New multicomponent domino reactions (MDRs) in water: highly chemo-, regio- and stereoselective synthesis of spiro{[1,3]dioxanopyridine}-4,6-diones and pyrazolo[3,4-*b*]pyridines†

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New multicomponent domino reactions (MDRs) have been established for the synthesis of spiro{pyrazolo[1,3]-dioxanopyridine}-4,6-diones, spiro{isoxazolo[1,3]dioxano-pyridine}-4,6-diones and pyrazolo[3,4-*b*]pyridines. The MDRs were conducted by reacting readily available and inexpensive starting materials in aqueous solution under microwave irradiation. A total of 26 examples were examined, and showed a broad substrate scope and high overall yields (76–93%). A new mechanism has been proposed to explain the reaction process and the resulting chemo-, regio- and stereoselectivity. The present green synthesis shows attractive characteristics such as the use of water as the reaction medium, one-pot conditions, short reaction periods (9–13 min), easy work-up/purification and reduced waste production without the use of any acids or metal promoters.

Multicomponent domino reactions (MDRs), particularly those performed in aqueous media, have become increasingly useful tools for the synthesis of chemically and biologically important compounds because of their environmentally friendly atom-economy and green characteristics.[1–3] These reactions enable multi-step synthesis to be conducted in a one-pot operation to obtain a variety of invaluable products. Therefore, MDRs can dramatically reduce the generation of chemical waste and reduce the cost of the starting materials. One-pot MDRs often shorten reaction periods, giving higher overall chemical yields than multiple-step syntheses, and can therefore reduce the use of energy and manpower.

In the past several years, we and others have developed various multicomponent domino reactions that can provide easy access to useful functionalized multiple ring structures of chemical and pharmaceutical interest.[4–7] For example, a new four-component domino reaction was established to provide easy access to multifunctionalized quinazoline derivatives.[4a] The reaction is easily performed by simply mixing readily available starting materials, aromatic aldehydes, cyclopentanone and cyanoacetamide with K_2CO_3 in ethylene glycol under microwave (MW) irradiation. Recently, we have also found that when aliphatic aldehydes were employed to replace their aromatic counterparts for the above MDR reaction, the quinazoline derivatives were not generated. Instead, the reaction was found to follow another pathway, leading to multi-functionalized tricyclo[6.2.2.0^{1,6}]dodecanes.[4b]

As a continuation of our research devoted to the development of multi-component domino reactions,[4–6] we would like to report a green chemo-, regio- and stereoselective MDR approach to type III spiro[1,3]dioxanopyridine derivatives that are of chemical and biomedical importance (Fig. 1). This reaction was achieved by reacting aldehydes, pyrazolo-amines or isoxazolo-amines, and Meldrum's acid as starting materials in water with microwave irradiation in the absence of any acid, metal catalyst, or promoter (Scheme 1).

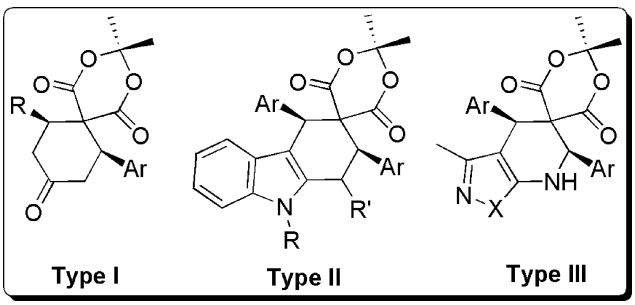
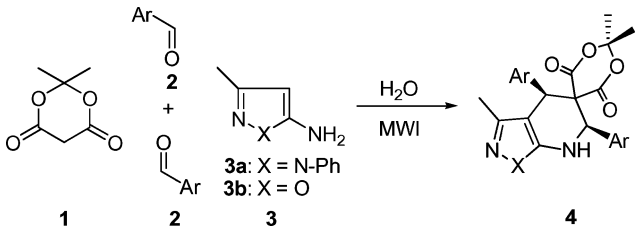


Fig. 1 Structures of three types of spiro{[1,3]dioxanopyridine}-4,6-diones.



Scheme 1

Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione)[8] and its derivatives have been widely utilized in organic synthesis, especially for multiple C–C bond formations[9] due to its adequate acidity (pK_a 4.83), steric rigidity, and notable tendency to re-generate acetone as an easily removed side-product. Spirocyclic

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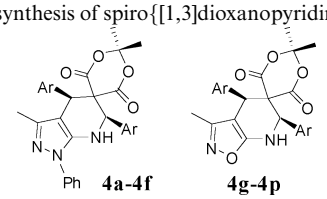
compounds containing a Meldrum's acid unit are very useful building blocks for the total synthesis of natural products and for medicinal research.[10,11] For example, they serve as precursors to exotic amino acids which are often used to enhance biological activities of peptides, peptidomimetics and proteins.[10] In 2003, Barbas III and coworkers established a new L-proline-catalyzed multicomponent transformation of Meldrum's acid into type I unsymmetrical spiro[5.5]undecanes.[9a] Recently, the synthesis of type II unsymmetrical spiroundecanes has been achieved by Sapi and coworkers.[12] To the best of our knowledge, a successful approach to spirocyclic compounds of type III, containing a Meldrum's acid unit and the fused isoxazolo[5,4-*b*]hydropyridine and pyrazolo[3,4-*b*]pyridine scaffolds, have not been documented in the literature.

It has been reported that when arylidene-Meldrum's acids were subjected to reaction with 3-methyl-1-phenylpyrazol-5-amine in refluxing toluene, isoxazolo[5,4-*b*]hydropyridines were produced in good chemical yields.[13] We have also found that the MDR of Meldrum's acid, aromatic aldehydes and 3-methyl-1-phenylpyrazol-5-amine in glycol leads to pyrazolo[3,4-*b*]pyridines in high yields.[6] Surprisingly, when we conducted MDR of the above three reactants by changing the ratio of three reactants under microwave irradiation in the aqueous phase, we found that the product is not the anticipated pyrazolo[3,4-*b*]pyridine. Instead, the multifunctionalized spiro{[1,3]dioxanopyridine}-4,6-dione **1a** was generated with high chemo-, regio- and stereoselectivity and good yield, as shown in Scheme 1.

Interestingly, the *N*-phenyl-based spiro{pyrazolo[1,3]-dioxanopyridine}-4,6-diones can only be generated in aqueous solution. Other polar solvents, such as *N*,*N*-dimethylformamide (DMF), glacial acetic acid (HOAc) and glycol resulted in pyrazolo[3,4-*b*]pyridines as the major products. This outcome was also found to be the case under solvent-free conditions. Since water is an efficient absorber of microwave irradiation, it often leads to the success of many organic reactions under environmentally friendly conditions.[14,15] Under this aqueous system, the MDR of Meldrum's acid (**1**), aromatic aldehydes (**2**) and 3-methyl-1-phenylpyrazol-5-amine (**3**) in a molar ratio of 1 : 2 : 1 resulted in spiro{pyrazolo[1,3]dioxanopyridine}-4,6-dione (**4a**) and produced a chemical yield of 81%. The reaction occurred rapidly at 100 °C, and was complete within a few minutes.

The substrate scope of this reaction was investigated by using various aryl aldehydes. As revealed in Table 1, aromatic aldehydes bearing either electron-withdrawing or electron-donating functional groups such as chloro, fluoro, bromo, methyl or methoxy were all found to be suitable for the reaction with Meldrum's acid (**1**) and 3-methyl-1-phenylpyrazol-5-amine (**3a**) to obtain spiro{pyrazolo[1,3]dioxanopyridine}-4,6-diones (**4a–f**) in very good yields of 80–86% (Table 1, entries 1–6). We also utilized 3-methylisoxazol-5-amine (**3b**) instead of 3-methyl-1-phenylpyrazol-5-amine (**3a**) for this reaction, and that it can react with Meldrum's acid (**1**) and various aromatic aldehydes bearing electron-withdrawing or electron-donating groups to afford the corresponding spiro{isoxazolo [1,3]dioxanopyridine}-4,6-diones (**4g–o**) within 9–13 min in very good yields (77–88%) and excellent selectivities (Table 1, entries 7–16). Even substrate (**2p**), which contains a 2-thienyl group, was proven to be effective for this reaction and produced the 2-thienyl-substituted spiro[1,3]dioxanopyridine (**4p**) in a yield of 78%.

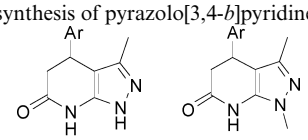
Table 1 MDR synthesis of spiro{[1,3]dioxanopyridine}-4,6-diones (**4**)



4a-4f **4g-4p**

Entry	Product **4**, Ar =	Time/min	Yield (%)
1	**4a** 4-ClC_6H_4	10	84
2	**4b** 4-$NO_2C_6H_4$	12	86
3	**4c** C_6H_5	9	82
4	**4d** 3,4-$(CH_3O)_2C_6H_3$	10	80
5	**4e** 3,4,5-$(CH_3O)_3C_6H_2$	11	81
6	**4f** 4-HO,3-$NO_2C_6H_3$	12	83
7	**4g** 4-FC_6H_4	10	88
8	**4h** 4-ClC_6H_4	12	84
9	**4i** 4-BrC_6H_4	11	83
10	**4j** 4-$CH_3OC_6H_4$	12	80
11	**4k** 4-$NO_2C_6H_4$	10	84
12	**4l** 2-ClC_6H_4	13	77
13	**4m** 3,4-$(CH_3O)_2C_6H_3$	12	82
14	**4n** C_6H_5	9	84
15	**4o** 3,4,5-$(CH_3O)_3C_6H_2$	12	81
16	**4p** Thien-2-yl	10	78

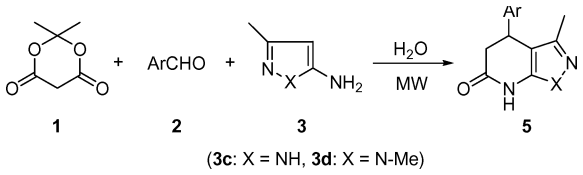
Table 2 MDR synthesis of pyrazolo[3,4-*b*]pyridines (**5**)



5a-5i **5j**

Entry	Product **5**, Ar =	Time/min	Yield (%)
1	**5a** 4-ClC_6H_4	7	89
2	**5b** 4-BrC_6H_4	6	93
3	**5c** 4-$CH_3C_6H_4$	8	90
4	**5d** 4-$(CH_3O)C_6H_4$	8	92
5	**5e** 3-$NO_2C_6H_4$	7	89
6	**5f** 2,3-$(CH_3O)_2C_6H_3$	8	89
7	**5g** 2,4-$Cl_2C_6H_3$	8	91
8	**5h** 4-HO,3-$NO_2C_6H_3$	7	88
9	**5i** C_6H_5	9	90
10	**5j** 4-ClC_6H_4	8	89

In addition, it was found that the group on the *N*-1 position of 3-methyl-pyrazol-5-amine (**3**) played a crucial role in controlling the chemoselectivity. Two *N*-H- and *N*-Me-based pyrazol-5-amines, 3-methylpyrazol-5-amine (**3c**) and 3-methyl-1-methylpyrazol-5-amine (**3d**), resulted in the formation of pyrazolo[3,4-*b*]pyridines (**5a–j**) in good to excellent yields of 84–93% without spiro{pyrazolo[1,3]dioxanopyridine}-4,6-diones being formed, under the same aqueous phase and microwave irradiation conditions (Table 2, Scheme 2). It should be noticed that in our previous synthesis of *N*-phenylpyrazolo[3,4-*b*]pyridines and 3-methylisoxazolo[5,4-*b*]pyridines,[6] a ratio of 1 : 1 : 1 for three reactants is required. However, in the present system, the reactants in a ratio 1 : 2 : 1 also resulted in pyrazolo[3,4-*b*]pyridine products predominantly. A similar broad substrate scope of aldehydes was observed for this process.



Scheme 2

All products were fully characterized by spectroscopic analysis, and the IR, ^{1}H and ^{13}C-NMR data were consistent with their structures (for the spectra of all pure products, see the ESI†). Furthermore, crystals of **4g** were obtained by careful recrystallization from a solution of DMF, and the structure was unambiguously confirmed by X-ray crystallography (Fig. 2). As expected, the two *para*-F-phenyl rings are parallel to the two carbonyl groups, and these two aromatic rings are also arranged on equatorial positions of a six-membered hydropyridine ring.

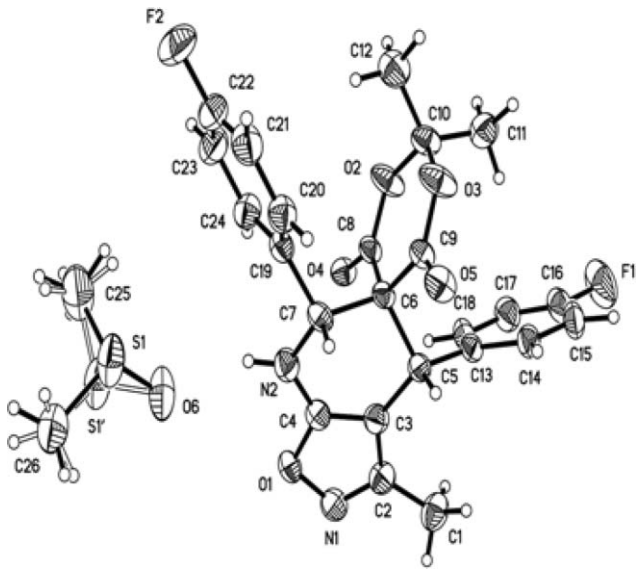
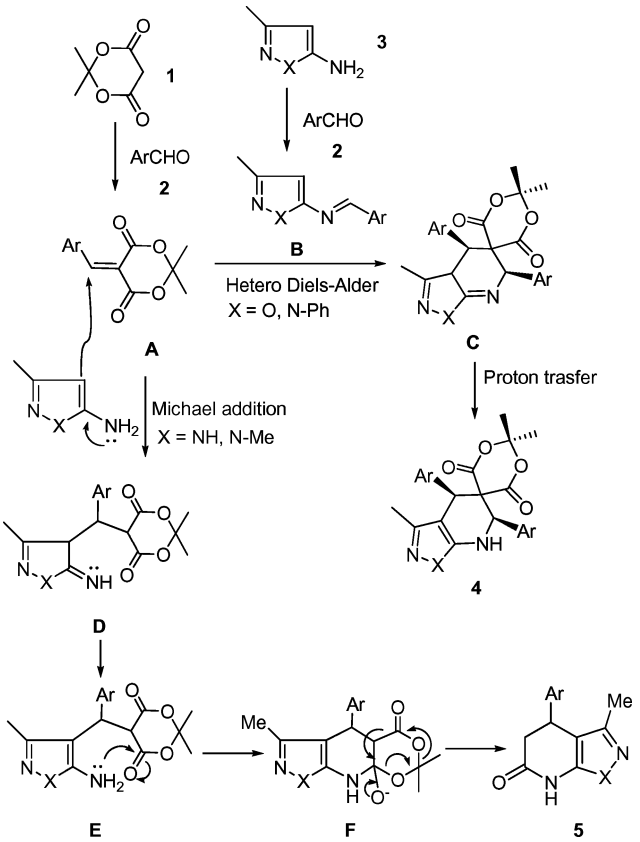


Fig. 2 ORTEP diagram of **4g**.

The mechanism of this MDR process is proposed as shown in Scheme 3. The first two steps involve the Knoevenagel reaction of Meldrum's acid (**1**) with aldehyde (**2**) to form an intermediate (**A**), and the condensation of aldehyde (**2**) with aromatic amine (**3**) to form an imine (**B**). The next step is the hetero-Diels–Alder reaction of the Knoevenagel adduct (**A**) with the aromatic imine (**B**), resulting in pyridine ring formation and intermediate (**C**), followed by proton transfer to obtain the final spiro{[1,3]dioxanopyridine}-4,6-dione product (**4**). As anticipated, the hetero-Diels–Alder reaction follows the *endo* rule, providing the product with the two aromatic rings arranged on the same side, as confirmed by X-ray structural analysis. The regiochemistry is directed by the polarity of intermediates **A** and **B**, in which the negatively charged α-position of the Knoevenagel adduct (**A**) attacks the positively charged imine carbon center.

This mechanism explains well why two equivalents of aldehyde are necessary to form the spiro{[1,3]dioxanopyridine}-4,6-dione (**4**) when 3-methyl-1-phenylpyrazol-5-amine (**3**) or 3-



Scheme 3

methylisoxazol-5-amine (**3b**) are employed as the substrates, due to the need of aldehyde for both the Knoevenagel reaction and the condensation reaction. At the same time, this mechanism can also explain why 3-methylpyrazol-5-amine (**3c**, X = NH) and 3-methyl-1-methylpyrazol-5-amine (**3d**, X = O) lead to the formation of pyrazolo[3,4-*b*]pyridines and *N*-phenylpyrazolo[3,4-*b*]pyridines (**5**); this is based on the fact that the amino group ($-NH_2$) in these substrates is more reactive and makes the Michael addition and the carbonyl addition of intermediate (**E**) occur at faster rates. It should be noted that the imine formation is expected to be reversible in the aqueous phase; this favors the second pathway in which the more reactive aromatic amine (**3**) is consumed by intermediate **A** at a faster rate. This is in contrast to the two former cases (X = O; N–Ph) in which the electron density of the $-NH_2$ group is 'withdrawn' by the stronger electronegative oxygen or shared by the *N*-phenyl ring. These two factors make the formation of imine **B** occur slowly.

In summary, new multicomponent domino reactions (MDRs) have been established to afford spiro{pyrazolo[1,3]-dioxanopyridine}-4,6-diones, spiro{isoxazolo[1,3]dioxanopyridine}-4,6-diones, and pyrazolo[3,4-*b*]pyridines that serve as versatile building blocks for both organic and medicinal research. The reactions were conducted in aqueous solution with microwave irradiation using readily available and inexpensive starting materials. A new mechanism has been proposed to explain the chemo-, regio- and stereoselectivity. This green synthesis shows several attractive characteristics such as the use of water as the reaction medium, simple conditions, short

reaction periods, easy work-up, and reduced waste production by the lack of any requirement for acids or metal promoters.

Experimental section

All microwave-assisted reactions were performed in a monomodal Emrys™ Creator from Personal Chemistry, Uppsala, Sweden. Typically, in a 10 mL Emrys™ reaction vial, Meldrum's acid as a CH-acid, aldehydes and amine in water (2 mL) were mixed and the vial then capped. The mixture was irradiated using microwaves at 200 W and 100 °C for the time specified. The automatic-mode stirring helped the mixing and uniform heating of the reactants. Upon completion (as monitored by TLC), the reaction mixture was cooled to room temperature and filtered to obtain the crude products, which were further purified by recrystallization from 95% EtOH.

General procedures for the synthesis of compounds 4 and 5

Preparation of compounds 4. In a 10 mL Emrys reaction vial, the Meldrum's acid (**1**, 1 mmol), aromatic aldehyde (**2**, 2 mmol), 3-methyl-1-phenylpyrazol-5-amine (**3a**) or 3-methylisoxazol-5-amine (**3b**) (1.0 mmol) and water (2.0 mL) were mixed and the vial then capped. The mixture was heated for a given time at 100 °C under microwave irradiation (initial power 100 W and maximum power 200 W). Upon completion (as monitored by TLC), the reaction mixture was cooled to room temperature and then poured into cold water. The solid product was collected by Büchner filtration and subsequently recrystallized from EtOH (95%) to give the pure products.

4′,6′-Bis(4-chlorophenyl)-2,2,3′-trimethyl-1′phenyl-1′,4′,6′,7′-tetrahydrospiro[[1,3]dioxane-5,5′-pyrazolo[3,4-*b*]pyridine]-4,6-dione (4a). White solid, mp: 205.7–206.1 °C. ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 8.35 (d, 1H, J = 2.0 Hz, NH), 7.33 (d, 4H, J = 7.2 Hz, ArH), 7.26 (d, 2H, J = 5.6 Hz, ArH), 7.08 (s, 1H, ArH), 5.11 (d, 1H, J = 2.0 Hz, CH), 4.92 (s, 1H, CH), 1.54 (s, 3H, CH_3), 0.64 (s, 3H, CH_3), 0.55 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 195.1, 175.2, 167.7, 161.0, 157.5, 154.8, 152.6, .145.2, 143.9, 139.5, 135.5, 130.4, 129.1, 128.9, 128.6, 128.4, 128.3, 125.3, 122.2, 121.1, 112.7, 105.3, 101.1, 58.1, 47.1, 28.3, 27.3, 13.8. IR (KBr, ν, cm^{-1}): 3196, 3120, 3011, 2982, 2903, 1633, 1539, 1490, 1432, 1362, 1251, 1126, 1080, 954, 873, 827, 681. HRMS (ESI): m/z calcd for: 562.1395 [M + H]$^+$, found: 562.1352.

Preparation of compounds 5. In a 10 mL Emrys reaction vial, the Meldrum's acid (**1**, 1 mmol), aromatic aldehyde (**2**, 1 mmol), 3-methylpyrazol-5-amine (**3c**) or 3-methyl-1-methylpyrazol-5-amine (**3d**) (1.0 mmol) and water (2.0 mL) were mixed and the vial then capped. The mixture was heated for a given time at 100 °C under microwave irradiation. Upon completion (as monitored by TLC), the reaction mixture was cooled to room temperature and then poured into cold water. The subsequent work-up was the same as in the above reactions.

4-(4-Chlorophenyl)-3-methyl-4,5-dihydro-1*H*-pyrazolo[3,4-*b*]pyridin-6(7*H*)-one (5a). White solid, mp: >300 °C. ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 11.84 (s, 1H, NH), 10.32 (s, 1H, NH), 7.37 (d, 2H, J = 8.0 Hz, ArH), 7.18 (d, 2H, J = 8.4 Hz, ArH), 4.17 (t, 1H, J = 6.4 Hz, CH), 2.80 (dd, 1H, J_1 = 7.2 Hz, J_2 = 16.0 Hz, CH_2), 2.53 (dd, 1H, J_1 = 5.6 Hz, J_2 = 16.0 Hz, CH_2), 1.84 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 169.3, 148.7, 142.8, 141.4, 134.7, 131.1, 128.8, 128.5, 112.7, 106.8, 101.5, 33.3, 9.4. IR (KBr, ν, cm^{-1}): 3179, 3132, 3049, 2985, 2905, 1638, 1539, 1489, 1414, 1365, 1230, 1087, 1015, 926, 883, 827, 678. HRMS (ESI): m/z calcd for: 262.0742 [M + H]$^+$, found: 262.0760.

Acknowledgements

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