv. Chim. Acta*, 1957, **40**, 257–260.

