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Multicomponent domino reactions of acetylenedicarboxylates: divergent synthesis of multi-functionalized pyrazolones and C-tethered bispyrazol-5-ols

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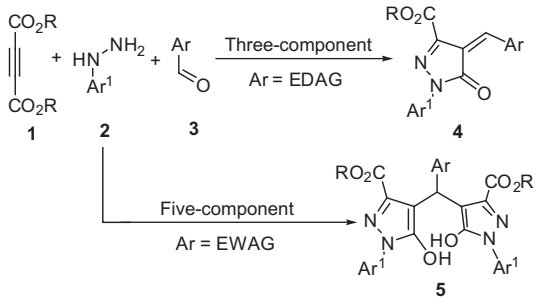
ABSTRACT

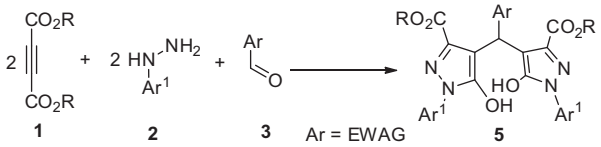
An efficient and practical methodology of selectively divergent synthesis of arylidene pyrazolones and C-tethered bispyrazol-5-ols via multicomponent domino reactions of acetylenedicarboxylates, phenylhydrazine and aromatic aldehydes has been developed. The electron-donating aryl groups (EDAG)-attached aldehydes resulted in the pyrazolone skeleton, whereas the electron-withdrawing aryl groups (EWAG) led to the C-tethered bispyrazol-5-ols with simultaneous formation of two new pyrazole rings.

The development of new methodologies aimed at improving synthetic efficiency is an important goal in contemporary organic synthesis. Multicomponent domino reactions (MDRs), which involve several bond-forming reactions in a one-pot manipulation, represent an attractive strategy in the facile assembly of molecular architecture.[1,2] Such reactions are able to create combinatorial libraries of complex and diverse structures in efficient fashion by virtue of their convergent nature. Several new designed multicomponent reactions have been reported recently,[3,4] including processes that take advantage of Huisgen 1,4-dipoles formed from the addition of nitrogen heterocycles or amines to electron-deficient alkynes.[5–10] Thus, domino reactions involving primary amines, acetylenedicarboxylates and a third component have been provided elegant procedures for the synthesis of various N- and N,O-heterocycles.[11–14] Still, the continuous development of new multicomponent domino reactions for the synthesis of multi-functionalized heterocycles from activated acetylenes is of great value.

Very recently, we have developed a series of multicomponent domino reactions (MDRs) that provided easy access to multiple functionalized ring structures of chemical and pharmaceutical interest.[15,16] During our continuous efforts on the development of useful multi-component domino reactions, herein, we would like to report another new divergent approach to regioselective synthesis of multi-functionalized pyrazolones and C-tethered bispyrazol-5-ols through the control of electronic effect of aryl aldehydes (Scheme 1). This reaction was achieved from the same starting materials such as aromatic aldehyde, aryl hydrazine and acetylenedicarboxylates in HOAc under microwave irradiation. The great aspect of the present domino reaction is shown by the fact that the selective construction of pyrazolone or C-tethered



Scheme 1. The divergent synthesis of multi-functionalized pyrazolones and C-tethered bispyrazol-5-ols.



Scheme 2. The synthesis of C-tethered bispyrazol-5-ols.

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Table 1
Solvent optimization for the synthesis of **4a**

Entry	Solvent	Time (min)	Yield[a] (%)
1	THF	10	8
2	EtOH	10	39
3	$HOCH_2CH_2OH$	10	53
4	AcOH	10	81

[a] Isolated yield.

bispyrazol-5-ols skeleton was readily achieved via HOAc promoted divergent reaction in a one-pot operation. The electron-donating aryl groups (EDAG)-attached aldehydes resulted in the pyrazolone skeleton, whereas the electron-withdrawing aryl groups (EWAG) led to the C-tethered bispyrazol-5-ols with simultaneous formation of two new pyrazole rings.

We devoted our efforts to the study of the reaction of dimethyl acetylenedicarboxylate (DMAD, **1a**) and phenylhydrazine **2** with 4-methylbenzaldehyde **3a** as a model reaction. Experiments were carried out in various solvents such as ethylene glycol, THF, ethanol and HOAc. Unfortunately, the reaction scarcely proceeded in THF at room temperature. The incomplete reaction was observed in ethylene glycol or ethanol.

When HOAc was used as the solvent, the reaction proceeded (Table 1) smoothly and the product **4a** was successfully isolated in 81% yield after 10 min at the room temperature.

With this result in hand, we went on to study the scope of the methodology. Using the optimized reaction conditions, a variety of structurally diverse aromatic aldehydes were investigated, and a series of new multi-functionalized pyrazolones were afforded in good yields. As shown in Table 2, at the beginning, we made a search for the aldehyde substrate scope, acetylenedicarboxylates **1** (dimethyl acetylenedicarboxylate, **1a**; diethyl acetylenedicarboxylate, **1b**) and phenylhydrazine **2a** were used as model substrates (Table 2), and the results indicated that aromatic aldehydes bearing electron donating groups such as methyl, dimethylamino, or methoxyl were able to affect the synthesis of compound **4**. Interestingly, when aromatic aldehydes with electron-donating groups employed in this system were replaced by their electron-withdrawing counterparts, the reaction occurred to another direction to form multi-functionalized C-tethered bispyrazol-5-ols **5** that belong to another family of important scaffolds for organic synthesis and drug design in pharmaceutical sciences such as fungicides, pesticides, insecticides and dyestuffs, and as the chelating and extracting reagents for different metal ions as well.[17] Thus, it is clear that the divergent pathways were controlled by the electronic effects of various groups on phenyl ring.

Next, with the aim to improve the yields of **5a** in Scheme 2, we increased the amount of acetylenedicarboxylates and phenylhydrazine simultaneously to the feed ratio of **1a**–**2**–**3** in 2:2:1 (Scheme 2). After several trials, we found that the reaction in acidic condition resulted in product **5a** in 89% chemical yield at room temperature. Under the optimized conditions mentioned above, the scope of this new MCR process was next examined using various readily available starting materials. As revealed in Table 2, a range of invaluable C-tethered bispyrazol-5-ols **5** can be synthesized in good to excellent yields. The results indicated that aromatic aldehydes bearing diverse electron-withdrawing functional groups such as nitro, fluoro, chloro or bromo were suitable for the synthesis of compounds **5**.

Moreover, the different heterocyclic aldehydes were further examined. The electron-donating heterocyclic aldehydes such as thiophene-2-carbaldehyde **3f**, indole-3-carbaldehyde **3g** resulted in the corresponding arylidene pyrazolones **4h**–**4k** (Table 2, entries 8–11), whereas C-tethered bispyrazol-5-ol derivatives **5h** , **5i** were generated when electron-withdrawing heterocyclic counterpart **3l** was employed (Table 2, entries 19 and 20). Thus, it may be found that the nature of substituent on formyl group played a crucial role in controlling the chemoselectivity. To further examine the scope of the methodology, other aryl hydrazines were employed, such as electron-donating component **2b** and electron-withdrawing group **2c.** Pleasantly, the corresponding arylidene pyrazolones **4l** (Table 2, entry 12) and C-tethered bispyrazol-5-ol derivatives **5j**, **5k** (Table 2, entries 22 and 23) were generated, respectively.

As shown in Figures 1 and 2, X-ray diffraction of single crystals of pyrazolones **4b** and C-tethered bispyrazol-5-ols **5d** has been

Table 2
Syntheses of arylidene pyrazolones **4** and bispyrazoles **5**[18,19]

Entry	**4** or **5**[a]	Ar	Ar[1]	R	Time (min)	Yield[b] (%)
1	**4a**	4-Tolyl (**3a**)	Phenyl (**2a**)	Methyl (**1a**)	10	81
2	**4b**	4-Methoxyphenyl (**3b**)	Phenyl (**2a**)	Ethyl (**1b**)	10	79
3	**4c**	3,4-Dimethoxyphenyl (**3c**)	Phenyl (**2a**)	Methyl (**1a**)	12	85
4	**4d**	3,4-Dimethoxyphenyl (**3c**)	Phenyl (**2a**)	Ethyl (**1b**)	12	86
5	**4e**	3,4,5-Trimethoxyphenyl (**3d**)	Phenyl (**2a**)	Methyl (**1a**)	15	91
6	**4f**	3,4,5-Trimethoxyphenyl (**3d**)	Phenyl (**2a**)	Ethyl (**1b**)	15	90
7	**4g**	4-Dimethylaminophenyl (**3e**)	Phenyl (**2a**)	Ethyl (**1b**)	13	83
8	**4h**	Thiophen-2-yl (**3f**)	Phenyl (**2a**)	Methyl (**1a**)	15	89
9	**4i**	Thiophen-2-yl (**3f**)	Phenyl (**2a**)	Ethyl (**1b**)	15	88
10	**4j**	1-*H*-indol-3-yl (**3g**)	Phenyl (**2a**)	Methyl (**1a**)	18	92
11	**4k**	1-*H*-indol-3-yl (**3g**)	Phenyl (**2a**)	Ethyl (**1b**)	18	91
12	**4l**	3,4,5-Trimethoxyphenyl (**3d**)	4-Methoxyphenyl (**2b**)	Methyl (**1a**)	17	89
13	**5a**	4-Chlorophenyl (**3i**)	Phenyl (**2a**)	Methyl (**1a**)	18	89
14	**5b**	4-Fluorophenyl (**3h**)	Phenyl (**2a**)	Methyl (**1a**)	15	86
15	**5c**	4-Chlorophenyl (**3i**)	Phenyl (**2a**)	Ethyl (**1b**)	20	89
16	**5d**	4-Bromophenyl (**3j**)	Phenyl (**2a**)	Methyl (**1a**)	18	91
17	**5e**	4-Bromophenyl (**3j**)	Phenyl (**2a**)	Ethyl (**1b**)	19	89
18	**5f**	4-Nitrophenyl (**3k**)	Phenyl (**2a**)	Methyl (**1a**)	15	82
19	**5g**	4-Nitrophenyl (**3k**)	Phenyl (**2a**)	Ethyl (**1b**)	18	79
20	**5h**	Pyridin-3-yl (**3l**)	Phenyl (**2a**)	Methyl (**1a**)	20	78
21	**5i**	Pyridin-3-yl (**3l**)	Phenyl (**2a**)	Ethyl (**1b**)	22	75
22	**5j**	4-Chlorophenyl (**3i**)	4-Bromophenyl (**2c**)	Methyl (**1a**)	25	84
23	**5k**	4-Bromophenyl (**3j**)	4-Bromophenyl (**2c**)	Methyl (**1a**)	25	79

[a] Solvents: HOAc (1.5 mL).
[b] Isolated yield.

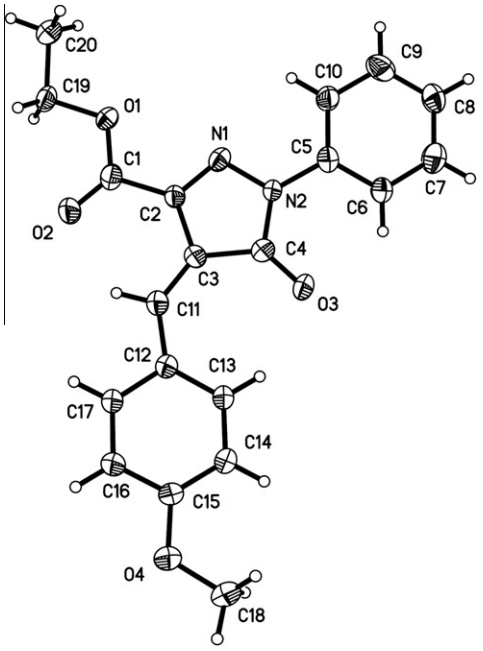
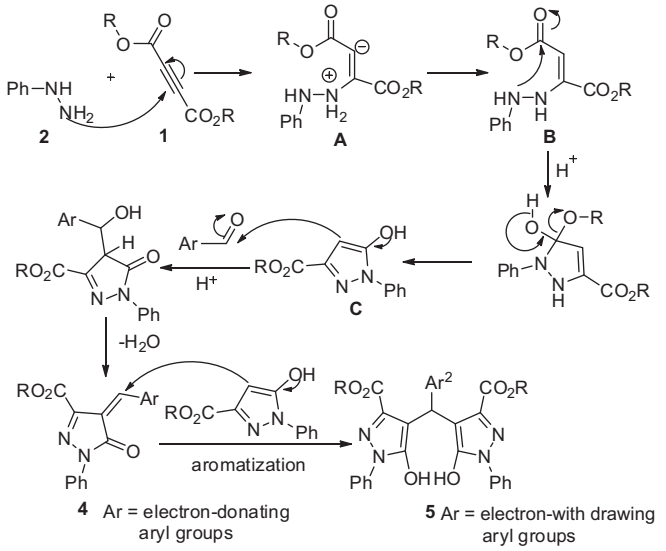


Figure 1. X-ray structure of **4b**.

unambiguously determined.[20] The structural elucidation and attribution of relative stereochemistry of the products have been characterized by ^{1}H and ^{13}C NMR and other analyses.

The mechanism of these domino reactions is proposed in Scheme 3. An initial condensation of acetylenedicarboxylate **1** and phenylhydrazine **2** generated 1,3-dipole intermediate **A**, which successively underwent proton transfer (**A** to **B**) and aminolysis of the ester group (**B** to **C**) generating the pyrazolone derivative **C** in situ. The pyrazolone derivative **C** was subjected with aromatic aldehydes leading to arylidene pyrazolones **4**. The polarity between C=C bonds in the benzyl position was induced by the electron-donating groups on phenyl ring, making its reactivity improve. So the arylidene pyrazolones with electron-withdrawing groups **4** were further reacted with pyrazolones generated in situ to give final C-tethered bispyrazol-5-ol derivatives **5**.

In conclusion, we have developed multi-component heterocyclization reactions (acetylenedicarboxylates, phenylhydrazine and aromatic aldehydes) as an alternative method for divergent synthesis of multi-functionalized pyrazolones and C-tethered bispyrazol-5-ols by controlling the nature of substituent on formyl group. The three-component reaction proceeds by domino [3+2] heterocyclization obtaining arylidenepyrazolones **4** in good yields, showing that the synthetic route allows us to build blocks of pyrazolone derivatives with a wide diversity of substituents. The five-component assembly gave the structurally different C-tethered bispyrazol-5-ol framework **5**. The ready accessibility of the starting materials, the broad compatibility of aldehyde substrates, and the generality of this process make the reaction highly valuable in view of the synthetic and medicinal importance of heterocycles of this type. Features of this strategy include the mild condition, convenient one-pot operation, short reaction periods of 10–25 min and excellent regio- and chemoselectivities.



Scheme 3. Proposed mechanisms for formation of products **4** or **5**.

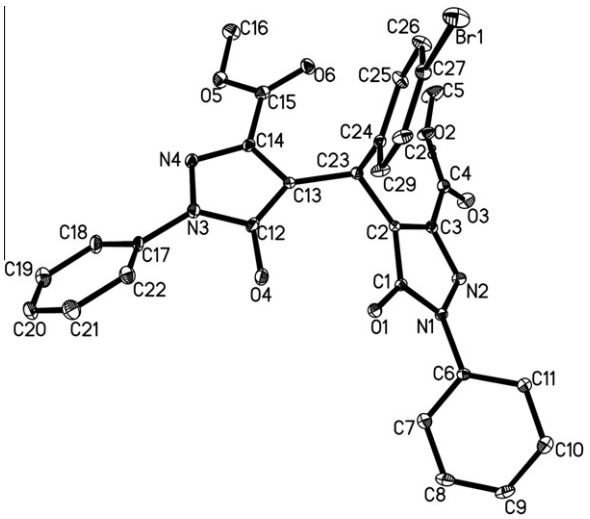


Figure 2. X-ray structure of **5d**.

Acknowledgments

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Supplementary data

Supplementary data associated (experimental details and spectroscopic characterization of all compounds along with ^{1}H, ^{13}C NMR, IR and mass spectra) with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.04.051.

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18. General procedure for the synthesis of compounds **4**: In a 10-mL reaction vial, acetylenedicarboxylate 1(1 mmol, 1.0 equiv), phenylhydrazine 2 (1 mmol, 1.0 equiv) and acetic acid (2 ml) were mixed and then stirred at room temperature for 1 min. Then the aromatic aldehyde **3a**–**3g** (1 mmol, 1.0 equiv) was added into the mixture. The new mixture was stirred at room temperature for 10–18 min. Upon completion as shown by TLC monitoring, the reaction mixture diluted with cold water. The solid product was filtered, and subsequently recrystallized from 50% EtOH to give the pure product. *(4Z)-Methyl 4-(3,4,5-trimethoxybenzylidene)-4,5-dihydro-5-oxo-1-phenyl-1H-pyrazole-3-carboxylate* (**4e**) Orange solid, mp: 173 °C; IR (KBr, ν, cm^{-1}): 1715, 1618, 1590, 1517, 1325, 1267, 1198, 1173, 1107, 1020, 990, 743. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.69 (s, 1H, CH), 8.07 (s, 2H, Ar-H), 7.90 (d, J = 8.0 Hz, 2H, Ar-H), 7.45 (t, J = 8.0 Hz, 2H, Ar-H), 7.29 (d, J = 7.2 Hz, 1H, Ar-H), 4.01 (s, 2H, OCH_3), 4.01 (s, 2H, OCH_3), 3.97 (s, 6H).^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 207.0, 162.1, 161.7, 153.4, 152.7, 144.0, 139.8, 137.7, 129.0, 128.7, 126.5, 122.1, 121.0, 112.7, 61.2, 56.4, 52.5, 30.9. HRMS (ESI) m/z: calcd for $C_{21}H_{20}N_2O_6$: 395.1242 $[M-H]^-$; found 395.1239.
19. General procedure for the synthesis of compounds **5**: In a 10-mL reaction vial, acetylenedicarboxylate **1** (2 mmol, 2.0 equiv), phenylhydrazine **2** (2 mmol, 2.0 equiv) and acetic acid (2 ml) were mixed and then stirred at room temperature for 1 min. Then the aromatic aldehyde **3h**–**3l** (1 mmol, 1.0 equiv) was added into the mixture. The new mixture was stirred at 40 °C for 15–22 min. Upon completion as shown by TLC monitoring, the reaction mixture diluted with cold water. The solid product was filtered, and subsequently recrystallized from 80% EtOH to give the pure product. *Ethyl 4-((3-(ethoxycarbonyl)-5-hydroxy-1-phenyl-1H-pyrazol-4-yl)(4-chlorophenyl)methyl)-5-hydroxy-1-phenyl-1H-pyrazole-3-carboxylate* (**5c**) White solid, mp: 194 °C; IR (KBr, ν, cm^{-1}): 1728, 1714, 1598, 1579, 1490, 1443, 1220, 1175, 1049, 1035, 824, 747, 671. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.80 (d, J = 7.5 Hz, 4H, Ar-H), 7.46 (t, J = 6.9 Hz, 4H, Ar-H), 7.40–7.24 (m, 6H, Ar-H), 6.76 (s, 1H, CH), 4.31 (q, J = 6.9 Hz, 4H, OCH_2), 1.31 (t, J = 7.0 Hz, 6H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 137.8, 137.2, 132.3, 129.0, 128.5, 128.2, 127.8, 123.2, 63.0, 32.5, 14.1. HRMS (ESI) m/z: calcd for $C_{31}H_{27}ClN_4O_6$: 585.1541 $[M-H]^-$; found 585.1518.
20. The single-crystal growth was carried out in co-solvent of EtOH and CH_3COCH_3 at room temperature. X-ray crystallographic analysis was performed with a Siemens SMART CCD and a Siemens P4 diffractometer. Crystal data for **4b**: $C_{20}H_{18}N_2O_4$, crystal dimension 0.43 × 0.41 × 0.14 mm, Monoclinic, space group $P2(1)/c$, a = 12.9240(11) Å, b = 18.8682(16) Å, c = 7.3157(6) Å, $\alpha = \gamma = 90^\circ$, β = 101.272(2)°, V = 1749.5(3) Å^3, Mr = 350.36, Z = 4, λ = 0.71073 Å, μ (Mo Kα) = 0.094 mm^{-1}, $F(000)$ = 736, R_1 = 0.0375, wR_2 = 0.0645. Crystal data for **5d**: $C_{29}H_{23}BrN_4O_6$, crystal dimension 0.30 × 0.24 × 0.13 mm, Monoclinic, space group P2(1)/c, a = 10.5957(11) Å, b = 12.1892(12) Å, c = 41.397(3) Å, $\alpha = \gamma = 90^\circ$, β = 96.3800(10)°, V = 5313.5(9) Å^3, Mr = 603.42, Z = 8, λ = 0.71073 Å, μ (Mo Kα) = 1.599 mm^{-1}, $F(000)$ = 2464, $R1$ = 0.0505, wR_2 = 0.0714.