HETEROCYCLES, Vol. 84, No. 2, 2012, pp. 765 - 774. © 2012 The Japan Institute of Heterocyclic Chemistry
Received, 24th June, 2011, Accepted, 1st August, 2011, Published online, 3rd August, 2011
DOI: 10.3987/COM-11-S(P)53

# MICROWAVE-ASSISTED MULTICOMPONENT REACTION IN WATER: HIGHLY STEREOSELECTIVE SYNTHESIS OF PYRIMIDINESPIROISOXAZOLO[5,4-*b*]PYRIDINE DERIVATIVES

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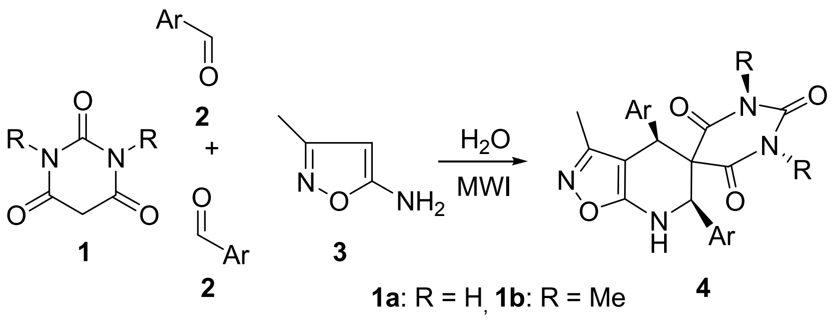
**Abstract** – A multicomponent reaction has been established for the synthesis of pyrimidinespiroisoxazolo[5,4-*b*]pyridines that can serve as versatile building blocks for both organic and medicinal research. The reasonable reaction mechanism has proposed to explain the resulting stereochemistry of products. The present green synthesis shows several advantages including operational simplicity and fast reaction rate, which makes it a useful and attractive process for library generation for drug discovery.

## INTRODUCTION

Organic synthesis has been taking advantage of water as readily available and environmentally friendly solvent because it has been recognized as an effective reaction medium with unique properties and possibilities for many reactions.[1,2] In the meanwhile, high density microwave irradiation has been proven to be a reliable and useful tool for accelerating organic reactions.[3] Under microwave irradiation, water can be rapidly heated to high temperature, enabling it to act like a less polar pseudo-organic solvent. In addition, the precise control of reaction temperature can be easily achieved due to the high heat capacity of water. Therefore, it has become clear that the advantage of multi-component reactions under microwave superheating in aqueous media offers a nearly synergistic strategy and greater potentials for making synthetic building blocks than traditional methods.[4,5]

Heterocyclic spirocompounds exhibiting structural rigidity due to their conformational restriction are of great interest in synthetic organic and medicinal chemistry.[6] The presence of a spirocarbon atom induces a relatively large steric strain and allows thermally base-, acid- or photo-promoted rearrangements leading to new and unexpected novel heterocycles.[6] In addition, assembling these spiral structures is of considerable interest in the pharmaceutical and agricultural chemistry because the spiropyrimidines and their derivatives are well-known compounds for their potential use as antibacterial agents.[7] So far, only a few studies concerning the synthesis of these active compounds have been reported in the literature.[8] However, their synthesis suffers from poor diastereoselectivity, limited substrate scope, long reaction time and the use of traditional organic solvents. In order to avoid these shortcomings, we devoted our efforts to find a new procedure of environmentally friendly, and easy to operate for the synthesis of those compounds. Recently, our group have developed various multicomponent reactions that can provide efficient synthesis of useful functionalized multiple ring structures of chemical and pharmaceutical interest,[9-11] which includes a new four-component reaction for an easy access to spiro[1,3]dioxano-pyridine derivatives.[9d]

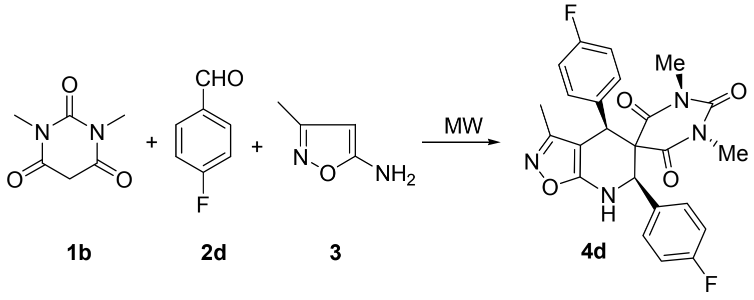
In continuation of our projects on the development of new multi-component reactions,[9-11] herein we report a highly stereoselective synthesis of new pyrimidinespiroisoxazolo[5,4-*b*]pyridines **4** through microwave-assisted multicomponent reactions in aqueous media (Scheme 1).



Scheme 1

## RESULTS AND DISCUSSION

For microwave-promoted reactions, the choice of an appropriate reaction media is of crucial importance not only for achieving high chemical yields but also for the effective control of stereoselectivity. To choose the optimum solvent, the reaction of 1,3-dimethylbarbituric acid **1b** with 4-fluorobenzaldehyde **2d** and 3-methylisoxazol-5-amine **3** at the ratio of 1:2:1 was examined under microwave irradiation and solvent-free condition or in polar organic solvents, such as *N,N*-dimethylformamide (DMF), glacial acetic acid (HOAc) and glycol (Scheme 2). These results are presented in Table 1. Interestingly, it was found that this reaction cannot yield the product **4d** efficiently except for the case performed in water.



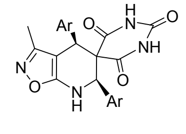
Scheme 2

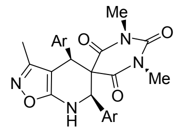
Table 1. Solvent optimization for the synthesis of **4d** under MW

| Entry | Solvent | T / °C | Time (min) | Yield (%) |
|---|---|---|---|---|
| 1 | AcOH | 100 | 12 | trace |
| 2 | ethylene glycol | 100 | 10 | trace |
| 3 | DMF | 100 | 15 | trace |
| 4 | water | 100 | 8 | 89 |
| 5 | none | 100 | 10 | trace |

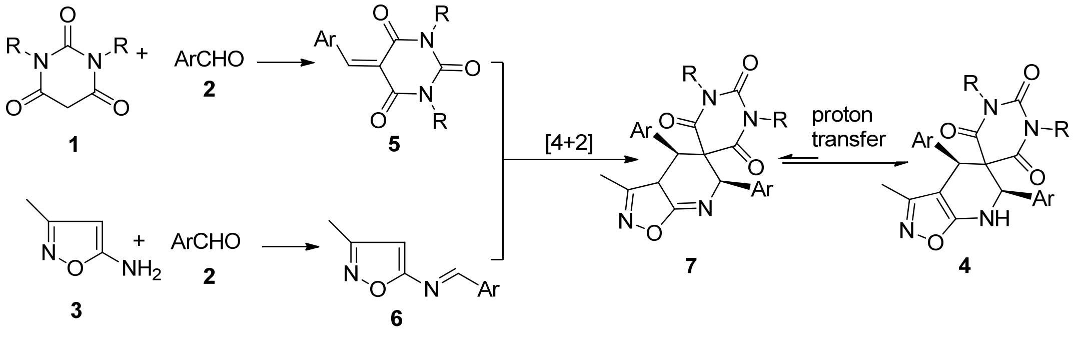
With this result in hand, we next examined the substrate scope of this reaction. Under the optimized reaction conditions, a variety of structurally diverse aromatic aldehydes were employed to yield a series of new pyrimidinespiroisoxazolo[5,4-*b*]pyridines with high *syn* stereoselectivity and concomitant formations of one quaternary carbon center and four new σ-bonds. As shown in Table 2, a series of aromatic aldehydes, either bearing electron-withdrawing groups (halogen and nitro group) or electron-donating groups (alkoxyl group), was treated with starting materials **1** and **3** to give the corresponding products **4** in good to excellent chemical yields (78-89%) under the same reaction condition. The results showed that the electronic nature of the substituents on phenyl ring has no significant effect on outcomes of this reaction.

Table 2. The synthesis of products **4**

| Entry | Product | | Ar | Time/min | Yield / % |
|---|---|---|---|---|---|
| 1 |  | **4a** | 4-$NO_2C_6H_4$ | 9 | 85 |
| 2 | | **4b** | 3-$NO_2C_6H_4$ | 11 | 86 |
| 3 | **4a-4c** | **4c** | 3,4,5-$(MeO)_3C_6H_2$ | 13 | 79 |

| | | | | | |
|---|---|---|---|---|---|
| 4 |  **4d-4h** | **4d** | 4-$FC_6H_4$ | 8 | 89 |
| 5 | | **4e** | 4-$ClC_6H_4$ | 9 | 84 |
| 6 | | **4f** | 4-$BrC_6H_4$ | 9 | 82 |
| 7 | | **4g** | 4-$MeC_6H_4$ | 12 | 80 |
| 8 | | **4h** | 2,4-$Cl_2C_6H_3$ | 10 | 78 |

A plausible reaction mechanism is proposed in Scheme 3, which is similar to one of our previous four-component domino reactions,[10d] The initial step involves the Knoevenagel reaction of barbituric acid (**1**) with an aldehyde (**2**) to form an intermediate (**5**). The condensation of the other aldehyde (**2**) with an aromatic amine (**3**) results in an imine (**6**). The next step is the hetero-Diels-Alder reaction of the Knoevenagel adduct (**5**) with the aromatic imine (**6**) resulting in formations of pyridine ring and intermediate (**7**), followed by proton transfer to give the final pyrimidinespiroisoxazolo[5,4-*b*]pyridines (**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 **5** and **6**, in which the negatively charged α-position of the Knoevenagel adduct (**5**) attacks the positively charged imine carbon center.



Scheme 3

All products have been fully characterized by spectroscopic analysis. The IR spectrum of compound **4a** showed strong absorptions at 3347 $cm^{-1}$ due to the NH group, and at 1718 and 1658 $cm^{-1}$ due to the C=O groups. The $^1H$ NMR spectrum of **4a** showed a broad singlet at $\delta = 11.33$ due to the NH protons, and two singlet at $\delta = 5.27$, 4.51 due to the two CH protons. Furthermore, the structure of **4h** was unambiguously confirmed by X-ray crystallographic analysis (Figure 1).

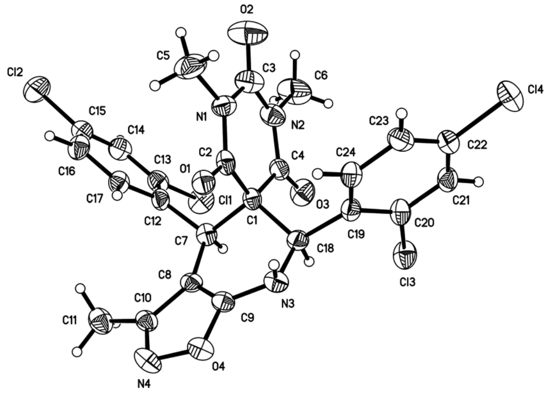


Figure 1. ORTEP diagram of **4h**[12]

In summary, a new multicomponent reaction has been established to afford pyrimidinespiro-isoxazolo[5,4-*b*]pyridines that can serve as versatile building blocks for both organic and medicinal research. This reaction takes advantage of microwave irradiation and using water as an environmentally benign reaction medium. The reaction shows a great scope of substrate for a variety of starting materials. A reasonable mechanism has been proposed to explain the resulting stereochemistry of pyrimidinespiro-isoxazolo[5,4-*b*]pyridine products. This green synthesis offers several advantages including operational simplicity and fast reaction rate, which makes it a useful and attractive process for library generation for drug discovery.

## EXPERIMENTAL

Microwave irradiation was carried out with Initiator from Biotage company, Sweden. Melting points were determined in open capillaries and were uncorrected. IR spectra were taken on a FT-IR-Tensor 27 spectrometer in KBr pellets and reported in cm$^{-1}$. $^1$H NMR spectra were measured on a Bruker DPX 400 MHz spectrometer in DMSO-$d_6$ with chemical shift ($\delta$) given in ppm relative to TMS as internal standard. HRMS (ESI) was determined by using microTOF-QII HRMS/MS instrument (BRUKER). X-Ray crystallographic analysis was performed with a Siemens SMART CCD and a Siemens P4 diffractometer

### Synthesis of 4 under Microwave Irradiation

In a 10 mL reaction vial, barbituric acid (**1**, 1.0 mmol), aromatic aldehydes (**2**, 2.0 mmol), 3-methylisoxazol-5-amine (**3**, 1.0 mmol), and water (2 mL) were mixed and then capped. The automatic mode stirring helped the mixing and uniform heating of the reactants. The mixture was heated by microwave irradiation at 100 °C for a given time. Upon completion, monitored by TLC, the reaction mixture was cooled to room temperature and filtered to give the crude products, which were further purified by recrystallization from 95% EtOH.[13-16]

**4a.**

**3-Methyl-4,6-bis(4-nitrophenyl)-6,7-dihydro-1'*H*,4*H*-spiro[isoxazolo[5,4-*b*]pyridine-5,5'-pyrimidine]-2',4',6'(3'*H*)trione**

White solid, mp 229-231 $^{o}$C; IR (KBr, *ν*, cm$^{-1}$): 3346, 3249, 3110, 2942, 1719, 1696, 1647, 1606, 1522, 1478, 1348, 1109, 1031, 861. $^{1}$H NMR (400MHz, DMSO-$d_6$) (*δ*, ppm): 11.61(s, 1H, NH), 11.27 (s, 1H, NH), 10.13 (s, 1H, NH), 8.29 (d, 2H, *J* = 8.8 Hz, ArH), 8.22 (d, 2H, *J* = 8.8 Hz, ArH), 7.54 (d, 2H, *J* = 8.8 Hz, ArH), 7.34 (d, 2H, *J* = 7.6 Hz, ArH), 5.20 (d, 1H, *J* = 1.6 Hz, CH), 1.58 (s, 3H, Me); HRMS (ESI): m/z calcd for: 493.1102 [M+H]$^+$, found: 493.1122.

**4b.**

**3-Methyl-4,6-bis(3-nitrophenyl)-6,7-dihydro-1'*H*,4*H*-spiro[isoxazolo[5,4-*b*]pyridine-5,5'-pyrimidine]-2',4',6'(3'*H*)trione**

White solid, mp 231-232 $^{o}$C; IR (KBr, *ν*, cm$^{-1}$): 3376, 3258, 3085, 2930, 1715, 1681, 1657, 1607, 1533, 1509, 1481, 1333, 1162, 1019, 850, 767; $^{1}$H NMR (400MHz, DMSO-$d_6$) (*δ*, ppm): 8.21 (s, 1H, NH), 7.35 (t, 3H, *J* = 2.8 Hz, ArH), 7.29-7.27 (m, 3H, ArH), 7.17-7.15 (m, 2H, ArH), 7.00 (d, 2H, *J* = 4.0 Hz, NH), 5.02 (d, 1H, *J* = 2.0 Hz, CH), 4.91 (s, 1H, CH), 1.56 (s, 3H, Me); HRMS (ESI): m/z calcd for: 493.1102 [M+H]$^+$, found: 493.1119.

**4c.**

**3-Methyl-4,6-bis(3,4,5-trimethoxyphenyl)-6,7-dihydro-1'*H*,4*H*-spiro[isoxazolo[5,4-*b*]pyridine-5,5'-pyrimidine]-2',4',6'(3'*H*)trione**

White solid, mp 211-213 $^{o}$C; IR (KBr, *ν*, cm$^{-1}$): 3327, 3264, 3087, 2951, 1724, 1694, 1654, 1592, 1555, 1475, 1374, 1130, 1028, 871, 772; $^{1}$H NMR (400MHz, DMSO-$d_6$) (*δ*, ppm): 12.39 (s, 1H, NH), 12.12 (s, 1H, NH), 8.08 (d, 1H, *J* = 2.4 Hz, NH), 6.52 (s, 2H, ArH), 6.31 (s, 2H, ArH), 4.86 (d, 1H, *J* = 2.8 Hz, CH), 4.74 (s, 1H, CH), 3.74 (s, 6H, Me), 3.67 (s, 6H, Me), 3.63 (s, 3H, Me), 3.62 (s, 3H, Me), 1.67 (s, 3H, Me); HRMS (ESI): m/z calcd for: 583.2035 [M+H]$^+$, found: 583.2044.

**4d.**

**4,6-Bis(4-fluorophenyl)-1',3,3'-trimethyl-6,7-dihydro-1'*H*,4*H*-spiro[isoxazolo[5,4-*b*]pyridine-5,5'-pyrimidine]-2',4',6'(3'*H*)trione**

White solid, mp 206-208 $^{o}$C; IR (KBr, *ν*, cm$^{-1}$): 3197, 2996, 2928, 1747, 1684, 1642, 1605, 1531, 1510, 1480, 1379, 1160, 834, 775; $^{1}$H NMR (400MHz, DMSO-$d_6$) (*δ*, ppm): 8.62 (s, 1H, NH), 8.38 (d, 1H, *J* = 5.2 Hz, ArH), 8.27 (d, 1H, *J* = 4.0 Hz, ArH), 7.62-7.61 (m, 1H, ArH), 7.39 (t, 1H, $J_1 = J_2 = 4.8$ Hz, ArH), 7.19 (t, 1H, *J* = 8.4 Hz, ArH), 7.12-7.19 (m, 1H, ArH), 7.09 (s, 1H, ArH), 5.37 (d, 1H, *J* = 2.0 Hz, CH), 5.00 (s, 1H, CH), 2.93 (s, 3H, Me), 2.71 (s, 3H, Me), 1.61 (s, 3H, Me).

HRMS (ESI): m/z calcd for: 467.1525 [M+H]$^+$, found: 467.1525.

**4e.**

**4,6-Bis(4-chlorophenyl)-1',3,3'-trimethyl-6,7-dihydro-1'*H*,4*H*-spiro[isoxazolo[5,4-*b*]pyridine-5,5'-pyrimidine]-2',4',6'(3'*H*)trione**

White solid, mp 217-219 $^{\circ}$C; IR (KBr, *ν*, cm$^{-1}$): 3185, 2997, 2934, 2900 1743, 1681, 1648, 1527, 1493, 1456, 1378, 1348, 1122, 1098, 1015, 820, 685, 613; $^{1}$H NMR (400MHz, DMSO-$d_6$) (*δ*, ppm): 8.06 (d, 1H, $J$ = 4.0 Hz, NH), 7.70 (dd, 2H, $J_1$ = 2.0 Hz, $J_2$ = 6.0 Hz, ArH), 7.47-7.43 (m, 3H, ArH), 7.21 (d, 1H, $J$ = 8.4 Hz, ArH), 6.95 (d, 1H, $J$ = 8.8 Hz, ArH), 5.59 (d, 1H, $J$ = 4.0 Hz, CH), 5.32 (s, 1H, CH), 3.35 (s, 6H, Me), 1.43 (s, 3H, Me); HRMS (ESI): m/z calcd for: 499.0934 [M+H]$^{+}$, found: 499.0954.

**4f.**

**4,6-Bis(4-bromophenyl)-1',3,3'-trimethyl-6,7-dihydro-1'*H*,4*H*-spiro[isoxazolo[5,4-*b*]pyridine-5,5'-pyrimidine]-2',4',6'(3'*H*)trione**

White solid, mp 212-213 $^{\circ}$C; IR (KBr, *ν*, cm$^{-1}$): 3184, 2994, 2956, 2896 1743, 1678, 1642, 1525, 1490, 1450, 1419, 1378, 1339, 1283, 1153, 1072, 1011, 817, 754, 669; $^{1}$H NMR (400MHz, DMSO-$d_6$) (*δ*, ppm): 8.52 (d, 1H, $J$ = 1.6 Hz, NH), 8.25 (d, 2H, $J$ = 8.8 Hz, ArH), 8.17 (d, 2H, $J$ = 8.8 Hz, ArH), 7.45 (d, 1H, $J$ = 8.8 Hz, ArH), 7.30 (d, 1H, $J$ = 8.4 Hz, ArH), 5.27 (d, 1H, $J$ = 1.6 Hz, CH), 5.16 (s, 1H, CH), 2.90 (s, 3H, Me), 2.73 (s, 3H, Me), 1.59 (s, 3H, Me); HRMS (ESI): m/z calcd for: 586.9924 [M+H]$^{+}$, found: 586.9977.

**4g.**

**1',3,3'-Trimethyl-4,6-dip-tolyl-6,7-dihydro-1'*H*,4*H*-spiro[isoxazolo[5,4-*b*]pyridine-5,5'-pyrimidine]-2',4',6'(3'*H*)trione**

White solid, mp 189-190 $^{\circ}$C; IR (KBr, *ν*, cm$^{-1}$): 3150, 2997, 2922, 2857, 1748, 1683, 1650, 1594, 1513, 1471, 1378, 1143, 1080, 838, 772; $^{1}$H NMR (400MHz, DMSO-$d_6$) (*δ*, ppm): 8.10 (d, 1H, $J$ = 4.0 Hz, NH), 7.14 (d, 2H, $J$ = 8.0 Hz, ArH), 7.08 (d, 2H, $J$ = 8.0 Hz, ArH), 7.03 (d, 2H, $J$ = 8.0 Hz, ArH), 6.88 (d, 2H, $J$ = 8.0 Hz, ArH), 4.95 (d, 1H, $J$ = 2.4 Hz, CH), 4.84 (s, 1H, CH), 2.85 (s, 3H, Me), 2.26 (s, 3H, Me), 2.04 (d, 1H, $J$ = 7.2 Hz, $CH_3$), 1.55 (s, 3H, Me); HRMS (ESI): m/z calcd for: 459.2027 [M+H]$^{+}$, found: 459.2012.

**4h.**

**4,6-Bis(2,4-dichlorophenyl)-1',3,3'-trimethyl-6,7-dihydro-1'*H*,4*H*-spiro[isoxazolo[5,4-*b*]pyridine-5,5'-pyrimidine]-2',4',6'(3'*H*)trione**

White solid, mp 221-222 $^{\circ}$C; IR (KBr, *ν*, cm$^{-1}$): 3168 (NH), 3024, 2822, 1731, 1685, 1652, 1631, 1590, 1549, 1475, 1339, 1129, 1019, 867, 769; $^{1}$H NMR (400MHz, DMSO-$d_6$) (*δ*, ppm): 8.10 (d, 1H, $J$ = 2.0 Hz, NH), 7.59-7.58 (m, 1H, ArH), 7.49-7.48 (m, 1H, ArH), 7.42-7.38 (m, 2H, ArH), 7.25-7.16 (m, 2H, ArH), 5.20 (d, 1H, $J$ = 2.0 Hz, CH), 4.38 (s, 1H, CH), 3.16 (s, 3H, Me), 2.74 (s, 3H, Me), 1.57 (s, 3H, Me); HRMS (ESI): m/z calcd for: 567.0155 [M+H]$^{+}$, found: 567.0128.

## ACKNOWLEDGEMENTS

We are grateful for financial support from the National Science Foundation of China (Nos. 21072163, 21002083 and 09KJB150011), Sci. Foundation in Interdisciplinary Major Res. Project of XZNU (No. 09XKXK01) and NIH (R21 DA031860-01) for their generous support.

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