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1,3-Dipolar cycloaddition of nitrile imines with α,β-unsaturated lactones, thiolactones and lactams: synthesis of ring-fused pyrazoles

Jay Zumbar Chandanshive [a], Pedro Blas González [a], William Tiznado [b], Bianca Flavia Bonini [a], Julio Caballero [c], Cristina Femoni [d], Mauro Comes Franchini [a,*]

[a] Dipartimento di Chimica Organica "A. Mangini", Università di Bologna, Viale Risorgimento 4, 40136 Bologna, Italy
[b] Departamento de Química, Facultad de Ciencias Exactas, Universidad Andres Bello, Avenida República 252, Chile
[c] Centro de Bioinformática y Simulación Molecular, Facultad de Ingenieria en Bioinformática, Universidad de Talca, 2 Norte 685, Casilla 721, Talca, Chile
[d] Dipartimento di Chimica Fisica e Inorganica, Università di Bologna, Viale Risorgimento 4, 40136 Bologna, Italy

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ABSTRACT

1,3-Dipolar cycloaddition of nitrile imines with α,β-unsaturated five- and six-membered lactones, thiolactones and lactams gave ring-fused pyrazoles. Regioisomeric mixtures have been obtained with the 5-substituted pyrazole as the major cycloadduct. Only with the five-membered lactone the major product was the 4-acyl derivative. Computational studies, the use of the topological analysis of the Fukui functions and the potential energy surfaces (PES) theory allowed a theoretical description of the local reactivity in agreement with the observed high regiochemistry and with the role of the heteroatom adjacent to the carbonyl group.

1. Introduction

The synthetic utility of the 1,3-dipolar cycloaddition (1,3-DC) reaction stems from its wide scope, and from the relevance of numerous targets achievable by this chemistry,[1] especially heterocycles; many 1,3-dipolar species are readily available and react with a variety of dipolarophiles containing heteroatoms. In particular, nitrogen-containing heterocycles have attracted widespread attention in the field of synthetic organic chemistry as well as in medicinal chemistry.[2] Among them, pyrazoles and their derivatives are present in a plethora of natural and synthetic compounds that are of considerable interest as they possess a wide range of biological properties. Indeed, pyrazoles display a broad spectrum of biological activities, being used as cholesterol-lowering, anti-inflammatory, anticancer, antidepressant and antipsychotic agents,[3] and are considered very important for pharmaceutical industries.[4] These heterocycles have also found applications in the agrochemical industry and recently in the field of photoprotectors, ultraviolet stabilizers and energetic materials.[5] So far, the main access to fully functionalized pyrazoles involves condensation reactions between hydrazines and 1,3-difunctional substrates such as 1,3-dicarbonyl compounds,[5] ynones[6] or β-aminoacrolein.[4] The second strategy is the 1,3-DC of diazoalkanes with unfunctionalised and carboxyalkyl acetylenes.[7] In addition, the 1,3-DC between alkynes and nitrile imines provides direct access to pyrazoles, but frequently as regioisomeric mixtures.[8]

Much work has been directed towards the design and synthesis of complex pyrazoles, giving particular relevance to the functionalization of the scaffold in different regions, and to the synthesis of ring-fused structures. Indeed, the preparation of pyrazole-fused ring derivatives seems to be very important and challenging from the synthetic point of view.[9]

Following our interest in the 1,3-DC,[10] we have reported the synthesis of pyrazoles using the 1,3-DC methodology of nitrile imines and functionalized acetylenes,[11a] and we have developed a protocol based on intramolecular cyclization starting from a sulfur-substituted acetylene, to obtain a ring-fused thieno-pyrazole.[11b] Moreover, a regiocontrolled one-pot synthesis of cycloalkenones fused with pyrazoles through the 1,3-DC of cyclic α,β-unsaturated ketones has been reported by us.[12] On the other hand, the 1,3-DC of nitrile imines with cyclic α,β-unsaturated lactones, thiolactones and lactams could provide, after aromatization of the initially

* Corresponding author. E-mail addresses: wtiznado@unab.cl (W. Tiznado), mauro.comesfranchini@unibo.it (M. Comes Franchini).

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formed pyrazoline, a general and direct access to pyrazoles fused with these frameworks (Fig. 1), and indeed the derivatives containing the pyrazole dihydropyridone core are targets of utmost importance in the pharmaceutical industry.[13]

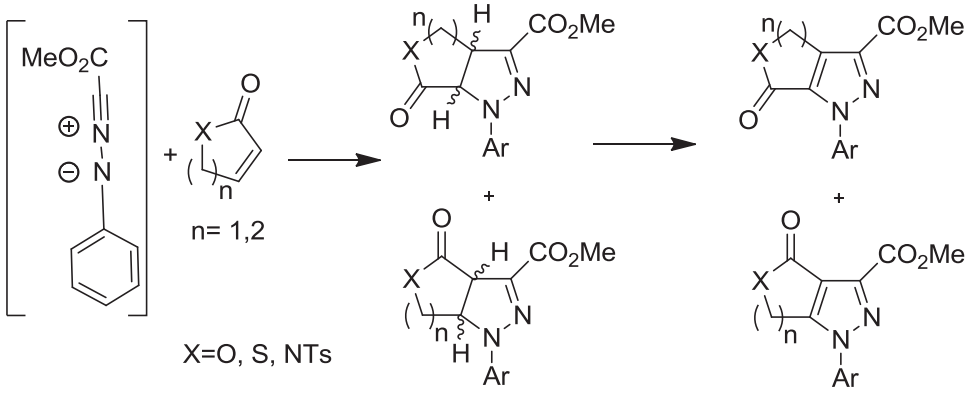
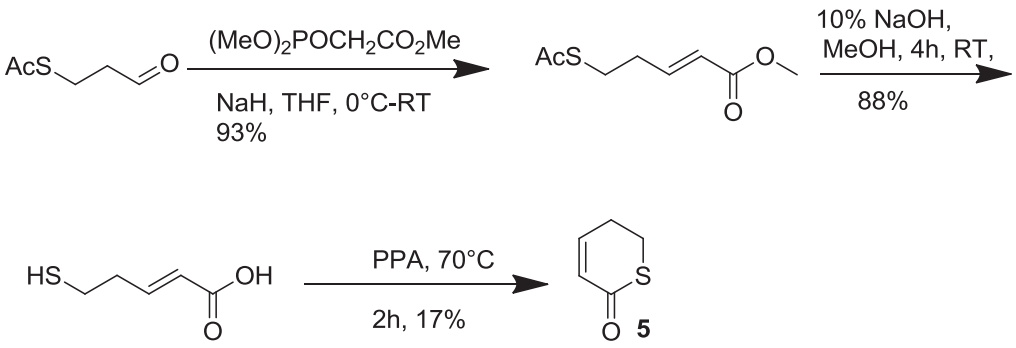


Fig. 1. General protocol for the synthesis of pyrazoles ring-fused with lactones, thiolactones and lactams.



Scheme 1. Synthesis of 5,6-dihydro-2*H*-thiopyran-2-one **5**.

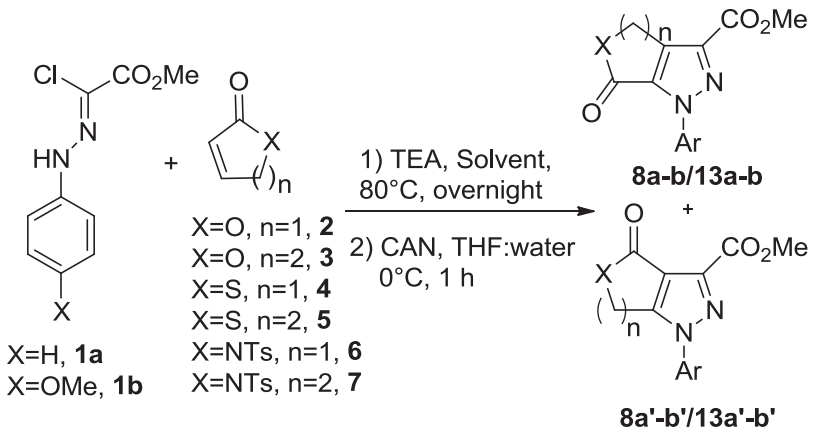
Among the 1,3-DC reactions of α,β-unsaturated lactones, an extensive investigation has been dedicated to the reaction with diazoalkanes,[14] chiral and achiral nitrones,[15,14a,b] and nitrile oxides.[16,14a,b] The reaction of α,β-unsaturated lactones with nitrile ylids[17] and the cycloaddition of chiral butenolides with azomethine ylids[18,14a] and with azides[19] have also been reported. No references were found on the 1,3-DC of simple unsaturated lactones and nitrile imines, and only the reaction of diphenyl nitrile imine with coumarin or its 3-substituted derivatives has been performed.[20] To our knowledge the use of α,β-unsaturated thiolactones as dipolarophiles in 1,3-DC has not yet been explored. An α,β-unsaturated lactam is a structural motif, that is, often found in bioactive molecules.[21] The use of such olefins as dipolarophiles in 1,3-DC for the production of bicyclic compounds of biological interest is not very extensive. As a dipole partner, the following 1,3-dipoles have been used: diazomethane,[22] nitrones,[23] nitrile oxides[24] and aryl azides.[19] The nitrile imines were the more studied 1,3-dipoles for the synthesis of potent inhibitors of blood coagulation factor Xa (FXa). In this case the starting material was a six-membered α,β-unsaturated lactam bearing a good leaving group such as chlorine or morpholine, useful for the aromatization.[13]

2. Results and discussion

Compounds **2**–**4** were commercially available, while 5,6-dihydro-2*H*-thiopyran-2-one **5**, unknown in the literature, was prepared (Scheme 1) starting from β-acetylthiopropionaldehyde[25] in a three-steps synthetic protocol. The two *N*-tosyl protected lactams **6** and **7** were prepared according to literature procedures.[26]

The Scheme 2 illustrates the synthesis of fused pyrazoles. The reaction of α,β-unsaturated lactones **2**, **3**, thiolactones **4**, **5** and lactams **6**, **7** with *C*-carboxymethyl-*N*-phenyl and *N*-*p*-OCH_3–phenyl nitrile imines,[12] generated 'in situ' from hydrazonoyl chlorides **1a**,**b**, was performed in dry dioxane at 80 °C for 18–24 h, using triethylamine (TEA) for the generation of the nitrile imine. In the case of the lactams, toluene had to be used to obtain better yields.

During the cycloaddition a partial aromatization of the initially formed bicyclic pyrazoline occurred in some cases; the reaction of six-membered thiolactone **5** with **1a** and **1b** (entries 7 and 8, Table 1) afforded fully aromatized products in 24 h, while five-membered thiolactone **4** with both **1a** and **1b** gave about 10% of aromatization at the end of cycloaddition. The aromatization was then completed by treatment of the crude product with cerium (IV) ammonium nitrate (CAN) as oxidizing agent. The yield of the products is referred to the sum of the two regioisomers **8a**–**b**/**13a**–**b** (5-acylpyrazoles) and **8a′**–**b′**/**-13a′**–**b′** (4-acylpyrazoles). The lower yields obtained with the dipole from **1a** showed that the *C*-carboxymethyl-*N*-*p*–OCH_3–phenyl nitrile imine is more reactive than the unsubstituted phenyl analogue. Also the size of the ring influenced the yield, lower yields were obtained with five-membered lactones, thiolactones and lactams. This might result from an increased tendency for the five-membered ring to undergo enolization, and from the initially formed strained fused pyrazolines. We observed similar results in the cycloaddition of these nitrile imines with cyclic α,β-unsaturated ketones.[12]



Scheme 2. 1,3-DC of **2**–**7** with dipoles from **1a**–**b**.

Table 1
1,3-DC of **2**–**7** with 1,3-dipoles from **1a**–**b**

Entry	1,3-dipole from	Dipolarophile	Cycloadducts	Yield %	Ratio 5-acyl/4-acyl
1	**1a**	**2**	**8a**–**8a′**	14	70:30
2	**1b**	**2**	**8b**–**8b′**	31	14:86
3	**1a**	**3**	**9a**–**9a′**	47	52:48
4	**1b**	**3**	**9b**–**9b′**	66	87:13
5	**1a**	**4**	**10a**–**10a′**	21	99:1
6	**1b**	**4**	**10b**–**10b′**	36	82:18
7	**1a**	**5**	**11a**–**11a′**	56	81:19
8	**1b**	**5**	**11b**–**11b′**	77	86:14
9	**1a**	**6**	**12a**–**12a′**	38	72:28
10	**1b**	**6**	**12b**–**12b′**	35	61:39
11	**1a**	**7**	**13a**–**13a′**	74	83:17
12	**1b**	**7**	**13b**–**13b′**	68	83:17

All the products were characterized by NMR and GC–MS analyses of the purified compounds after complete aromatization. The structural assignment of the regioisomers was based on X-ray diffraction analyses[27] performed on **8b**, **9a′**, **11a**, **11b**, **12b**, **13a**, **13b**. In order to assign the regiochemistry of the other adducts we used other observations. The 5-acyl derivative was found to be non polar compared to the 4-acyl derivative (Rf difference=0.3–0.4) and was always eluted first in the column chromatography. Also the ^{1}H NMR pattern in the aromatic region was a distinguishing factor of the five-membered derivatives of lactones **8**, thiolactones **10** and lactams **12**. For example, the 5-acyl derivative **8b** (X-ray available), had the ortho hydrogens of the *p*-OMe-phenyl at 8.05 and the *meta* hydrogens at 7.03 ppm; in the 4-acyl derivative, the *ortho* and *meta* aromatic hydrogens were at 7.51 and 7.03 ppm, respectively. Similar behaviour was found in the other five-membered lactones, thiolactones and lactams, and allowed the structural assignment of the regioisomers. This deshielding effect of the ortho protons is probably due to interactions between the carbonyl and the hydrogen of the aryl group bonded to N1 of the pyrazole in the 5-acyl derivative. In the case of six-membered lactones, thiolactones and lactams, this deshielding effect of the aromatic hydrogen was not observed, probably because of the non coplanarity of the six-membered ring. In these cases there still remained the discriminating effect of the different polarity of the 5-acyl and 4-acyl regioisomers. Furthermore we found a distinguishing factor in the ^{1}H NMR spectrum of the aliphatic region. For example, product **9a** had H4 at 3.31 ppm, whereas **9a'** had H7 at 3.16 ppm (X-ray available); this could be due to the shielding effect of the aromatic ring, that is, not coplanar with the bicyclic scaffold. This effect was also found in compounds **9b** (*H4*=3.30), **9b′** (*H7*=3.09), **11a** (*H4*=3.41), **11a′** (*H7*=3.21), **11b** (*H4*=3.41), **11b′** (*H7*=3.16), **13a** (*H4*=3.29), **13a′** (*H4*=3.16), **13b** (*H4*=3.28), **13b′** (*H7*=3.10).

A complete description of the crystal structures is reported in the Supplementary data section, as well as all the crystal data and details of the data collections and refinements (see Table 2-SI). As a general comment, in all the products except **8b** and **12b**, the pyrazole is never coplanar with the ester function and aryl groups, probably due to packing efficiency. Torsion angles going from about −18° to −55° are observed. Compound **8b** is the only one virtually flat, as in **12b** the protective *N*-tosyl group is forced to form a torsion angle of 105.77° with the rest of the molecule, therefore the solid packing of the former is arranged in parallel sheets along the *b* axis (Fig. 2-SI). The crystal structures of two of the major products, **11a** and **12b**, are illustrated in Fig. 2(a) and (b), while all the others are reported in the Supplementary data section (Figs. 1–5-SI).

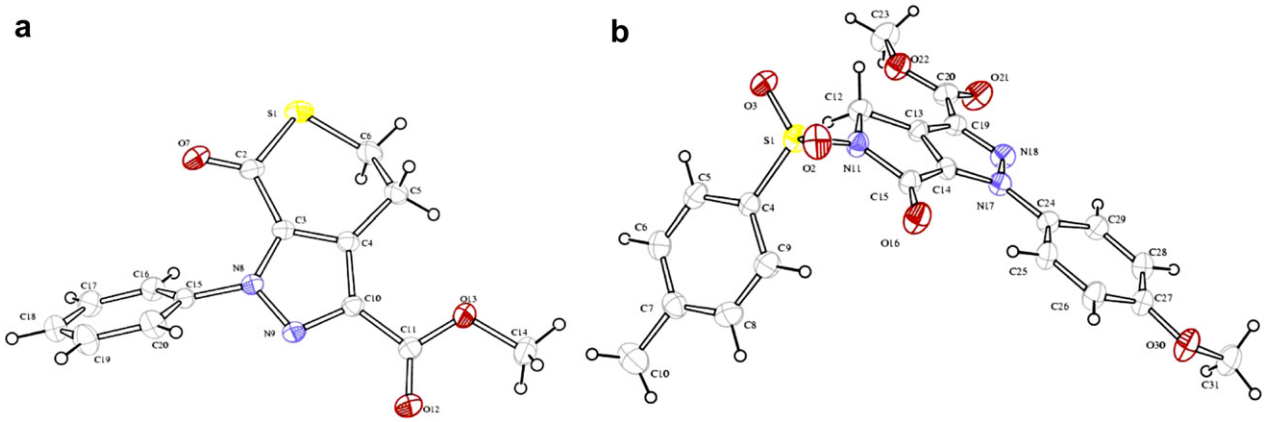


Fig. 2. X-ray structures of the ring-fused pyrazoles **11a** (a) and **12b** (b) (ellipsoids are at 30% probability).

It appeared from Table 1 that the nitrile imine from **1a** gave a large prevalence of the 5-acyl derivative with five-membered lactone **2** (entry 1), thiolactone **4** (entry 5) lactam **6** (entry 9) and with six-membered thiolactone **5** (entry 7) and lactam **7** (entry 11). A balanced mixture of 5- and 4-acyl derivatives has been obtained with six-membered lactone **3** (entry 3). The nitrile imine from **1b** gave also the 5-acyl derivative as the major product (entries 4, 6, 8, 10, 12) but a deviant result, with inversion of regiochemistry with the five-membered lactone **2** (entry 2). The regioisomeric ratio is influenced by the *X* moiety and by the nature of the nitrile imine; a very high regioselectivity in favour of the 5-acyl derivative has been found when *X*=S. A ratio up to 99:1 has been found with α,β-unsaturated 5- and six-membered thiolactones. The regioselectivity in favour of the 5-acyl derivative, decreased gradually going from lactams (*X*=*N*-*p*-Tosyl) to lactones (*X*=O).

The regiochemical results obtained in the 1,3-DC of five-membered dipolarophiles with *p*-MeO-dipole are summarised in Fig. 3, and are compared with that obtained previously by us[12] with cyclopentenone (**c-2-one**).

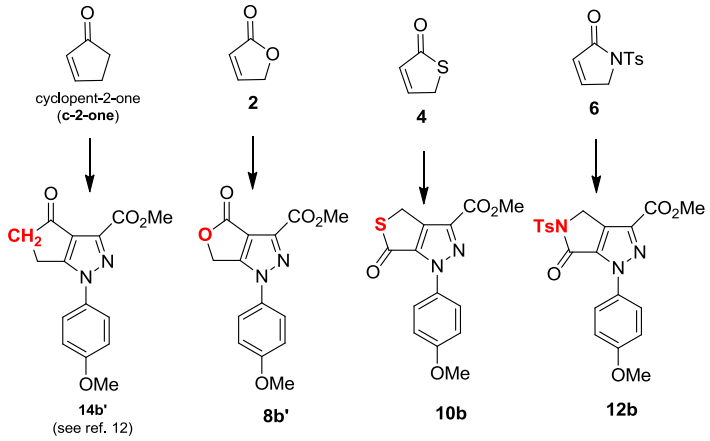


Fig. 3. Summary of the different regiochemistry obtained from different dipolarophiles **2**, **4**, **6** and **c-2-one** with dipole from **1b**.

2.1. Theoretical analysis

As was previously discussed there are some intriguing and not obvious regioselectivity trends in the studied 1,3-DC reactions. Inversion of regioselectivity was previously observed in the DC of the nitrile imine from **1b** activated by TEA and 2-cyclopentenone (**c-2-one**). To explain it, we proposed an intermediate of the *p*-MeO-dipole with TEA prior to the 1,3-dipole formation as reactive intermediate with **c-2-one**; this intermediate was labelled as **M-II** to differentiate of the 1,3-dipole, which was identified as **M-I** (Fig. 4).[12]

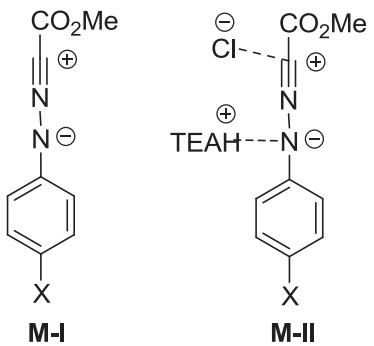


Fig. 4. Models for the dipoles used in 1,3-dipolar cycloaddition.

2.2. Energies analysis

The 1,3-DC has two reactive channels associated with the formation of 5-acyl and 4-acyl derivatives. In this study we have considered only the first reaction step (see Fig. 1) of the 1,3-dipole (**M-I**) **1b** and the five-member ring dipolarophiles (**c-2-one**, **2**, **4**, **6**) to produce pyrazoline intermediates. Therefore, four transition state (TS) pairs (TS/TS′) and the corresponding cycloadducts have been localized and characterized in the potential energy surface (**PES**).

The computed activation barrier energies for **1b**+**c-2-one** reaction in the formation of 5-acyl (**1b**+**c-2-one**→TS-**14b**) derivatives (7.6 kcal-mol^{-1}) is smaller than the activation barrier involved in the formation of the 4-acyl (**1b**+**2-c-one**→TS-**14b′**) derivative (10.9 kcal-mol^{-1}), as reported in Table 1 of the Supplementary data (Table 1-SI). When the dipolarophiles are **2** and **4**, the activation barriers associated with the 5-acyl derivatives are almost 3.3 kcal mol^{-1} smaller than the barrier energies associated with the 4-acyl derivatives, and when dipolarophile is **6** (*X*=*N*-*p*-Tosyl) this barrier difference is lower by 0.9 kcal mol^{-1}. Therefore, if **1b** (**M-I**) reacts with dipoles: **c-2-one**, **2**, **4** and **6**, the 5-acyl derivative should be the preferred product due to its lower barrier energies compared with the 4-acyl derivatives. In all cases the 5-acyl derivatives are the thermodynamically preferred products (most negative ones) compared with the 4-acyl derivatives. The reactions involving **1a** dipole presents almost the same trend shown by **1b**. The energies associated with dipole **1a** and dipolarophile **4**, as well as all the other reaction energies, are reported in Table 1-SI. The **PES** analysis predicts that in all evaluated reactions the 5-acyl derivatives should be the major regioisomer product if **1b** and **1a** react in their activated dipole form (**M-I**) with all five-membered rings dipolarophiles, but as was previously noted, in some specific cases the 4-acyl derivatives are obtained as the major product. Therefore, the **PES** analysis validates our previous hypothesis,[12] that in some cases, the intermediate forms previously to the formation of the 1,3-dipole and could be the reactive species against dipolarophiles in the pyrazole synthesis.

2.3. Justification of the intermediate form M-II of dipole as the reactive species in these 1,3-DC

The analysis of the regioselectivity depending on the experimental conditions allowed us to propose some requirements for the intermediate-dipole **M-II** to be the reactive species in this 1,3-DC: (a) the intermediate **M-II** must be sufficiently reactive, clearly

the intermediate of the p-MeO-dipole (**1b**) is the most reactive compared to the intermediate of the **1a** dipole in terms of the global nucleophilicity index (see Table 2), (b) the dipolarophile should be small due to the sterically protective environment around the reactive region in the intermediate-dipole (surrounding groups and TEA), and because the **M-II** is expected to have a short half-life, then any reaction involving it, will be kinetically controlled. In summary, only the dipole-intermediate **1b** (**M-II**) could be the reactive species against small dipolarophiles; among the studied dipolarophiles, when X=$-C_2H_4-$ and $-C_3H_6-$ (with n=1) in our previous work,[12] and X=NTs in the present work, the dipolarophile is too large to react with the dipole-intermediate **1b** form, therefore the 1,3-dipole (**M-I**) will be the reactive species. However, when X=O and S (dipolarophiles **2** and **4**), the effect changes as both are comparatively as small as **c-2-one**, which was proposed to react with the dipole-intermediate **M-II** form. The differences in regiochemistry when these two dipolarophiles are used in the reaction will be discussed in the following paragraphs in terms of global and local reactivity descriptors.

Table 2
Global properties and global electrophilicity for nitrile imines and cycloalkenes involved in 1,3-dipolar cycloaddition reactions

			HOMO	LUMO	μ (a.u.)	η (a.u.)	ω (eV)	N (a.u.)
Dipole	**M-I**	**1a**	−0.2169	−0.0629	−0.1399	0.1541	1.73	0.7831
		1b	−0.2018	−0.0568	−0.1293	0.1450	1.57	0.7982
	M-II	**1a**	−0.1664	−0.0204	−0.0934	0.1460	0.81	0.8336
		1b	−0.1582	−0.0164	−0.0874	0.1418	0.73	0.8418
Dipolarophile	**c-2-one**		−0.2376	−0.0443	−0.1409	0.1933	1.40	0.7624
	2		−0.2851	−0.0478	−0.1664	0.2373	1.59	0.7149
	4		−0.2539	−0.0575	−0.1557	0.1964	1.68	0.7461
	6		−0.2568	−0.0499	−0.1533	0.2070	1.55	0.7432

2.4. Analyses of the global and local reactivity indexes

To gain more insight about the reactivity of these systems we have evaluated some electronic-based reactivity descriptors. In Table 2, the electronic chemical potential, μ, chemical hardness, η, global electrophilicity index, ω, and global nucleophilicity index, N, are displayed for the dipoles considering both models (**M-I** and **M-II**) and the five-membered set of dipolarophile reagents. The electronic chemical potential, μ, of the dipoles are higher than those for the dipolarophiles. Therefore, the predicted charge transfer (CT) in these 1,3-DC reactions will take place from the dipole to the dipolarophiles in a normal-electron-demand (NED) fashion.

The question that remains unanswered is: why the regiochemistry with dipolarophile **4** is different from the one with dipolarophile **c-2-one**? Fig. 5 shows the best Fukui predicted interaction between reagents, when **M-II** is proposed in the reactions. The Fukui dipolarophile values correspond to the **c-2-one**; the values for all other dipolarophiles (**2**, **4** and **6**) are almost the same therefore are not reported here. The black square encloses the reactive region, while the regions presenting substituents that could sterically disfavour or favour the reaction are enclosed in red squares. The terminal methyl groups of TEA have been deleted to allow a better view of the region of interest. The Fukui topological analysis successfully describes the experimentally observed inversion in regioselctivity of dipolarophiles **c-2-one** and **2**, but erroneously predicts that dipolarophile **4** should present the same inversion to give the 4-acyl derivative as the major product.

To explain the different regioselectivity between O and S we propose that repulsive interaction between S and Cl will be higher

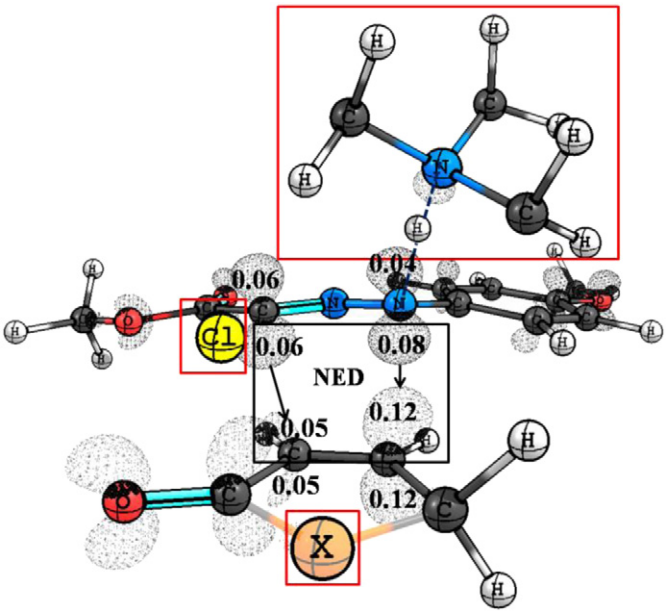


Fig. 5. Local Fukui function predictions of the most probable interaction between the dipole from intermediate **1b** (**M-II**) and dipolarophile **c-2-one** (X=CH_2). The same trends are presented when dipoles **2**, **4**, and **6** are used in the simulation. Enclosed in a black square is the reactive region, and enclosed in red squares are the groups that could favour or disfavour the interactions by electrostatic effects.

than repulsive interaction between O and Cl (see Fig. 5) when both reagents interact. This argument is based on the larger size of the S compared to O, therefore the surrounding electronic density in the former will be most polarisable, resulting in a high repulsive interaction with the electronic density around the chloride. This statement needs further analysis and will be addressed using a methodology, which allows us to visualize electronic charge density excess or deficiency around the reactive regions of the molecules. This method combines electronic charge density and molecular electrostatic potential values (MEP).

2.5. Molecular electrostatic analysis

To verify the previously proposed hypothesis about repulsive interaction between Cl around the dipole and O or S of the dipolarophiles **2** and **4**, we have calculated the electrostatic potential ($V(r)$) in both dipolarophiles and in the intermediate reactive species **M-II**, and mapped it over an isodensity surface corresponding to 0.002 a.u. This surface just encloses the Van der Waals volumes of the individual atoms in the molecule and is thus a good representation of the reactive regions around the molecules.[27] The maximum and minimum $V(r)$ values are 0.05 and −0.05 a.u., respectively. Therefore, regions rich in electronic charge density will present negative values of $V(r)$ and regions deficient in electron charge density will present positive values of $V(r)$.

As we can see in Fig. 6, the electronic charge density is concentrated in small regions in dipolarophile **2**, whereas in dipolarophile **4** the electronic charge density is distributed in a large surface around S. The electron charge density in **M-II** remains constant in both the hypothetical reactions, and the interaction with dipole **4** (S) should be the most disfavoured by the higher repulsive effects, as indicated in the Fig. 6. This will be the reason why dipole **4** does not react with the intermediate-dipole **1b** (**M-II**) to produce the 4-acyl derivative, whereas dipole **2** is favoured to react in this form.

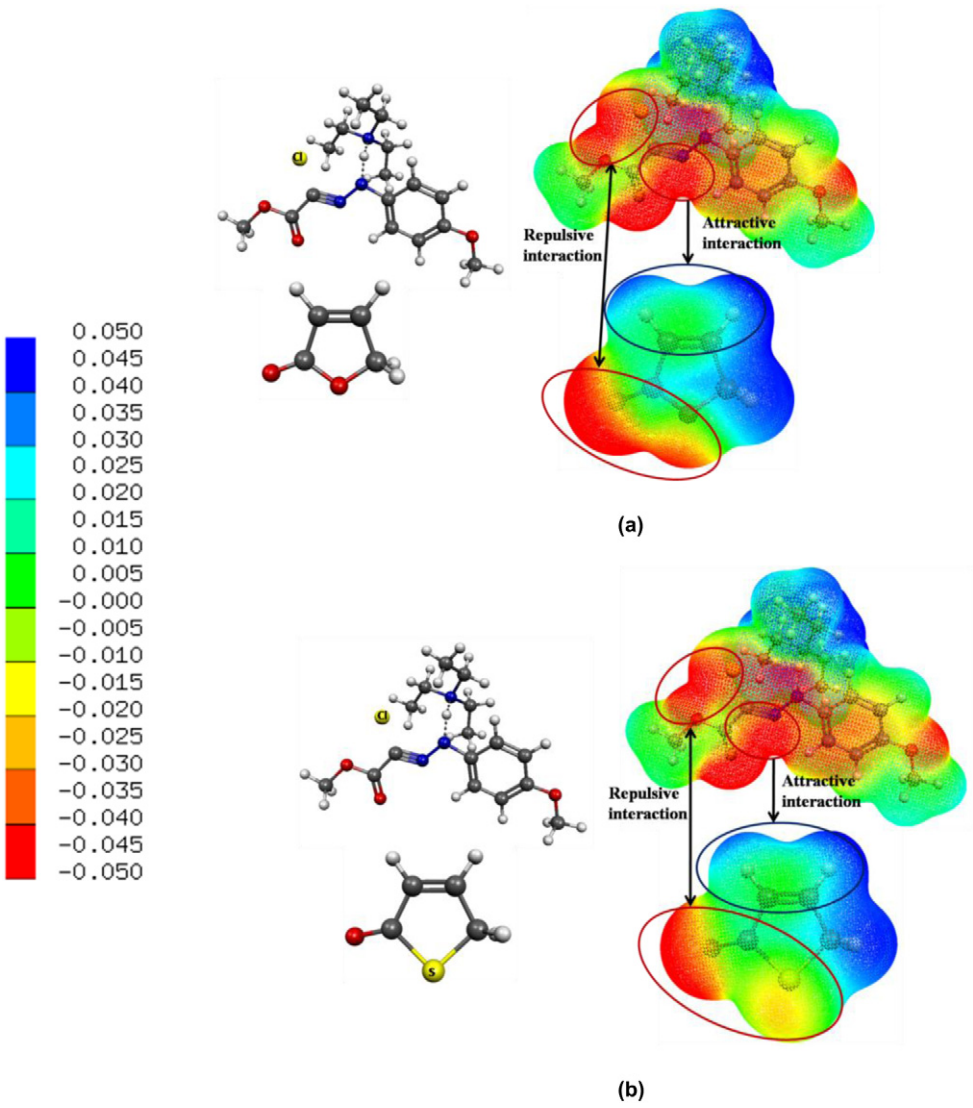


Fig. 6. B3LYP/6–31G(d) 0.002 au isodensity surface with superimposed electrostatic potential for (a) interaction between dipole **1b** (**M-I**) with dipolarophile **2** (*X*=O) and (b) interaction between dipole **1b** (**M-I**) with dipolarophile **4** (*X*=S). In both cases, the maximum and minimum potential values are 0.05 and −0.05 au, respectively. The molecular structures and the colour scale of the MEP are displayed on the left.

2.6. Some insights about the isomeric ratio

Finally, another important experimental result that deserves to be discussed is the higher isomeric ratio in favour of the 5-acyl derivative (99:1) for the reaction of **1a** with **4**. From our previously discussed results we summarized some important remarks: only the intermediate-dipole **1b** (**M-II**) is reactive enough (higher nucleophilicity) to react against small dipoles, like the five-membered 2-cyclopentenone and the five-membered lactone, which do not present appreciable steric effects; in all other cases the 1,3-dipole **1b** (**M-I**) is expected to be the prevailing reagent, and 1,3-dipole **1a** (**M-I**) should be the unique reagent. Therefore, the product distribution could be analyzed in terms of activation and reaction energies reported in Table 1-SI. Because the concentration of negative charge around S compared with O is only slightly larger, it is possible to say that in small quantities the intermediate **1b** (**M-II**) could react with **4**, to gives small amounts of the 4-acyl derivative, justifying the 82:18 experimental ratio. When the reaction is between **1a** with **4**, the 5-acyl derivative is the kinetic and thermodynamically preferred product and there is no presence of an intermediate reactive form of dipole, which agrees very well with the 99:1 experimental ratios. It is interesting to note that higher regioselectivity of this dipolarophile is in agreement with the higher reactivity (ω=1.68, in Table 2). Making the same analysis to the reaction with dipolarophile **6**, the 5-acyl derivative is only 0.9 and 1.2 kcal/mol kinetically and thermodynamically more favoured than 4-acyl derivative, therefore it is reasonable to expect the possible presence of 4-acyl derivatives, in agreement with the 72:28 experimental observed ratio.

3. Conclusion

In conclusion, we have developed a simple one-pot two-step method for the regiocontrolled synthesis of pyrazoles fused with lactones, thiolactones and lactams based on the 1,3-DC of nitrile imines with the corresponding α,β-unsaturated dipolarophiles. In all the cases, the 5-acyl substituted pyrazole is the major product, with a ratio of 5-acyl/4-acyl up to 99:1, except with the five-membered α,-β-unsaturated lactone (ratio 5-acyl/4-acyl 14:86). The effect of a substituent in the para-position of the aryl on the dipole, the nature and size of the dipolarophiles, and their effect on yields and regiochemistry have been investigated. To

rationalize the experimental results a theoretical model including the possibility of reactive intermediate forms of the dipole, the size of the dipolarophile and the electrostatic interactions between the reactive forms has been developed.

The reported methodology appears to be suitable for the control of the regiochemistry of this 1,3-DC and could be potentially useful for applications in medicinal chemistry. Computer-assisted syntheses of ring-fused pyrazoles of this type are currently being investigated as multikinase inhibitors.

4. Experimental section

4.1. General experimental information

^{1}H NMR and ^{13}C NMR spectra were recorded using $CDCl_3$ or CD_3OD or DMSO-d_6 solutions at 300, 400 and 600 MHz for ^{1}H and 75.46, 100.6 and 150.92 MHz for ^{13}C. Chemical shifts (δ) are reported in parts per million relative to $CHCl_3$ (δ=7.26 for ^{1}H and δ=77.0 for 13C). *J* values are given in Hertz. ^{1}H NMR and ^{13}C NMR assignments were made by DEPT, gCOSY and gHSQC experiments. IR spectra were recorded in solvent as specified. Mass spectra (MS) were obtained with an electronic impact EI source (ESIMS). High Resolution Mass Spectra (HRMS) were recorded on a micromass LCT spectrometer using electrospray (ES^+) ionisation techniques. Reactions were conducted in oven-dried (120 °C) glassware under a positive Ar atmosphere. Transfer of anhydrous solvents or mixtures was accomplished with oven-dried syringes/septum techniques. THF was distilled from sodium/benzophenone just prior to use and stored under Ar. Toluene was distilled from sodium. Et_2O was distilled from phosphorus pentoxide. CH_2Cl_2 was passed through basic alumina and distilled from CaH_2 prior to use. Other solvents were purified by standard procedures. Light petroleum ether refers to the fraction with bp 40–60 °C. The reactions were monitored by TLC performed on silica gel plates (Baker-flex IB2-F). Column chromatography was performed with Merck silica gel 60 (70–230 mesh). Preperative TLC was carried out on glass plates using a 1 mm layer of Merck silica gel 60 Pf 254. All chemicals were used as obtained or purified as needed.

4.2. Synthesis of 5,6-dihydro-2*H*-thiopyran-2-one (5)

A solution of NaH (0.4 g, 10.0 mmol, 60% dispersion in mineral oil) in dry THF (15 ml) was cooled to 0 °C and methyl 2-(dimethoxyphosphoryl) acetate (1.68 g, 9.2 mmol) was added slowly over 5 min. The resulting mixture was stirred at 0 °C for a further 20 min, then *S*-3-oxopropyl ethanethioate[26] (1 g, 8.4 mmol) dissolved in dry THF was introduced and the resulting mixture was stirred at room temperature for further 1–2 h. After completion, water was added and extracted with EtOAc (3×20 ml). Combined organic layers were washed with brine, dried over $MgSO_4$ and evaporated in *vacuo*. The (*E*)-methyl 5-(acetylthio)pent-2-enoate (1.4 g, 93%) was directly used for next step. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.34 (s, 3H), 2.44–2.54 (qd, *J*=7.1 and 1.6 Hz, 2H), 2.98 (t, *J*=7.1 Hz, 2H), 3.74 (s, 3H), 5.87 (dt, *J*=15.6 and 1.5 Hz, 1H), 6.90 (dt, *J*=15.6 and 6.54 Hz, 1H).

(*E*)-Methyl 5-(acetylthio)pent-2-enoate (1.4 g, 7.4 mmol) was dissolved in MeOH (10 ml) then 10% NaOH (10 ml) was added. The resulting reaction mixture was then stirred at room temperature for overnight. After completion, reaction mixture was extracted with EtOAc (3×20 ml). Combined organic layers were washed with brine, dried over $MgSO_4$ and evaporated in vacuo to give (*E*)-5-mercaptopent-2-enoic acid (0.87 g, 88%) as oil, which was directly used for next step.

(*E*)-5-Mercaptopent-2-enoic acid (0.8 g, 6.0 mmol) was added to PPA (10 ml) and heated to 70 °C for 2 h. After completion, ice water was added to reaction and extracted with DCM (3×15 ml). Combined organic layers were washed with water and brine, dried over $MgSO_4$ and evaporated in vacuo to give 5,6-dihydro-2*H*-thiopyran-2-one (**5**) (0.12 g, 17%) as oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.57–2.65 (m, 2H), 3.21 (t, *J*=6.3 Hz, 2H), 6.11 (dt, *J*=10.8, 1.8 Hz, 1H), 6.91 (dt, *J*=10.9, 4.8 Hz, 1H).

4.3. General procedure for the 1,3-dipolar cycloaddition

To a stirred solution of dipolarophile **2**–**7** (1 equiv) and **1a** or **1b** (1 equiv for **2**–**5** and 2 equiv for **6** and **7**) in freshly distilled dioxane (5 mL for **2**–**5**) or toluene (5 mL for **6** and **7**) under an argon atmosphere was added triethylamine (2.5 equiv for **2**–**5** and 5 equiv for **6** and **7**). The reaction was heated at 80 °C overnight. After completion, the reaction mixture was allowed to cool and filtered through a bed of Celite and washed with DCM (5 mL). The filtrate was then evaporated in vacuo to give a dark red crude oil. The crude product was directly used in the oxidation stage.

4.4. General procedure for CAN oxidation of cycloadducts

The crude cycloaddition product was suspended in THF:H_2O (6:8, 10 ml) at 0 °C. Cerium (IV) ammonium nitrate (CAN) (2.5 equiv) was then added slowly in portions. After complete addition, the reaction was allowed to stirr at 0 °C for a further 1–2 h. After completion, THF was evaporated in vacuo and the aqueous layer was extracted with ethyl acetate (3×10 ml). The organic layer was then washed with water (15 ml) and brine. The combined organic layers were dried over $MgSO_4$ and then evaporated in vacuo. The crude residue was purified by column chromatography to give the corresponding title compounds.

*4.4.1. Methyl 6-oxo-1-phenyl-4,6-dihydro-1H-furo[3,4-c]pyrazole-3-carboxylate and methyl 4-oxo-1-phenyl-4,6-dihydro-1H-furo[3,4-c]pyrazole-3-carboxylate (**8a** and **8a′**).* Compounds **8a** and **8a′** were obtained as a yellow oil following the general procedure for the 1,3-DC followed by the oxidation with CAN and separated by chromatography on silica gel (10–50% EtOAc/hexane). The two regioisomers were further separated by preparative TLC plates (50% EtOAc/hexane).

*4.4.2. Methyl 6-oxo-1-phenyl-4,6-dihydro-1H-furo[3,4-c]pyrazole-3-carboxylate (**8a**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.00 (s, 3H), 5.41 (s, 2H), 7.31–8.30 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 52.9, 65.8, 120.7 (2C), 127.3, 128.9, 129.8 (2C), 136.1, 138.3, 142.5, 158.4, 161.1; IR (CCl_4): ν=3068, 2953, 1780, 1725, 1576, 1436, 1374, 1276, 1138, 1032, 984 cm^{-1}. EIMS: *m*/*z* 258 (M^+). HRMS calcd for $C_{13}H_{10}N_2O_4$ 258.0641, found 258.0643.

*4.4.3. Methyl 4-oxo-1-phenyl-4,6-dihydro-1H-furo[3,4-c]pyrazole-3-carboxylate (**8a′**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.04 (s, 3H), 5.45 (s, 2H), 7.36–7.78 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 53.1, 64.1, 119.6 (2C), 125.8, 129.3, 130.3 (2C), 130.6, 137.9, 139.2, 158.2, 160.5; IR (CCl_4): ν=3068, 2953, 1780, 1725, 1576, 1436, 1374, 1276, 1138, 1032, 984 cm^{-1}. EIMS: *m*/*z* 258 (M^+). HRMS calcd for $C_{13}H_{10}N_2O_4$ 258.0641, found 258.0645.

*4.4.4. Methyl 1-(4-methoxyphenyl)-6-oxo-4,6-dihydro-1H-furo[3,4-c]pyrazole-3-carboxylate and methyl 1-(4-methoxyphenyl)-4-oxo-4,6-dihydro-1H-furo[3,4-c]pyrazole-3-carboxylate (**8b** and **8b′**).* Compounds **8b** and **8b′** were obtained as a solid and yellow oil, respectively following the general procedure for the 1,3-DC followed by the oxidation with CAN and separated by chromatography on silica gel (10–50 % EtOAc/hexane). The two regioisomers were further separated by preparative TLC plates (50% EtOAc/hexane).

*4.4.5. Methyl 1-(4-methoxyphenyl)-6-oxo-4,6-dihydro-1H-furo[3,4-c]pyrazole-3-carboxylate (**8b**).* Mp=190–191 °C; ^{1}H NMR

(300 MHz, $CDCl_3$): δ 3.86 (s, 3H), 3.99 (s, 3H), 5.40 (s, 2H), 7.01 (d, J=9.1 Hz, 2H), 8.05 (d, J=9.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 52.9, 55.8, 65.8, 114.8 (2C), 122.3 (2C), 131.7, 135.4, 135.6, 142.1, 158.6, 160.0, 161.2; IR (CCl_4): ν=2954, 2909, 2223, 1755, 1720, 1612, 1559, 1505, 1442, 1254, 1119, 1065, 951 cm^{-1}. EIMS: m/z 288 (M^+). HRMS calcd for $C_{14}H_{12}N_2O_5$ 288.0746, found 288.0742.

*4.4.6. Methyl 1-(4-methoxyphenyl)-4-oxo-4,6-dihydro-1H-furo[3,4-c]pyrazole-3-carboxylate (**8b**′).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.87 (s, 3H), 4.04 (s, 3H), 5.39 (s, 2H), 7.03 (d, J=9.2 Hz, 2H), 7.52 (d, J=9.2 Hz, 2H); ^{13}C NMR (200 MHz, $CDCl_3$): δ 53.1, 55.9, 63.9, 155.3 (2C), 117.1, 121.3 (2C), 131.2, 138.8, 157.7, 160.0, 160.6, 160.7; IR (CCl_4): ν=2954, 2909, 2223, 1755, 1720, 1612, 1559, 1505, 1442, 1254, 1119, 1065, 951 cm^{-1}. EIMS: m/z 288 (M^+). HRMS calcd for $C_{14}H_{12}N_2O_5$ 288.0746, found 288.0741.

*4.4.7. Methyl 7-oxo-1-phenyl-1,4,5,7-tetrahydropyrano[3,4-c]pyrazole-3-carboxylate and methyl 4-oxo-1-phenyl-1,4,6,7-tetrahydropyrano[4,3-c]pyrazole-3-carboxylate (**9a** and **9a**′).* Compounds **9a** and **9a**′ were obtained as solids following the general procedure for the 1,3-DC followed by the oxidation with CAN and separated by chromatography on silica gel (10–50 % EtOAc/hexane). The two regioisomers were further separated by preparative TLC plates (50% EtOAc/hexane).

*4.4.8. Methyl 7-oxo-1-phenyl-1,4,5,7-tetrahydropyrano[3,4-c]pyrazole-3-carboxylate (**9a**).* Mp=183–184 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.31 (t, J=6.0 Hz, 2H), 3.98 (s, 3H), 4.64 (t, J=6.0 Hz, 2H), 7.44–7.63 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.1, 52.5, 69.1, 125.3 (2C), 129.0 (2C), 129.3, 129.6 (2C), 138.8, 139.6, 156.6, 162.1. IR (CCl_4): ν=2997, 2955, 1751, 1724, 1599, 1509, 1439, 1367, 1265, 1240, 1139, 1101, 1003, 948 cm^{-1}. EIMS: m/z 272 (M^+). HRMS calcd for $C_{14}H_{12}N_2O_4$ 272.0797, found 272.0793.

*4.4.9. Methyl 4-oxo-1-phenyl-1,4,6,7-tetrahydropyrano[4,3-c]pyrazole-3-carboxylate (**9a**′).* Mp=141–142 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.16 (t, J=5.9 Hz, 2H), 4.00 (s, 3H), 4.52 (t, J=5.9 Hz, 2H), 7.46–7.57 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.4, 53.0, 66.4, 110.5, 123.9 (2C), 129.5, 129.9 (2C), 137.6, 144.1, 146.5, 159.5, 161.3; IR (CCl_4): ν=2997, 2955, 1751, 1724, 1599, 1509, 1439, 1367, 1265, 1240, 1139,c1101, 1003, 948 cm^{-1}. EIMS: m/z 272 (M^+); HRMS calcd for $C_{14}H_{12}N_2O_4$ 272.0797, found 272.0795.

*4.4.10. Methyl 1-(4-methoxyphenyl)-7-oxo-1,4,5,7-tetrahydropyrano[3,4-c]pyrazole-3-carboxylate and methyl 1-(4-methoxyphenyl)-4-oxo-1,4,6,7-tetrahydropyrano[4,3-c]pyrazole-3-carboxylate (**9b** and **9b**′).* Compounds **9b** and **9b**′ were obtained as solids following the general procedure for the 1,3-DC followed by the oxidation with CAN and separated by chromatography on silica gel (10–50 % EtOAc/hexane). The two regioisomers were further separated by preparative TLC plates (50% EtOAc/hexane).

*4.4.11. Methyl 1-(4-methoxyphenyl)-7-oxo-1,4,5,7-tetrahydropyrano[3,4-c]pyrazole-3-carboxylate (**9b**).* Mp=218–219 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.30 (t, J=6.1 Hz, 2H), 3.86 (s, 3H), 3.98 (s, 3H), 4.63 (t, J=6.1 Hz, 2H), 6.97 (d, J=8.9 Hz, 2H), 7.49 (d, J=8.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.1, 52.5, 55.7, 69.1, 114.1 (2C), 126.6 (2C), 129.2, 129.3, 131.9, 139.2, 156.8, 160.4, 162.2; IR (CCl_4): ν=3000, 2954, 2052, 1755, 1723, 1592, 1559, 1509, 1444, 1391, 1254, 1100, 1065, 951 cm^{-1}. EIMS: m/z 302 (M^+). HRMS calcd for $C_{15}H_{14}N_2O_5$ 302.0903, found 302.0900.

*4.4.12. Methyl 1-(4-methoxyphenyl)-4-oxo-1,4,6,7-tetrahydropyrano[4,3-c]pyrazole-3-carboxylate (**9b**′).* Mp=113–114 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.09 (t, J=6.2 Hz, 2H), 3.86 (s, 3H), 3.99 (s, 3H), 4.51 (t, J=6.2 Hz, 2H), 7.01 (d, J=9.3 Hz, 2H), 7.42 (d, J=9.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.2, 52.9, 55.9, 66.4, 114.9 (2C), 125.4 (2C), 128.2, 130.6, 143.8, 146.5, 159.6, 160.4, 161.4; IR (CCl_4): ν=3000, 2954, 2052, 1755, 1723, 1592, 1559, 1509, 1444, 1391, 1254, 1100, 1065, 951 cm^{-1}. EIMS: m/z 302 (M^+). EIMS: m/z 302 (M^+); HRMS calcd for $C_{15}H_{14}N_2O_5$ 302.0903, found 302.0901.

*4.4.13. Methyl 6-oxo-1-phenyl-4,6-dihydro-1H-thieno[3,4-c]pyrazole-3-carboxylate (**10a**).* Compound **10a** was obtained as a solid following the general procedure for the 1,3-DC followed by the oxidation with CAN and separated by chromatography on silica gel (20% EtOAc/hexane).

*4.4.14. Methyl 6-oxo-1-phenyl-4,6-dihydro-1H-thieno[3,4-c]pyrazole-3-carboxylate (**10a**).* Mp=194 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.00 (s, 3H), 4.43 (s, 2H), 7.38–7.53 (m, 3H), 7.79–7.86 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 27.2, 52.7, 123.2 (2C), 129.2, 129.4 (2C), 137.8, 138.0, 142.6, 143.2, 161.6, 182.2; IR (CCl_4): ν=3075, 2957, 2361, 1754, 1721, 1698, 1501, 1464, 1372, 1294, 1202, 1132, 1048, 881 cm^{-1}. EIMS: m/z 274 (M^+). HRMS calcd for $C_{13}H_{10}N_2O_3S$ 274.0412, found 274.0413.

*4.4.15. Methyl 1-(4-methoxyphenyl)-6-oxo-4,6-dihydro-1H-thieno[3,4-c]pyrazole-3-carboxylate and methyl 1-(4-methoxyphenyl)-4-oxo-4,6-dihydro-1H-thieno[3,4-c]pyrazole-3-carboxylate (**10b** and **10b**′).* Compounds **10b** and **10b**′ were obtained as a solid and yellow oil, respectively following the general procedure for the 1,3-DC followed by the oxidation with CAN and separated by chromatography on silica gel (10–50% EtOAc/hexane). The two regioisomers were further separated by preparative TLC plates (50% EtOAc/hexane).

*4.4.16. Methyl 1-(4-methoxyphenyl)-6-oxo-4,6-dihydro-1H-thieno[3,4-c]pyrazole-3-carboxylate (**10b**).* Mp=180–181 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.85 (s, 3H), 3.99 (s, 3H), 4.41 (s, 2H), 6.98 (d, J=9.1Hz, 2H), 7.72 (d, J=9.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 27.1, 52.7, 55.8, 114.4 (2C), 124.7(2C), 131.2, 137.4, 142.1, 142.9, 160.2, 161.8, 182.3; IR (CCl_4): ν=2957, 2361, 1753, 1722, 1698, 1594, 1514, 1439, 1255, 1160, 1132, 1050, 883 cm^{-1}. EIMS: m/z 304 (M^+). HRMS calcd for $C_{14}H_{12}N_2O_4S$ 304.0518, found 304.0515.

*4.4.17. Methyl 1-(4-methoxyphenyl)-4-oxo-4,6-dihydro-1H-thieno[3,4-c]pyrazole-3-carboxylate (**10b**′).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.88 (s, 3H), 4.00 (s, 3H), 4.35 (s, 2H), 7.03 (d, J=8.8 Hz, 2H), 7.55 (d, J=8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.5, 52.9, 55.9, 115.1(2C), 123.8 (2C), 124.9, 130.4, 136.9, 157.8, 160.3, 160.8, 182.7; IR (CCl_4): ν=2957, 2361, 1753, 1722, 1698, 1594, 1514, 1439, 1292, 1255, 1160, 1132, 1050, 883 cm^{-1}. EIMS: m/z 304 (M^+). HRMS calcd for $C_{14}H_{12}N_2O_4S$ 304.0518, found 304.0517.

*4.4.18. Methyl 7-oxo-1-phenyl-1,4,5,7-tetrahydrothiopyrano[3,4-c]pyrazole-3-carboxylate and methyl 4-oxo-1-phenyl-1,4,6,7-tetrahydrothiopyrano[4,3-c]pyrazole-3-carboxylate (**11a** and **11a**′).* Compounds **11a** and **11a**′ were obtained as solids following the general procedure for the 1,3-DC and separated by chromatography on silica gel (10–50% EtOAc/hexane). The two regioisomers were further separated by preparative TLC plates (50% EtOAc/hexane).

*4.4.19. Methyl 7-oxo-1-phenyl-1,4,5,7-tetrahydrothiopyrano[3,4-c]pyrazole-3-carboxylate (**11a**).* Mp=206–207 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.41(m, 2H), 3.50 (m, 2H), 3.95 (s, 3H), 7.40–7.50 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.5, 31.6, 52.4, 125.8 (2C), 128.9 (2C), 129.6, 131.3, 134.2, 139.7, 140.0, 162.4, 180.9; IR (CCl_4): ν=3065, 2954, 1747, 1682, 1601, 1566, 1501, 1450, 1263, 1149, 1074, 967,

889 cm^{-1}. EIMS: *m/z* 288 (M^+). HRMS calcd for C14H12N2O3S 288.0569, found 288.0566.

*4.4.20. Methyl 4-oxo-1-phenyl-1,4,6,7-tetrahydrothiopyrano[4,3-c] pyrazole-3-carboxylate (**11a′**).* Mp=154–155 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 3.21 (m, 2H), 3.30 (m, 2H), 3.97 (s, 3H), 7.39–7.65 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.2, 29.8, 53.3, 125.1 (2C), 129.7, 129.8 (2C), 137.6, 142.7, 147.8, 162.0, 183.3; IR (CCl_4): ν=3065, 2954, 1747, 1682, 1601, 1566, 1501, 1450, 1263, 1149, 1074, 967, 889 cm^{-1}. EIMS: *m/z* 288 (M^+). HRMS calcd for C14H12N2O3S 288.0569, found 288.0563.

*4.4.21. Methyl 1-(4-methoxyphenyl)-7-oxo-1,4,5,7-tetrahydrothiopyrano[3,4-c]pyrazole-3-carboxylate and methyl 1-(4-methoxyphenyl)-4-oxo-1,4,6,7-tetrahydrothiopyrano[4,3-c]pyrazole-3-carboxylate (**11b** and **11b′**).* Compounds **11b** and **11b′** were obtained as a solid and yellow oil, respectively following the general procedure for the 1,3-DC and separated by chromatography on silica gel (10–50 % EtOAc/hexane). The two regioisomers were further purified by preperative TLC plates (50% EtOAc/hexane).

*4.4.22. Methyl 1-(4-methoxyphenyl)-7-oxo-1,4,5,7-tetrahydrothiopy-rano[3,4-c]pyrazole-3-carboxylate (**11b**).* Mp=201–202 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 3.41 (m, 2H), 3.49 (m, 2H), 3.83 (s, 3H), 3.95 (s, 3H), 6.92 (d, *J*=8.7 Hz, 2H), 7.35 (d, *J*=8.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.6, 31.6, 52.4, 55.7, 114.0 (2C), 127.0 (2C), 131.1, 132.8, 134.1, 139.7, 160.3, 162.5, 181.0; IR (CCl_4): ν=3003, 2955, 2837, 1722, 1668, 1593, 1515, 1438, 1250, 1179, 1131, 1038, 891 cm^{-1}. EIMS: *m/z* 318 (M^+). HRMS calcd for $C_{15}H_{14}N_2O_4S$ 318.0674, found 318.0679.

*4.4.23. Methyl 1-(4-methoxyphenyl)-4-oxo-1,4,6,7-tetrahydrothiopyrano[4,3-c]pyrazole-3-carboxylate (**11b′**).* ^1H NMR (300 MHz, $CDCl_3$): δ 3.16 (m, 2H), 3.30 (m, 2H), 3.87 (s, 3H), 3.97 (s, 3H), 7.01 (d, *J*=8.3 Hz, 2H), 7.36 (d, *J*=8.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.2, 29.7, 53.0, 55.9, 114.9 (2C), 126.5 (2C), 130.5, 142.2, 148.0, 156.1, 160.5, 162.1, 183.3; IR (CCl_4): ν=3003, 2955, 2837, 1722, 1668, 1593, 1515, 1438, 1250, 1179, 1131, 1038, 891 cm^{-1}. EIMS: *m/z* 318 (M^+). HRMS calcd for $C_{15}H_{14}N_2O_4S$ 318.0674, found 318.0675.

*4.4.24. Methyl 6-oxo-1-phenyl-5-tosyl-1,4,5,6-tetrahydropyrrolo [3,4-c]pyrazole-3-carboxylate and methyl 4-oxo-1-phenyl-5-tosyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole-3-carboxylate (**12a** and **12a′**).* Compounds **12a** and **12a′** were obtained as a yellowish solid and yellow foam following the general procedure for the 1,3-DC (in toluene) followed by the oxidation with CAN and separated by chromatography on silica gel (1/9 EtOAc/hexane). The two regioisomers were further separated by preparative TLC plates (CH_2Cl_2).

*4.4.25. Methyl 6-oxo-1-phenyl-5-tosyl-1,4,5,6-tetrahydropyrrolo [3,4-c]pyrazole-3-carboxylate (**12a**).* Mp: 184–189 °C, ^1H NMR (300 MHz, $CDCl_3$): δ 2.44 (s, 3H), 4.00 (s, 3H), 4.96 (s, 2H), 7.32–7.51 (m, 5H), 7.98–8.12 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.0, 45.7, 52.7, 121.3, 128.5, 128.9, 129.7, 130.3, 134.8, 135.2, 137.0, 138.2, 145.9, 155.3, 161.2; IR (CCl_4): ν=2928, 2855, 1741, 1559, 1467, 1177, 1097 cm^{-1}. EIMS: *m/z* 411 (M^+). HRMS calcd for $C_{20}H_{17}N_3O_5S$ 411.0891, found 411.0896.

*4.4.26. Methyl 4-oxo-1-phenyl-5-tosyl-1,4,5,6-tetrahydropyrrolo [3,4-c]pyrazole-3-carboxylate (**12a′**).* ^1H NMR (400 MHz, $CDCl_3$): δ 2.43 (s, 3H), 3.98 (s, 3H), 5.10 (s, 2H), 7.34 (d, *J*=8.6 Hz, 2H), 7.45 (tt, *J*=7.3 and 1.2 Hz, 1H), 7.55 (tt, *J*=7.3 and 1.7 Hz, 2H), 7.64 (dt, *J*=7.3 and 1.4 Hz, 2H), 8.02 (d, *J*=8.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.9, 45.9, 53.1, 120.1, 120.7, 121.5, 128.6, 129.1, 129.7, 130.1, 130.3, 135.9, 137.9, 145.6, 150.9, 157.6, 160.5; IR (CCl_4): ν=2928, 2855, 1741, 1559, 1467, 1177, 1097 cm^{-1}. EIMS: *m/z* 411 (M^+). HRMS calcd for $C_{20}H_{17}N_3O_5S$ 411.0891, found 411.0898.

*4.4.27. Methyl 1-(4-methoxyphenyl)-6-oxo-5-tosyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole-3-carboxylate and methyl 1-(4-methoxyphenyl)-4-oxo-5-tosyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole-3-carboxylate (**12b** and **12b′**).* Compounds **12b** and **12b′** were obtained as a white solid and white foam following the general procedure for the 1,3-DC (in toluene) followed by the oxidation with CAN and separated by chromatography on silica gel (1/9 EtOAc/hexane). The two regioisomers were further separated by preparative TLC plates (CH_2Cl_2).

*4.4.28. Methyl 1-(4-methoxyphenyl)-6-oxo-5-tosyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole-3-carboxylate (**12b**).* Mp: 213–218 °C, ^1H NMR (400 MHz, $CDCl_3$): δ 2.43 (s, 3H), 3.88 (s,3H), 4.00 (s, 3H), 4.98 (s, 2H), 6.93–9.97 (d, *J*=8.5 Hz, 2H), 7.35 (d, *J*=8.0 Hz, 2H), 8.01 (m, 2H), 8.07 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.0, 45.5, 52.9, 55.8, 114.7, 122.7, 128.5, 130.2, 131.6, 134.4, 135.2, 136.5, 137.2, 145.8, 155.4, 160.0, 161.2; IR (CCl_4): ν=3071, 2954, 1944, 1725, 1600, 1264, 1098 cm^{-1}. ESIMS: *m/z* 464 (M^++23). HRMS calcd for $C_{21}H_{19}N_3NaO_6S$ 464.0892, found 464.0896.

*4.4.29. Methyl 1-(4-methoxyphenyl)-4-oxo-5-tosyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole-3-carboxylate (**12b′**).* ^1H NMR (400 MHz, $CDCl_3$): δ 2.43 (s, 3H), 3.87 (s, 3H), 3.98 (s, 3H), 5.04 (s, 2H), 7.03(d, *J*=8.9 Hz, 2H), 7.34 (d, *J*=8.0 Hz, 2H), 7.54 (d, *J*=9.0 Hz, 2H), (d, *J*=8.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.9, 45.7, 53.1, 55.9, 115.3, 119.9, 121.9, 128.5, 130.1, 131.2, 135.4, 139.2, 145.6, 150.5, 157.8, 160.0, 160.7; IR (CCl_4): ν=3071, 2954, 1944, 1725, 1600, 1264, 1098 cm^{-1}. EIMS: *m/z* 441 (M^+). HRMS calcd for $C_{21}H_{19}N_3O_6S$ 441.0995, found 441.0997.

*4.4.30. Methyl 7-oxo-1-phenyl-6-tosyl-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylate and methyl 4-oxo-1-phenyl-5-tosyl-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine-3-carboxylate (**13a** and **13a′**).* Compounds **13a** and **13a′** were obtained as a white solid and yellow foam following the general procedure for the 1,3-DC (in toluene) followed by the oxidation with CAN and separated by chromatography on silica gel (1/9 EtOAc/hexane). The two regioisomers were further separated by preparative TLC plates (CH_2Cl_2).

*4.4.31. Methyl 7-oxo-1-phenyl-6-tosyl-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylate (**13a**).* Mp: 195–198 °C, ^1H NMR (300 MHz, $CDCl_3$): δ 2.41 (s, 3H), 3.29 (t, *J*=6.8 Hz, 2H), 3.95 (s, 3H), 4.34 (t, *J*=6.8 Hz, 2H), 7.29 (d, *J*=8.4 Hz, 2H), 7.38–7.41 (m, 5H), 7.89 (d, *J*=8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.9, 22.1, 46.8, 52.5, 125.6, 128.7, 128.9 (2C), 129.5, 129.8, 132.1, 136.0, 139.1, 139.4, 145.2, 155.7, 162.2; IR (CCl_4): ν=2984, 2360, 1710, 1559, 1264, 1174 cm^{-1}. ESIMS: *m/z* 448 (M^++23). HRMS calcd for $C_{21}H_{19}N_3NaO_5S$ 448.0943, found 448.0948.

*4.4.32. Methyl 4-oxo-1-phenyl-5-tosyl-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine-3-carboxylate (**13a′**).* ^1H NMR (400 MHz, $CDCl_3$): δ 2.43 (s, 3H), 3.16 (t, *J*=6.3 Hz, 2H), 3.95 (s, 3H), 4.29 (t, *J*=6.3 Hz, 2H), 7.33 (d, *J*=8.0 Hz, 2H), 7.44–7.57 (m, 5H), 7.92 (d, *J*=8.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.9, 24.0, 45.1, 53.0, 123.9, 128.8, 129.6, 129.8, 129.9 (2C), 134.0, 136.3, 137.6, 145.0, 146.7, 158.3, 165.6; 1040. IR (CCl_4): ν=2984, 2360, 1710, 1559, 1264, 1174 cm^{-1}. EIMS: *m/z* 425 (M^+). HRMS calcd for $C_{21}H_{19}N_3O_5S$ 425.1046, found 425.

4.4.33. Methyl 1-(4-methoxyphenyl)-7-oxo-6-tosyl-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylate and methyl 1-(4-methoxyphenyl)-4-oxo-5-tosyl-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-

*c]pyridine-3-carboxylate (**13b** and **13b′**).* Compounds **13b** and **13b′** were obtained as a white solid and yellow foam following the general procedure for the 1,3-DC (in toluene) followed by the oxidation with CAN and separated by chromatography on silica gel (1/9 EtOAc/hexane). The two regioisomers were further separated by preparative TLC plates (CH_2Cl_2).

*4.4.34. Methyl 1-(4-methoxyphenyl)-7-oxo-6-tosyl-4,5,6,7-tetra-hydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylate (**13b**).* Mp: 167–172 °C, ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.41 (s, 3H), 3.28 (t, J=6.3 Hz, 2H), 3.83 (s, 3H), 3.95 (s, 3H), 4.34 (t, J=6.3 Hz, 2H), 6.89 (d, J=9.1 Hz, 2H), 7.29 (d, J=8.5 Hz, 2H), 7.36 (d, J=9.1 Hz, 2H), 7.90 (d, J=8.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.9, 22.1, 46.9, 52.4, 55.8, 114.1, 126.9, 128.8, 128.9, 129.5, 129.8, 132.0, 132.3, 136.1, 139.1, 145.2, 155.8, 160.3, 162.2; IR (CCl_4): ν=2928, 2856, 2360, 1726, 1576, 1516, 1465, 1263 cm^{-1}. ESIMS: m/z 478 (M^++23). HRMS calcd for $C_{22}H_{21}N_3NaO_6S$ 478.1049, found 478.1043.

*4.4.35. Methyl 1-(4-methoxyphenyl)-4-oxo-5-tosyl-4,5,6,7-tetra-hydro-1H-pyrazolo[4,3-c]pyridine-3-carboxylate (**13b′**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.41 (s, 3H), 3.10 (t, J=6.3 Hz, 2H), 3.87 (s, 3H), 3.93 (s, 3H), 4.28 (t, J=6.3 Hz, 2H), 7.01 (d, J=9.0 Hz, 2H), 7.32 (d, J=8.2 Hz, 2H), 7.36 (d, J=9.1 Hz, 2H), 7.90 (d, J=8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.9, 23.8, 45.2, 53.1, 55.8, 114.9, 125.7, 128.8, 128.9, 129.5, 130.6, 136.4, 143.8, 144.9, 146.7, 158.4, 160.4, 161.6; IR (CCl_4): ν=2928, 2856, 2360, 1726, 1576, 1516, 1465, 1263 cm^{-1}. EIMS: m/z 455 (M^+). HRMS calcd for $C_{22}H_{21}N_3O_6S$ 455.1151, found 455.1150.

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Supplementary data

Supplementary data related to this article can be found online at doi:10.1016/j.tet.2012.02.068.

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