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Chemodivergent, multicomponent domino reactions in aqueous media: L-proline-catalyzed assembly of densely functionalized 4*H*-pyrano[2,3-*c*]pyrazoles and bispyrazolyl propanoates from simple, acyclic starting materials†

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A library of 4*H*-pyrano[2,3-*c*]pyrazol-6-amines was synthesized in excellent yield employing an L-proline-catalyzed, on-water four-component domino reaction from hydrazines, β-dicarbonyl compounds, nitriles and dialkyl acetylenedicarboxylates that generates two rings by the creation of C–C (two), C–N, C=N and C–O bonds and presumably involves a sequence of hydrazone formation, cyclocondensation, Michael, [1,3]-hydrogen shift, Michael addition and 6-*exo*-*dig* annulation steps. When alkyl propiolates were employed, a three-component reaction took place furnishing alkyl 3,3-bis(5-hydroxy-1*H*-pyrazol-4-yl)propanoates *via* a double Michael domino process.

Introduction

One of the most important aspects of modern synthetic methodology is the need to develop methods with a low environmental impact. Taking into account that organic solvents are the main source of waste from synthetic work, the development of methods with diminished use of organic solvents is of high priority. Water is the reaction medium used by nature in all biosynthetic routes, and has the advantage of being abundantly available, non-hazardous, non-flammable, redox-stable and cheap. Consequently, water is close to being an ideal green solvent, preferable to alternatives such as ionic liquids.[1] In addition, water facilitates novel solvation and molecular assembly processes leading to remarkable modes of reactivity and selectivity.[2]

On the other hand, the development of synthetic methods able to yield molecular diversity and complexity from simple and inexpensive starting materials *via* the generation of several bonds in a single synthetic operation, ideally in a single step, has also become one of the main challenges for organic synthesis,[3] and is also of great relevance to green chemistry because of the diminished generation of waste from organic solvents and chromatographic stationary phases associated with a lower number of intermediate purification steps. In this context, multicomponent reactions (MCRs)[4] have emerged as a powerful tool to achieve synthetic efficiency, as they have unique advantages such as convergence, operational simplicity, facile automation, flexibility, and pot, atom and step economy (PASE),[5] besides diminished waste generation. MCRs enable the expedient assembly of structurally complex molecules and also furnish structurally diverse libraries of drug-like molecules,[6,7] thereby playing a pivotal role in lead identification and optimization processes in drug discovery programmes.[8] Another approach to the generation of molecular diversity involves the use of chemodivergent reactions, which give differentiated products upon subtle changes in the reaction conditions or in the structure of the starting materials and are thus of interest for the rapid preparation of structurally diverse organic compounds. However, chemodivergent multicomponent reactions are almost unknown in the literature.[9] Furthermore, the development of multicomponent reactions in aqueous environments is a recent endeavour that has received relatively little attention.[10,11]

The dihydropyrano[2,3-*c*]pyrazole scaffold represents an interesting template in medicinal chemistry, and its derivatives possess useful biological and pharmacological properties.[12] The methods available for the synthesis of dihydropyrano[2,3-*c*]pyrazoles include a two-component reaction of

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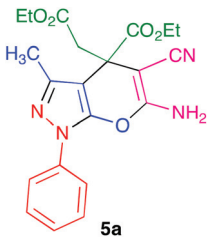
†Electronic supplementary information (ESI) available: Copies of ^{1}H- and ^{13}C-NMR spectra of all compounds, 2D-NMR and HRMS spectra for selected compounds and X-ray diffraction data for compounds **5g** and **7a**. CCDC 896612 and 894543. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3gc37128j

pyrazolones with aldehydes in the presence of tetrabutylammonium hydrogen sulfate in acetonitrile or xylene[13] and three-component reactions of (i) 1*H*-pyrazol-5(4*H*)-one, malononitrile and aldehydes,[14] or substituted piperidin-4-ones.[15] Four-component reactions of unsubstituted hydrazines, β-keto esters, malononitrile or ethyl cyanoacetate and aldehydes[16] or ketones are also known.[17] However, these methods lack generality and do not allow the presence of functional groups at certain positions such as C-4, thus restricting the possibility of generating molecular diversity from the MCR products.

In this context, in the present paper we describe work that proves that the L-proline catalyzed multicomponent reaction in water between phenylhydrazines, β-ketoesters and acetylene mono- or dicarboxylates in the presence of activated nitriles follows two chemodivergent pathways, depending on the structure of the acetylene component. The choice of acetylene-derived esters as electrophiles was motivated by the highly functionalized nature of the products arising from them, which will facilitate their future use in diversity-oriented synthesis. The present work forms a part of our ongoing research programme on the development of novel multi-component and domino reactions for the construction of biologically important heterocyclic ring systems.[10b,18] The choice of L-proline as the catalyst was based on the fact that it is an eco-friendly and abundantly available bifunctional organocatalyst capable of playing multiple catalytic roles as an acid, base, or nucleophile, forming enamine and iminium cations. Being amphoteric and soluble in water, it also facilitates chemical transformations in concert, similar to enzymatic catalysis, and in fact L-proline has been described as "the smallest enzyme".[19] The versatile catalytic ability of L-proline is reflected in its applications in diverse organic transformations such as aldol[20] and Knoevenagel[21] condensations, Michael addition,[22] and some multicomponent reactions,[23] among others.



5a

Fig. 1 Structure of compound **5a**, synthesized during the optimization studies.

Table 1 Optimization of the synthesis of compound **5a**[a]

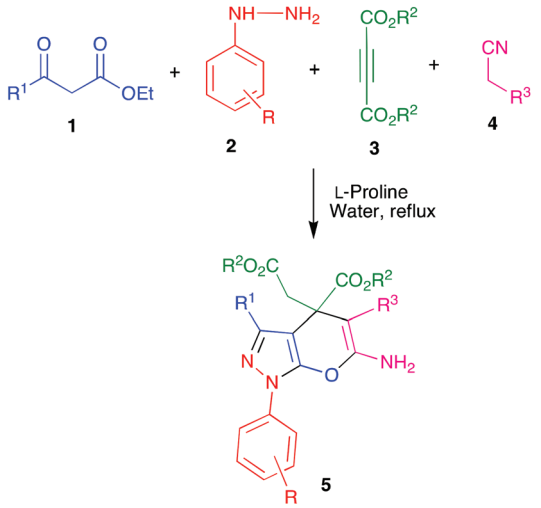
Entry	Additive	Solvent	Reaction time (h)	Yield of **5a**[b] (%)
1	Et_3N	Water	6	78
2	Methylamine	Water	5	73
3	Benzylamine	Water	5	71
4	Pyrrolidine	Water	6	68
5	Piperidine	Water	6	63
6	DBU	Water	7	59
7	DABCO	Water	7	54
8	K_2CO_3	Water	6	64
9	L-Proline	Water	3	97
10	L-Proline	EtOH	5	66
11	L-Proline	MeOH	6	64
12	L-Proline	CH_3CN	8	56
13	L-Proline	DMF	6	62
14	L-Proline	None[c]	5	73
15	None	Water	8	0
16	PPTS	Water	10	58
17	Et_3N/CF_3CO_2H	Water	12	10
18	Pyrrolidine/HCO_2H	Water	7	70
19	TsOH	Water	10	0[d]
20	CH_3CO_2H	Water	10	0[d]

[a] All reactions carried out with ethyl acetoacetate (1 mmol), phenylhydrazine (1 mmol), diethyl acetylenedicarboxylate (1 mmol), malononitrile (1 mmol) and a catalyst (0.3 eq. for L-proline, 1 eq. for other additives) in solvents heated to reflux. [b] Yield of the isolated product. [c] This reaction was performed at 100 °C. [d] 3-Methyl-1-phenyl-2-pyrazolin-5-one (intermediate **I** in Scheme 3) was obtained in these cases (42% and 95% yield, respectively).

Results and discussion

We began our study with the optimization of the four-component reaction in water between equimolecular amounts of ethyl acetoacetate, phenylhydrazine, diethyl acetylenedicarboxylate and malononitrile. This reaction was initially carried out in the presence of 1 eq. of triethylamine under reflux for 6 h, and afforded ethyl 6-amino-5-cyano-4-(2-ethoxy-2-oxoethyl)-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole-4-carboxylate **5a** (Fig. 1).

This model reaction afforded compound **5a** in 78% yield (Table 1, entry 1). It was also investigated employing as bases equimolecular amounts of other amines, including methylamine (entry 2), benzylamine (entry 3), pyrrolidine (entry 4), and piperidine (entry 5), with similar results in all cases. The yield was slightly lower when DBU (entry 6) or DABCO (entry 7) was employed, and did not improve upon use of potassium carbonate (entry 8). Interestingly, when L-proline was used, the reactivity was much improved, since 30 mol% of the additive was sufficient to enable the reaction to go to completion in 3 h affording an excellent yield of 97%, rendering the process catalytic with respect to the base (Table 1, entry 9). When the same reagents were mixed in other solvents such as ethanol (entry 10), methanol (entry 11), acetonitrile (entry 12) and *N*,*N*-dimethylformamide (entry 13), as well as under solvent-free conditions (entry 14), lower yields of the product were observed. These observations led to the conclusion that water is the solvent of choice for this proline-promoted transformation, although a control experiment proved that water alone cannot promote the reaction (entry 15). One clear advantage of the L-proline–water combination was that it afforded products that could be rendered very pure by simple recrystallization from ethanol or by filtration through a pad of silica gel. In order to provide additional data for the mechanistic discussion (see below), we also examined the role of three equimolecular base/acid combinations, which may be viewed as related to proline in that the latter simultaneously contains carboxylic



Scheme 1 Four-component synthesis of 4*H*-pyrano[2,3-*c*]pyrazole derivatives **5**.

and amino functions. An equimolecular mixture of pyridine and toluenesulfonic acid (PPTS) gave 58% of compound **5a** (entry 16). While a mixture of triethylamine and trifluoroacetic acid gave a poor result (entry 17), the pyrrolidine–formic acid combination, which is more closely related to proline, afforded a respectable 70% yield (entry 18), although a longer reaction time (7 h) and one equivalent of this mixture were needed. Purely acidic additives, such as toluenesulfonic acid and acetic acid, did not afford compound **5a**, but instead gave the pyrazolinone derivative arising from condensation between phenylhydrazine and ethyl acetoacetate.

After determining the optimal conditions, the scope of the reaction was further examined. As shown in Scheme 1 and Table 2, the four-component reactions of ethyl acetoacetate or ethyl 3-oxohexanoate **1** (1 mmol), phenylhydrazines **2** (1 mmol), dialkyl acetylenedicarboxylates **3** (1 mmol) and malononitrile or ethyl cyanoacetate **4** (1 mmol) in the presence of L-proline (0.3 mmol) in water under reflux for 3–3.5 h afforded

Table 2 One-pot, four-component synthesis of 3-alkyl-1-aryl-1,4-dihydropyrano[2,3-*c*]pyrazol-6-amines **5**[a]

Cmpd.	R	R^1	R^2	R^3	Time (h)	Yield[b] (%)
5a	H	CH_3	C_2H_5	CN	3.0	97
5b	H	CH_3	CH_3	CN	3.0	94 (87)
5c	H	CH_3	C_2H_5	CO_2Et	3.5	92
5d	H	CH_3	CH_3	CO_2Et	3.5	93 (86)
5e	2,5-$(CH_3)_2$	CH_3	C_2H_5	CN	3.0	97
5f	4-Cl	CH_3	CH_3	CO_2Et	3.5	95
5g	H	$CH_2CH_2CH_3$	CH_3	CN	3.0	96
5h	4-F	CH_3	CH_3	CO_2Et	3.5	92 (83)
5i	4-F	CH_3	CH_3	CN	3.5	90 (85)

[a] All reactions carried out with ethyl acetoacetate (1 mmol), phenylhydrazine (1 mmol), diethyl acetylenedicarboxylate (1 mmol), malononitrile (1 mmol) and L-proline (0.3 eq.). [b] Yields after filtration through a pad of silica gel; in brackets, yields after recrystallization from ethanol.

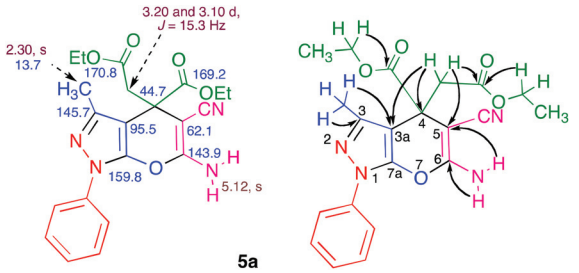


Fig. 2 Selected ^1H and ^{13}C chemical shifts and summary of the HMBC experiments performed on **5a**.

a series of 3-alkyl-1-aryl-1,4-dihydropyrano[2,3-*c*]pyrazol-6-amines **5a–5i** in excellent yield.

The structure of compounds **5** was established from one- and two-dimensional NMR spectroscopic data, as illustrated in Fig. 2 for compound **5a** as a representative example. The ^1H NMR spectrum of **5a** has a singlet at 2.30 ppm, ascribable to methyl hydrogens at C-3. The diastereotopic 1′-CH_2 hydrogens appear as doublets at 3.10 and 3.20 ppm (J = 15.3 Hz). These assignments are evident from the HMBCs of diastereotopic proton, (H-1′) with (i) the carbonyl carbon at 169.2 ppm, (ii) the quaternary carbon C-4 at 44.7 ppm and (iii) C-5 and C-3a at 62.1 and 95.5 ppm respectively. The methyl hydrogens at C-3 also show HMBCs with C-3 and C-3a at 145.7 and 95.5 ppm respectively. The NH_2 protons appear as a singlet at 5.12 ppm, which shows HMBCs with C-6 and C-5 at 143.9 and 62.1 ppm respectively. Finally, the conclusions obtained by NMR were confirmed by X-ray diffraction of a single crystal of compound **5g** (Fig. 3). Because of the chiral nature of L-Pro, we wished to ascertain whether there was any enantiodifferentiation in the formation of compounds **5**. However, all of them failed to show any measurable optical rotation, and analysis of representative compounds **5a** and **5f** using a chiral HPLC column showed them to be racemic. Not unexpectedly in view of this lack of enantioselection, D-proline and racemic proline in water under reflux for 3 h led to identical yields of racemic **5a** (93% and 90%).

During our studies on the scope of the reaction, we found that replacement of dialkyl acetylenedicarboxylates **3** by ethyl

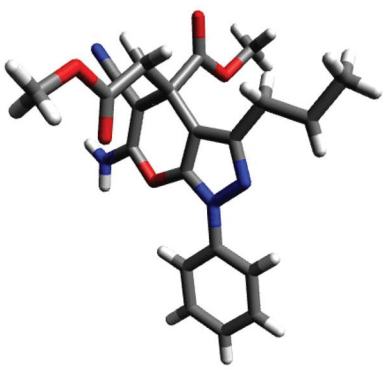
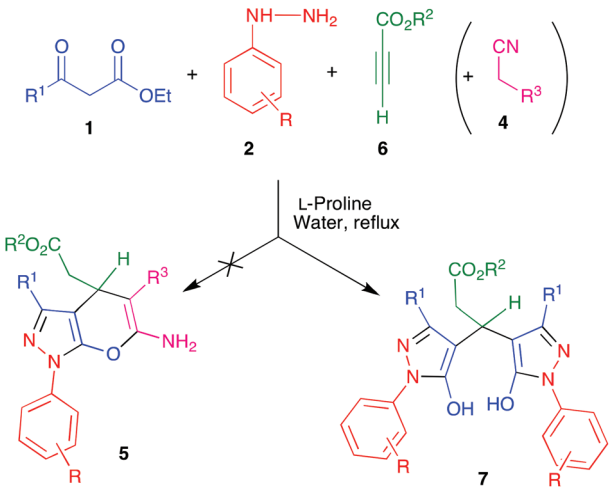


Fig. 3 X-Ray diffraction study of compound **5g**.



Scheme 2 Synthesis of 3,3-bis(1*H*-pyrazol-4-yl)propanoate derivatives **7**.

propiolate led to the exclusive formation of ethyl 3,3-bis-(5-hydroxy-3-alkyl-1-phenyl-1*H*-pyrazol-4-yl)propanoate **7a** in good yield, revealing that in this case the activated nitrile was excluded from the multicomponent process. Indeed, the same result was obtained when malononitrile was not added to the reaction mixture. This observation led us to synthesize a small library of compounds **7** from the pseudo-five component reactions of ethyl acetoacetate or ethyl 3-oxohexanoate **1** (2 mmol), phenylhydrazines **2** (2 mmol) and methyl propiolate or ethyl propiolate **6** (1 mmol) in the presence of L-proline (30 mol%), in water under reflux for 3–3.5 h (Scheme 2 and Table 3).

The structure of compounds **7** was confirmed by the X-ray diffraction study of a single crystal of **7a** (Fig. 4). It is interesting to note that, against the behavior normally observed for 2-pyrazolin-5-ones, both pyrazole rings in **7a** are in the lactim tautomeric form, which is presumably stabilized by intramolecular hydrogen bonding.

A plausible mechanism for the formation of compounds **5** and **7** is depicted in Scheme 3. The first reaction, common to both mechanisms, probably involves the generation of pyrazolone **I** by the formation of a hydrazone from the starting

Table 3 Synthesis of alkyl 3,3-bis(5-hydroxy-3-alkyl-1-phenyl-1*H*-pyrazol-4-yl)-propanoates **7**[a]

Cmpd.	R	R^1	R^2	Time (h)	Yield[b] (%)
5a	H	CH_3	CH_3	3.0	95 (86)
5b	H	CH_3	C_2H_5	3.0	96
5c	Cl	CH_3	CH_3	3.5	94
5d	Cl	CH_3	C_2H_5	3.5	91
5e	H	$CH_2CH_2CH_3$	CH_3	3.0	96

[a] All reactions carried out with ethyl acetoacetate (1 mmol), phenylhydrazine (1 mmol), diethyl acetylenedicarboxylate (1 mmol), malononitrile (1 mmol) and L-proline (0.3 eq.). [b] Yields after filtration through a pad of silica gel; in brackets, yields after recrystallization from ethanol.

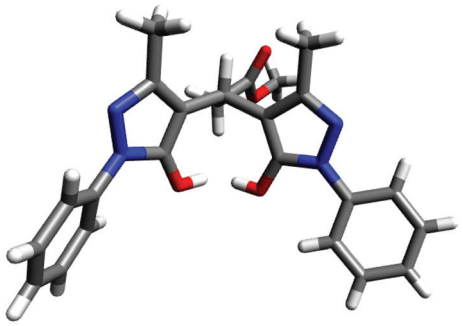
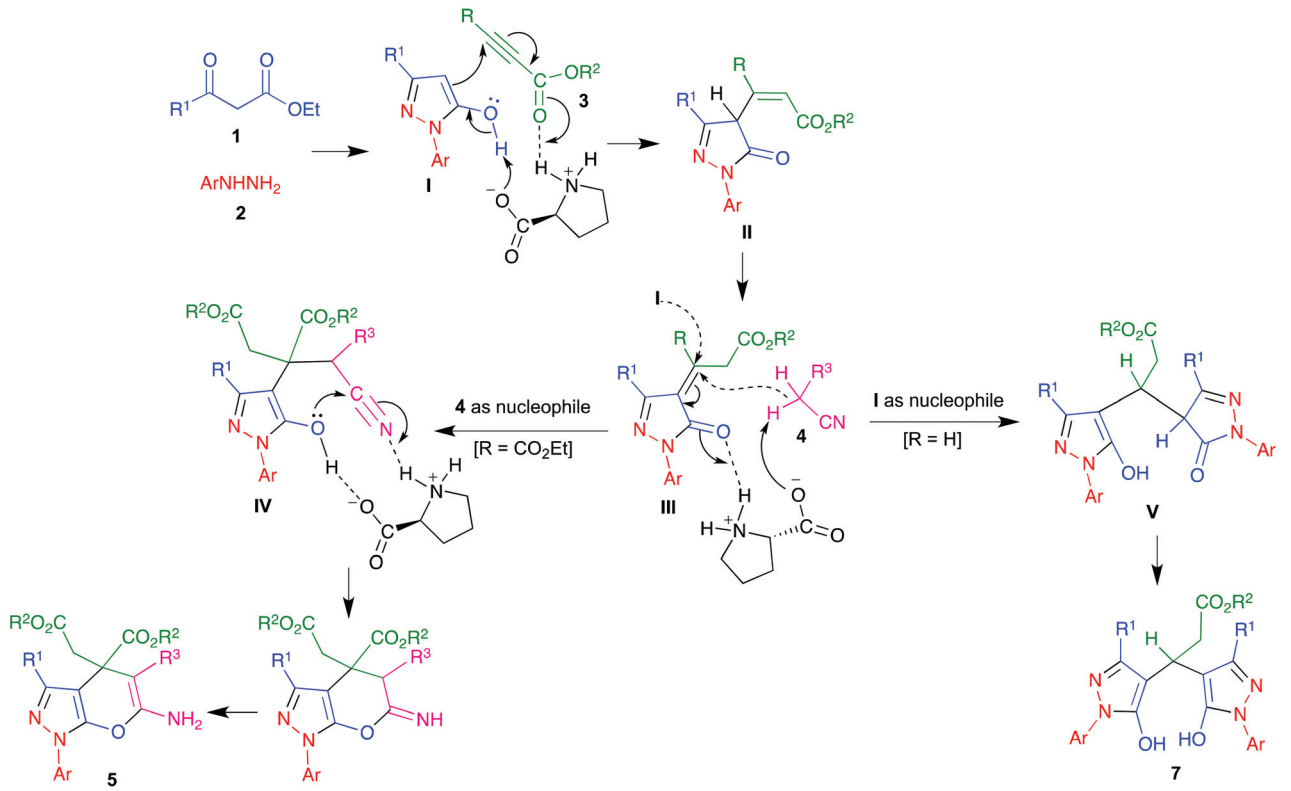


Fig. 4 X-Ray diffraction structure of compound **7a**.

β-ketoester **1** and phenylhydrazine **2**, followed by a subsequent cyclocondensation. A subsequent Michael addition of **I** to the acetylenedicarboxylate **3** furnishes intermediate **II**, which isomerizes to **III** *via* a [1,3] hydrogen shift. The next step involves a new Michael addition to the enone system in **III**, for which two nucleophiles are available in the reaction medium, namely a second molecule of **I** or the activated nitrile **4**. Owing to steric hindrance, in the case of R = CO_2Et, **III** selectively reacts with the less hindered nucleophile **4** and affords intermediate **IV**, which upon annulation with a concomitant tautomerization results in the formation of the observed final products **5**. On the other hand, for the case R = H the only observed reaction involves the participation of **I** as the nucleophile, leading to intermediate **V** and then to the observed product **7** by tautomerism.

In many of these steps, including the initial reaction between phenylhydrazine and the starting β-ketoester, the L-proline zwitterion, which is the predominant species in aqueous solution, can conceivably play dual catalytic roles, acting as an acid and a base in concert, and this explains the fact that the other bases investigated for this transformation were less efficient than L-proline. The greater efficiency of proline in comparison to the pyrrolidine–formic acid mixture can be ascribed to entropic factors associated with the presence of acidic and basic functions in the same molecule.

The greater efficacy of water in this transformation compared to other solvents investigated such as methanol, ethanol, acetonitrile and DMF suggests that the reactions described here belong to the "on-water" type,[24] which is rather uncommon for multicomponent reactions[25] and involves hydrogen bonding with the oxygen atom of water molecules surrounding the suspended oily globules containing the reactants. This type of mechanism also explains the fact that we have observed some promotion of the reaction by potassium carbonate (Table 1, entry 8), which is explained by the same type of association with hydroxide anions present in the aqueous phase, which are generated by hydrolysis of the carbonate anion, and which may assist both the formation of pyrazolinone intermediate **I** by deprotonating phenylhydrazine molecules and the annulation of **IV** that leads ultimately to the formation of **5** (Scheme 3).



Scheme 3 Mechanistic rationalization of the processes leading to compounds **5** and **7**.

Conclusions

In conclusion, the present work describes eco-friendly multicomponent protocols for the synthesis in excellent yields of 3-alkyl-1-aryl-1,4-dihydropyrano[2,3-*c*]pyrazol-6-amines by the creation of two rings and two C–C, one C–N, one C═N and one C–O bonds, or alkyl 3,3-bis(5-hydroxy-3-alkyl-1-phenyl-1*H*-pyrazol-4-yl)propanoates by the generation of two rings and two C–C, two C–N and two C═N bonds, employing water as the reaction medium and L-proline as the catalyst. This new methodology is endowed with advantages such as short reaction time, excellent yields and ease of operation. Our study also discloses a subtle dependence of the product-selectivity of the reactions on the nature of the alkyne component employed, which renders these processes one of the rare cases of chemodivergent multicomponent reactions performed in an aqueous reaction medium.

Experimental section

Melting points were measured in open capillary tubes and are uncorrected. The ^{1}H NMR, ^{13}C NMR, H,H-COSY, C,H-COSY and HMBC spectra were recorded on a Bruker (Avance) 300 MHz NMR instrument using TMS as an internal standard and $CDCl_3$ as solvent. Standard Bruker software was used throughout. Chemical shifts are given in parts per million (δ scale) and coupling constants are given in hertz. Silica gel-G plates (Merck) were used for TLC analysis with a mixture of petroleum ether (60–80 °C) and ethyl acetate as an eluent. Elemental analyses were performed on a Perkin Elmer 2400 Series II Elemental CHNS analyzer. HRMS measurements were performed by the CAI de Espectrometría de Masas, Universidad Complutense, using an FTMS Bruker APEX QIV instrument. Optical rotation values were measured using an AUTOPOL-IV digital polarimeter (readability ±0.001°). HPLC analyses were performed on an SCL-10ATVP SHIMADZU instrument. Compounds **5a** and **5f** were analyzed using a chiral cell OD-H column using hexane/2-propanol as an eluent.

General procedure for the synthesis of 3-alkyl-1-aryl-1,4-dihydropyrano[2,3-*c*]pyrazol-6-amines 5a–5i

A mixture of ethyl acetoacetate or ethyl 3-oxohexanoate (**1**) (1 mmol), phenylhydrazines (**2**) (1 mmol), dialkyl acetylenedicarboxylates (**3**) (1 mmol), malononitrile or ethyl cyanoacetate (**4**) (1 mmol) and L-proline (30 mol%) in water (5 mL) was heated under reflux for 3.0–3.5 h. After completion of the reaction (TLC), the solid that separated was filtered, washed with water and purified by recrystallization from ethanol (compounds **5b**, **5d**, **5h**, **5i**) or by filtration through a pad of silica gel using petroleum ether–ethyl acetate (7 : 3 v/v). Characterization data for compounds **5** are given below.

Ethyl 6-amino-5-cyano-4-(2-ethoxy-2-oxoethyl)-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole-4-carboxylate (5a)

Yield, 398 mg (97%) after silica gel filtration. Colorless solid, mp 112–113 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 1.09 (t, J = 7.1 Hz, 3H), 1.30 (t, J = 7.2 Hz, 3H), 2.30 (s, 3H), 3.11 (d, J = 15.3 Hz, 1H), 3.20 (d, J = 15.3 Hz, 1H), 4.00 (q, J = 7.2 Hz, 2H), 4.26 (q, J = 7.2 Hz, 2H), 5.13 (s, 2H, NH_2), 7.28–7.31 (m, 1H), 7.42 (t, J = 7.7 Hz, 2H), 7.59 (d, J = 7.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 13.7, 13.9, 14.0, 40.3, 44.7, 60.4, 62.1, 62.5, 95.5, 117.7, 121.3, 126.9, 129.2, 137.3, 144.0, 145.7, 159.8, 169.2, 170.8; Anal. Calcd for $C_{21}H_{22}N_4O_5$: C, 61.45; H, 5.40; N, 13.65. Found: C, 61.56; H, 5.47; N, 13.56.

Methyl 6-amino-5-cyano-4-(2-methoxy-2-oxoethyl)-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole-4-carboxylate (5b)

Yield, 359 mg (94%) after silica gel filtration or 332 mg (87%) after recrystallization from ethanol. Colorless solid, mp 198–199 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 2.28 (s, 3H), 3.14 (d, J = 15.9 Hz, 1H), 3.23 (d, J = 15.9 Hz, 1H), 3.58 (s, 3H), 3.80 (s, 3H), 5.04 (s, 2H, NH_2), 7.27–7.33 (m, 1H), 7.43 (t, J = 7.8 Hz, 2H), 7.60 (d, J = 7.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 13.6, 40.0, 44.7, 51.7, 53.3, 62.1, 95.5, 117.7, 121.5, 127.0, 129.2, 137.3, 144.0, 145.5, 159.8, 169.6, 171.3; Anal. Calcd for $C_{19}H_{18}N_4O_5$: C, 59.68; H, 4.74; N, 14.65. Found: C, 59.59; H, 4.62; N, 14.76.

Diethyl 6-amino-4-(2-ethoxy-2-oxoethyl)-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole-4,5-dicarboxylate (5c)

Yield, 421 mg (92%) after silica gel filtration. Colorless solid, mp 172–173 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 1.04 (t, J = 7.1 Hz, 3H), 1.20–1.30 (m, 6H), 2.24 (s, 3H), 3.22 (d, J = 15.0 Hz, 1H), 3.30 (d, J = 15.0 Hz, 1H), 3.92 (q, J = 6.9 Hz, 2H), 4.10–4.24 (m, 4H), 6.78 (s, 2H, NH_2), 7.24–7.29 (m, 1H), 7.41 (t, J = 7.7 Hz, 2H), 7.64 (d, J = 7.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 13.1, 13.9, 14.0, 14.1, 40.9, 44.4, 59.9, 61.4, 78.4, 97.7, 121.1, 126.5, 129.1, 137.6, 144.0, 145.2, 160.5, 168.5, 170.7, 172.7; Anal. Calcd for $C_{23}H_{27}N_3O_7$: C, 60.38; H, 5.95; N, 9.19. Found: C, 60.31; H, 6.05; N, 9.25.

5-Ethyl 4-methyl 6-amino-4-(2-methoxy-2-oxoethyl)-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole-4,5-dicarboxylate (5d)

Yield, 399 mg (93%) after silica gel filtration or 369 mg (86%) after recrystallization from ethanol. Colorless solid, mp 211–212 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 1.26 (t, J = 7.1 Hz, 3H), 2.22 (s, 3H), 3.23 (d, J = 15.6 Hz, 1H), 3.31 (d, J = 15.6 Hz, 1H), 3.48 (s, 3H), 3.69 (s, 3H), 4.11–4.29 (m, 2H), 6.75 (s, 2H, NH_2), 7.26–7.30 (m, 1H), 7.42 (t, J = 7.8 Hz, 2H), 7.65 (d, J = 7.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 13.1, 14.2, 40.3, 44.2, 51.2, 52.5, 60.0, 78.2, 97.5, 121.3, 126.6, 129.1, 137.6, 144.1, 145.0, 160.7, 168.4, 171.1, 173.3. HRMS (ESI): Calcd for $C_{21}H_{23}N_3O_7Na$ (M^+ + Na): 452.14337. Found: 452.14282. Anal. Calcd for $C_{21}H_{23}N_3O_7$: C, 58.74; H, 5.40; N, 9.79. Found: C, 58.86; H, 5.48; N, 9.69.

Ethyl 6-amino-5-cyano-1-(2,5-dimethylphenyl)-4-(2-ethoxy-2-oxoethyl)-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazole-4-carboxylate (5e)

Yield, 426 mg (97%) after silica gel filtration. Colorless solid, mp 152–153 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 1.13–1.17 (m, 3H), 1.28–1.33 (m, 3H), 2.08 (s, 3H), 2.28 (s, 3H), 2.34 (s, 3H), 3.08–3.24 (m, 2H), 4.02 (q, J = 6.8 Hz, 2H), 4.23–4.30 (m, 2H), 4.84 (s, 2H, NH_2), 7.10–7.27 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 13.7, 14.0, 14.1, 16.8, 20.6, 40.3, 44.9, 60.4, 62.4, 94.0, 117.8, 128.0, 129.6, 130.2, 130.8, 132.3, 135.2, 136.6, 144.8, 145.3, 159.8, 169.2, 170.9. HRMS (ESI): Calcd for $C_{23}H_{26}N_4O_5Na$ (M^+ + Na): 461.18009. Found: 461.17954. Anal. Calcd for $C_{23}H_{26}N_4O_5$: C, 63.00; H, 5.98; N, 12.78. Found: C, 63.08; H, 5.87; N, 12.90.

5-Ethyl 4-methyl 6-amino-1-(4-chlorophenyl)-4-(2-methoxy-2-oxoethyl)-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazole-4,5-dicarboxylate (5f)

Yield, 441 mg (95%) after silica gel filtration. Colorless solid, mp 219–220 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 1.26 (t, J = 7.1 Hz, 3H), 2.20 (s, 3H), 3.23 (d, J = 15.9 Hz, 1H), 3.31 (d, J = 15.9 Hz, 1H), 3.49 (s, 3H), 3.69 (s, 3H), 4.13–4.27 (m, 2H), 6.77 (s, 2H, NH_2), 7.36–7.39 (m, 2H) 7.60–7.63 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 13.1, 14.2, 40.2, 44.1, 51.3, 52.6. 60.1, 78.3, 97.9, 122.2, 129.9, 132.1, 136.2, 144.2, 145.4, 160.6, 168.3, 171.1, 173.2. HRMS (ESI): Calcd for $C_{21}H_{22}ClN_3O_7Na$ (M^+ + Na): 486.10440 (^{35}Cl) and 488.10145 (^{37}Cl). Found: 486.10385 and 488.10090. Anal. Calcd for $C_{21}H_{22}ClN_3O_7$: C, 54.37; H, 4.78; N, 9.06. Found: C, 54.43; H, 4.69; N, 8.99.

Methyl 6-amino-5-cyano-4-(2-methoxy-2-oxoethyl)-1-phenyl-3-propyl-1,4-dihydropyrano[2,3-*c*]pyrazole-4-carboxylate (5g)

Yield, 393 mg (96%) after silica gel filtration. Colorless solid, mp 158–159 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 1.00 (t, J = 7.4 Hz, 3H), 1.64–1.81 (m, 2H), 2.52–2.57 (m, 2H), 3.15 (d, J = 16.2 Hz, 1H), 3.23 (d, J = 15.9 Hz, 1H), 3.56 (s, 3H), 3.78 (s, 3H), 5.10 (s, 2H, NH_2), 7.27–7.32 (m, 1H), 7.42 (t, J = 7.8 Hz, 2H), 7.62 (d, J = 8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 13.9, 21.2, 29.7, 40.0, 44.6, 51.6, 53.2, 61.7, 95.2, 117.7, 121.4, 126.9, 129.1, 137.4, 143.9, 149.0, 160.0, 169.8, 171.6; Anal. Calcd for $C_{21}H_{22}N_4O_5$: C, 61.45; H, 5.40; N, 13.65. Found: C, 61.35; H, 5.46; N, 13.57.

5-Ethyl 4-methyl 6-amino-1-(4-fluorophenyl)-4-(2-methoxy-2-oxoethyl)-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazole-4,5-dicarboxylate (5h)

Yield, 412 mg (92%) after silica gel filtration or 371 mg (83%) after recrystallization from ethanol. Colorless solid, mp 97–98 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 1.25 (t, J = 7.2 Hz, 3H), 2.19 (s, 3H), 3.22 (d, J = 16.2 Hz, 1H), 3.30 (d, J = 15.9 Hz, 1H), 3.48 (s, 3H), 3.68 (s, 3H), 4.09–4.27 (m, 2H), 6.78 (s, 2H, NH_2), 7.06–7.12 (m, 2H) 7.57–7.62 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 13.0, 14.2, 40.3, 44.2, 51.2, 52.5, 60.0, 78.2, 97.5, 115.8, 116.1, 123.0, 123.1, 133.8, 144.1, 145.0, 159.5,

160.6, 162.8, 168.3, 171.1, 173.2; Anal. Calcd for $C_{21}H_{22}FN_3O_7$: C, 56.37; H, 4.96; N, 9.39; Found: C, 56.28; H, 4.90; N, 9.46.

Methyl 6-amino-5-cyano-1-(4-fluorophenyl)-4-(2-methoxy-2-oxoethyl)-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazole-4-carboxylate (5i)

Yield, 360 mg (90%) after silica gel filtration or 340 mg (85%) after recrystallization from ethanol. Colorless solid, mp 214–215 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 2.27 (s, 3H), 3.15 (d, J = 15.9 Hz, 1H), 3.23 (d, J = 16.2 Hz, 1H), 3.58 (s, 3H), 3.80 (s, 3H), 4.98 (s, 2H, NH_2), 7.10–7.16 (m, 2H) 7.55–7.60 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 12.7, 43.7, 50.7, 52.2, 57.7, 94.6, 114.9, 115.2, 117.7, 121.8, 121.9, 132.9, 143.4, 144.5, 158.4, 160.0, 161.6, 168.7, 170.9; Anal. Calcd for $C_{19}H_{17}FN_4O_5$: C, 57.00; H, 4.28; N, 13.99. Found: C, 57.10; H, 4.36; N, 13.90.

General procedure for the synthesis of alkyl 3,3-bis(5-hydroxy-3-alkyl-1-phenyl-1*H*-pyrazol-4-yl)propanoates 7a–7e

A mixture of ethyl acetoacetate or ethyl 3-oxohexanoate (**1**) (2 mmol), phenylhydrazines (**2**) (2 mmol), methyl propiolate or ethyl propiolate (**6**) (1 mmol), and L-proline (30 mol%) in water was heated to reflux for 3.0–3.5 h. After completion of the reaction (TLC), the solid that separated was filtered, washed with water and purified by recrystallization from ethanol (compound **7a**) or by filtration through a pad of silica gel using petroleum ether–ethyl acetate (6 : 4 v/v). Characterization data for compounds **7** are given below.

Methyl 3,3-bis(5-hydroxy-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-propanoate (7a)

Yield, 411 mg (95%) after silica gel filtration or 372 mg (86%) after recrystallization from ethanol. Colorless solid, mp 201–202 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 2.01 (s, 6H), 3.04 (d, J = 7.5 Hz, 2H), 3.56 (s, 3H), 3.86–3.88 (m, 1H), 7.08 (t, J = 7.5 Hz, 2H), 7.24–7.30 (m, 4H), 7.55 (d, J = 7.5 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 11.4, 25.4, 36.1, 51.5, 105.5, 121.4, 126.2, 128.8, 136.9, 146.0, 157.8, 172.8. HRMS (ESI): Calcd for $C_{24}H_{24}N_4O_4$ (M^+ + 1): 433.18856. Found: 433.18703. Anal. Calcd for $C_{24}H_{24}N_4O_4$ C, 66.65; H, 5.59; N, 12.96. Found: C, 66.77; H, 5.52; N, 12.90.

Ethyl 3,3-bis(5-hydroxy-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-propanoate (7b)

Yield, 426 mg (96%) after silica gel filtration. Colorless solid, mp 165–166 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 1.12 (t, J = 7.2 Hz, 3H), 2.03 (s, 6H), 3.04 (d, J = 7.8 Hz, 2H), 3.89 (t, J = 7.8 Hz, 1H), 4.00 (q, J = 7.2 Hz, 2H), 7.10 (t, J = 7.5 Hz, 2H), 7.26–7.31 (m, 5H), 7.57 (d, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 11.5, 14.1, 25.7, 36.5, 60.3, 105.9, 121.3, 126.2, 128.9, 137.1, 146.2 158.0, 172.4. HRMS (ESI): Calcd for $C_{25}H_{26}N_4O_4Na$ (M^+ + Na): 469.18518. Found: 469.18087. Anal. Calcd for $C_{25}H_{26}N_4O_4$: C, 67.25; H, 5.87; N, 12.55. Found: C, 67.14; H, 5.96; N, 12.47.

Methyl 3,3-bis(1-(4-chlorophenyl)-5-hydroxy-3-methyl-1*H*-pyrazol-4-yl)propanoate (7c)

Yield, 471 mg (94%) after silica gel filtration. Colorless solid, mp 128–129 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 2.26 (s, 6H), 3.12 (d, J = 7.8 Hz, 2H), 3.62 (s, 3H), 4.05 (t, J = 7.7 Hz, 1H), 7.26–7.32 (m, 4H), 7.56–7.59 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 11.6, 25.6, 36.3, 51.6, 106.0, 122.3, 129.0, 131.7, 135.6, 146.6, 158.1, 172.7. HRMS (ESI): Calcd for $C_{25}H_{24}Cl_2N_4O_4Na$ (M^+ + Na): 537.10723. Found: 537.10668. Anal. Calcd for $C_{24}H_{22}Cl_2N_4O_4$: Elemental Analysis: C, 57.49; H, 4.42; N, 11.17. Found: C, 57.39; H, 4.36; N, 11.26.

Ethyl 3,3-bis(1-(4-chlorophenyl)-5-hydroxy-3-methyl-1*H*-pyrazol-4-yl)propanoate (7d)

Yield, 469 mg (91%) after silica gel filtration. Colorless solid, mp 125–126 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 1.15 (t, J = 6.9 Hz, 3H), 2.20 (s, 6H), 3.06 (d, J = 7.5 Hz, 2H), 3.99–4.06 (m, 3H), 7.25 (d, J = 8.4 Hz, 4H), 7.49 (d, J = 8.4 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 11.5, 14.1, 25.6, 36.6, 60.5, 105.8, 122.3, 128.9, 131.7, 135.4, 146.5 158.0, 172.2; Anal. Calcd for $C_{25}H_{24}Cl_2N_4O_4$: C, 58.26; H, 4.69; N, 10.87. Found: C, 58.35; H, 4.63; N, 10.95.

Methyl 3,3-bis(5-hydroxy-1-phenyl-3-propyl-1*H*-pyrazol-4-yl)-propanoate (7e)

Yield, 469 mg (96%) after silica gel filtration. Colorless solid, mp 154–155 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 0.95 (t, J = 7.4 Hz, 6H), 1.47–1.66 (m, 4H), 2.44 (t, J = 7.8 Hz, 4H), 3.05 (d, J = 7.5 Hz, 2H), 3.56 (s, 3H), 4.00 (t, J = 7.7 Hz, 1H), 7.07–7.13 (m, 2H), 7.24–7.29 (m, 4H), 7.54 (d, J = 8.4 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 14.0, 14.1, 22.3, 22.4, 25.6, 28.3, 36.8, 51.4, 51.5, 105.2, 121.4, 126.1, 128.7, 137.0, 150.1, 157.9, 172.6; Anal. Calcd for $C_{28}H_{32}N_4O_4$: C, 68.83; H, 6.60; N, 11.47; Found: C, 68.71; H, 6.67; N, 11.53.

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