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# Building libraries of skeletally diverse scaffolds from novel heterocyclic active methylene compound through multi-component reactions

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ABSTRACT

Libraries of skeletally diverse potential bioactive polycyclic/spirocyclic heterocyclic compounds; 2-amino-7,9-dimethyl-5-oxo-4-aryl-4,5,6,7-tetrahydropyrano[2,3-*d*]pyrazolo[3,4-*b*]pyridine-3-carbonitrile, 2′-amino-7′,9′-dimethyl-2,5′-dioxo-6′,7′-dihydro-5′*H*-spiro[indoline-3,4′-pyrano[2,3-*d*]pyrazolo[3,4-*b*]pyridine]-3′-carbonitrile, and 5,5′-(arylmethylene)bis(4-hydroxy-1,3-dimethyl-1*H*-pyrazolo[3,4-*b*]pyridin-6(7*H*)-one) have been synthesized through a multi-component reaction using novel heterocyclic active methylene compound 4-hydroxy-1,3-dimethyl-1*H*-pyrazolo[3,4-*b*]pyridine-6(7*H*)-one as one of the building blocks. This protocol can be considered to be an efficient and eco-friendly strategy for diversity oriented synthesis.



Diversity oriented synthesis (DOS),[1] which aims at building skeletally diverse scaffolds using readily available building blocks is emerging as an important area of research in synthetic organic chemistry to address the challenge posed by chemical genetics.[2] In general, creating skeletal diversity through a multi-step reaction involving up to five steps is accepted as a DOS protocol.[3] Achieving DOS through multi-component reactions (MCRs)[4] is visualized as an efficient and eco-friendly strategy. One of the important strategies adopted in DOS is Build/Couple/Pair (BCP) strategy.[3,5] MCR is being used in couple phase[6] of BCP to build a poly functional substrate which is further manipulated to create skeletally diverse scaffolds. But, creating skeletal diversity in the couple phase itself can be considered as an innovation in achieving DOS. Our research group is actively engaged in developing multi-component reaction protocols for building libraries of skeletally diverse heterocyclic scaffolds.[7] Pyrazolopyridine scaffold is present in several inhibitors viz., CDK1,[8] protein kinases,[9] human immunodeficiency virus (HIV) reverse transcriptase,[10] and cGMP degradation inhibitors,[11] and CCR1 antagonist.[12] In addition this scaffold is reported to possess herbicidal and fungicidal activities.[11] Moreover, pyran skeleton is another important core in a number of natural products[13] and photochromic materials.[14] Therefore a polycyclic heterocyclic scaffold possessing both these skeletons can be an important scaffold to explore biological pathways. Moreover, developing a spirocyclic scaffold with pyrazolopyridine core is expected to improve the biological properties shown by oxindole moiety.[15]

Designing novel building blocks which can be used in MCR to achieve skeletal diversity is a challenging task. Active methylene compounds are very important building blocks used in several MCRs.[16] Diverse and complex polycyclic heterocyclic scaffolds can be accessed in one step through MCR by employing heterocyclic compounds possessing an active methylene unit as a part of the ring. 4-Hydroxyquinolin-2(1*H*)-one[17] and 4-hydroxy-2*H*-chromen-2-one[18] are a few such scaffolds used in several MCRs. Design and synthesis of novel heterocyclic active methylene compounds and their use in MCR to achieve skeletal diversity might significantly contribute in populating the chemical space. We herein report an eco-friendly reaction protocol for the synthesis of novel heterocyclic active methylene compound 4-hydroxy-1,3-dimethyl-1*H*-pyrazolo[3,4-*b*]pyridine-6(7*H*)-one **3a**, and demonstrated its use in MCR for creating diverse heterocyclic scaffold libraries viz., 2-amino-7,9-dimethyl-5-oxo-4-aryl-4,5,6,7-tetrahydropyrano[2,3-*d*]pyrazolo[3,4-*b*]pyridine-3-carbonitrile **6a–6q**, 2′-amino-7′,9′-dimethyl-2,5′-dioxo-6′,7′-dihydro-5′*H*-spiro[indoline-3,4′-pyrano[2,4-*d*]pyrazolo[3,4-*b*]pyridine]-3′-carbonitrile **8a–8g**, and 5,5′-(aryl methylene)bis(4-hydroxy-1,3-dimethyl-1*H*-pyrazolo[3,4-*b*]pyridin-6(7*H*)-one) **9a–9f**.

A solvent free two component reaction between 1,3-dimethyl-1*H*-pyrazol-5-amine **1** and diethyl malonate **2** resulted in two scaffolds viz., 4-hydroxy-1,3-dimethyl-1*H*-pyrazolo[3,4-*b*]pyridine-6(7*H*)-one **3a** and $N^1$,$N^3$-bis(1,3-dimethyl-1*H*-pyrazol-5-yl)malonamide **3b** in the ratio of 71:19 (yield 90%). But the reaction did not occur in ethanol under reflux condition (Scheme 1).

A three-component reaction with heterocyclic active methylene compound **3a**, 4-methylbenzaldehyde **5d**, and malononitrile **4** was

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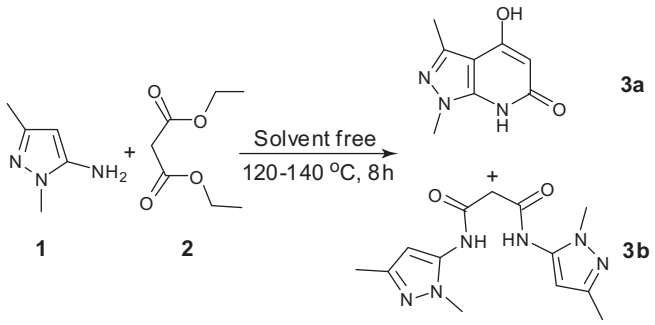



**Scheme 1.** Solvent-free synthesis of novel building block.

performed in water at room temperature using different acid and base catalysts (Table 1).

The reaction time and yield of the product were significantly influenced by the nature of the catalyst (Table 1, entries 1–11). The reaction was catalyzed only by bases. Base might activate the nucleophile. The reaction was found to occur very fast with excellent yield (99%) when piperidine (10 mol %) was used as catalyst (Table 1, entry 11). The product was characterized to be 2-amino-7,9-dimethyl-5-oxo-4-p-tolyl-4,5,6,7-tetrahydropyrano [2,3-*d*]pyrazolo[3,4-*b*]pyridine-3-carbonitrile scaffold **6d**.

The reaction was also performed in several organic solvents using piperidine (10 mol %) as catalyst (Table 2, entries 1–10).

Good to excellent yield (70–99%) of the product **6d** was obtained in all the solvents, but the reaction occurred very fast in water (Table 2, entry 10). Therefore the three-component reaction was performed in water using piperidine (10 mol %) as catalyst with several aromatic and heteroaromatic aldehydes **5a–5q** (Table 3, entries 1–17). The crystal structure[19] of compound **6k** is shown in Figure 1.

Use of isatin derivatives **7a–7g** as carbonyl component in the three-component reaction (reaction 1) resulted in 2′-amino-7′,9′-dimethyl-2,5′-dioxo-6′,7′-dihydro-5′*H*-spiro[indoline-3,4′-pyrano [2,3-*d*]pyrazolo[3,4-*b*]pyridine]-3′-carbonitrile scaffold **8a–8g** in

**Table 2**
Solvent optimization for three-component synthesis of **6d**[a]

| Entry | Solvent | Temp (°C) | Time | Yield[b] (%) |
|---|---|---|---|---|
| 1 | $CH_3CN$ | 30 | 8 h | 79 |
| 2 | $CH_3CN$ | Reflux | 1 h | 80 |
| 3 | *i*PrOH | 30 | 10 min | 77 |
| 4 | *t*BuOH | 30 | 15 min | 72 |
| 5 | DCM | 30 | 30 min | 81 |
| 6 | $CHCl_3$ | 30 | 10 min | 85 |
| 7 | DMSO | 30 | 20 min | 70 |
| 8 | DMF | 30 | 15 min | 90 |
| 9 | Ethanol | 30 | 8 min | 85 |
| 10 | Water | 30 | 5 min | 99 |

[a] The reactions were performed with 4-hydroxy-1,3-dimethyl-1*H*-pyrazolo[3,4-*b*]pyridine-6(7*H*)-one (2 mmol), 4-methyl benzaldehyde (2 mmol), malononitrile (2 mmol), piperidine (10 mol %), and solvent (10 mL).
[b] Yields of isolated products.

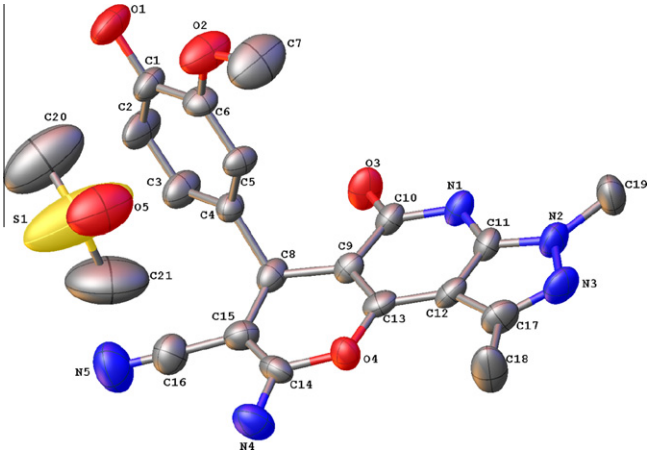
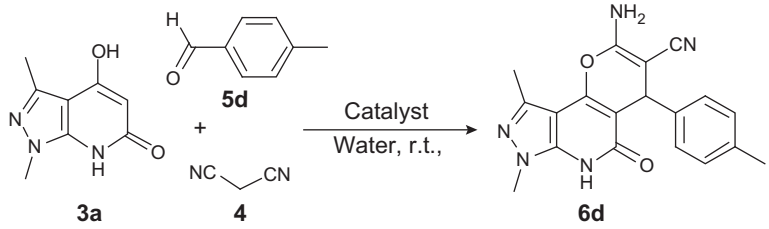



**Figure 1.** Crystal structure of compound **6k** DMSO solvate (the solvent molecule is disordered).

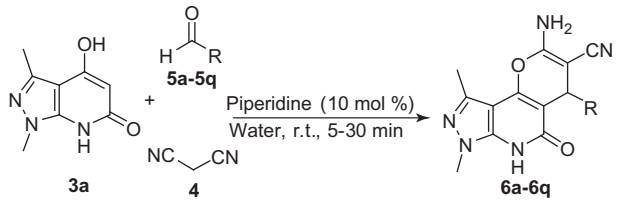
**Table 1**
Optimization of three-component reaction condition[a]




| Entry | Catalyst (mol %) | Time | Yield of **6d**[b] (%) |
|---|---|---|---|
| 1 | TsOH (10) | 12 h | Trace |
| 2 | $FeCl_3$ (10) | 12 h | Trace |
| 3 | $ZnCl_2$ (10) | 12 h | Trace |
| 4 | $K_2CO_3$ (10) | 12 h | 50 |
| 5 | $NH_4OAc$ (10) | 60 min | 70 |
| 6 | $Et_3N$ (10) | 60 min | 58 |
| 7 | $Et_2NH$ (10) | 60 min | 66 |
| 8 | DBU (10) | 60 min | 52 |
| 9 | L-Proline (10) | 60 min | 69 |
| 10 | Imidazole (10) | 60 min | 68 |
| 11 | Piperidine (10) | 5 min | 99 |

[a] The reactions were carried out with 4-hydroxy-1,3-dimethyl-1*H*-pyrazolo[3,4-*b*]pyridine-6(7*H*)-one (2 mmol), 4-methyl benzaldehyde (2 mmol), malononitrile (2 mmol), and water (10 mL) at 30 °C.
[b] Yields of isolated products.

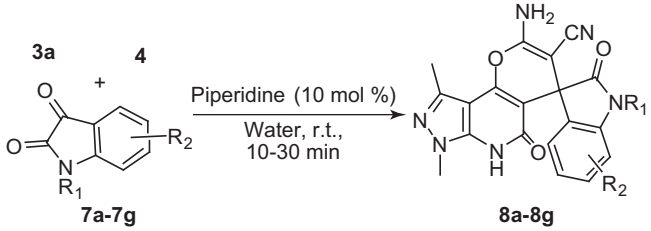
**Table 3**
Three-component synthesis of **6a–6q** catalyzed by piperidine (reaction 1)[a]




| Entry | R | Time (min) | Product **6** | Yield[b] (%) |
|---|---|---|---|---|
| 1 | $C_6H_5$ **5a** | 5 | **6a** | 95 |
| 2 | 2′-MeO-$C_6H_4$ **5b** | 5 | **6b** | 98 |
| 3 | 4′-MeO-$C_6H_4$ **5c** | 5 | **6c** | 97 |
| 4 | 4′-Me-$C_6H_4$ **5d** | 5 | **6d** | 99 |
| 5 | 4′-$NO_2$-$C_6H_4$ **5e** | 5 | **6e** | 86 |
| 6 | 4′-Cl-$C_6H_4$ **5f** | 5 | **6f** | 85 |
| 7 | 3′-Br-$C_6H_4$ **5g** | 5 | **6g** | 80 |
| 8 | 4′-F-$C_6H_4$ **5h** | 5 | **6h** | 97 |
| 9 | 4′-OH-$C_6H_4$ **5i** | 10 | **6i** | 95 |
| 10 | 3′, 4′-$(OH)_2$-$C_6H_3$ **5j** | 10 | **6j** | 84 |
| 11 | 3′-MeO,4′-OH-$C_6H_3$ **5k** | 10 | **6k** | 98 |
| 12 | 2′,3′-$(MeO)_2$-$C_6H_3$ **5l** | 20 | **6l** | 75 |
| 13 | 3′,4′-$(MeO)_2$-$C_6H_3$ **5m** | 20 | **6m** | 82 |
| 14 | 2′,4′,5′-$(MeO)_3$-$C_6H_2$ **5n** | 30 | **6n** | 60 |
| 15 | 3′,4′,5′-$(MeO)_3$-$C_6H_2$ **5o** | 30 | **6o** | 65 |
| 16 | 2′-Thiophenyl **5p** | 15 | **6p** | 90 |
| 17 | 2′-Furanyl **5q** | 15 | **6q** | 82 |

[a] The reactions were carried out with 4-hydroxy-1,3-dimethyl-1*H*-pyrazolo[3,4-*b*]pyridine-6(7*H*)-one (2 mmol), aldehyde (2 mmol), malononitrile (2 mmol), piperidine (10 mol %), and water (10 mL) at 30 °C.
[b] Yields of isolated products.

**Table 4**
Three-component synthesis of spiro[pyranopyrazolopyridine-indoline]diones[a] **8a–8g**




| Entry | $R_1$ | $R_2$ | Time (min) | Product **8** | Yield[b] (%) |
|---|---|---|---|---|---|
| 1 | H | H **7a** | 10 | **8a** | 80 |
| 2 | Methyl | H **7b** | 10 | **8b** | 94 |
| 3 | Benzyl | H **7c** | 20 | **8c** | 98 |
| 4 | Allyl | H **7d** | 15 | **8d** | 92 |
| 5 | Propargyl | H **7e** | 30 | **8e** | 88 |
| 6 | H | 7-F **7f** | 10 | **8f** | 93 |
| 7 | H | 5-$NO_2$ **7g** | 10 | **8g** | 91 |

[a] Reaction condition: 4-Hydroxy-1,3-dimethyl-1*H*-pyrazolo [3,4-*b*]pyridine-6(7*H*)-one (2 mmol), isatin (2 mmol), malononitrile (2 mmol), piperidine (10 mol %), and water (10 mL) at 30 °C.
[b] Yields of isolated products.

good yields (80–98%) under the same reaction condition (Table 4). The crystal structure[19] of compound **8a** is given in Figure 2.

The reaction is suggested to occur through the mechanism shown in Scheme 2.

Then a pseudo three-component reaction was performed with two equivalents of 4-hydroxy-1,3-dimethyl-1*H*-pyrazolo[3,4-*b*]pyridine-6(7*H*)-one **3a** and one equivalent of aldehyde in water (5 mL) to obtain 5,5′-(arylmethylene)bis(4-hydroxy-1,3-dimethyl-1*H*-pyrazolo[3,4-*b*]pyridin-6(7H)-one) **9** (reaction 2).

Though the reaction resulted from moderate to good yield of the product **9** with aromatic and heteroaromatic aldehydes (Table 5, entries 1–6), the reaction did not occur when isatin was used as carbonyl building block in this pseudo three-component reaction (Table 5, entry 7). The observed difference in the reactivity of isatin as compared to aldehydes in this pseudo three-component reaction (reaction 2) can be ascribed to the inherent difference in the reactivity of aldehyde and ketone. Moreover the active methylene moiety of **3a** is not sufficiently reactive to bring out Knoevenagel condensation with isatin **7**. The less reactivity of this moiety is also reflected in the difference in the reaction time of three-component reaction (reaction 1) and pseudo three-component reactions (reaction 2). The crystal structure[19] of compound **9d** is given in Figure 3.

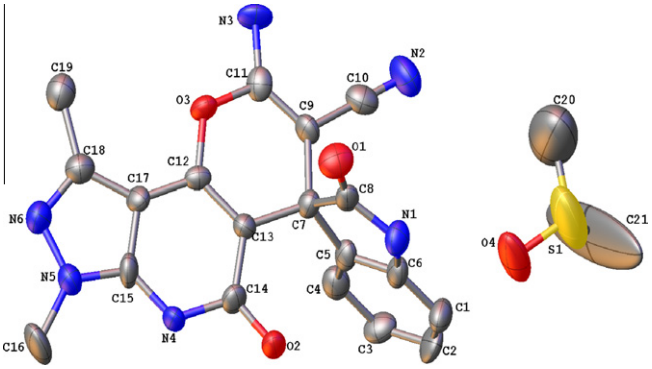
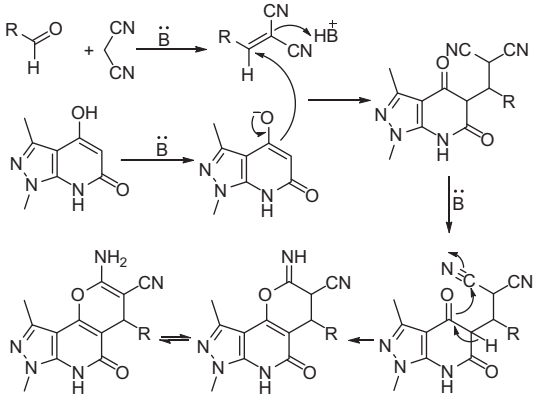


**Figure 2.** Crystal structure of **8a** DMSO solvate (the solvent molecule is disordered).



**Scheme 2.** Plausible mechanism for the formation of **6**.

In conclusion, we have described the synthesis of a novel heterocyclic active methylene compound under a solvent-free condition. Use of this scaffold to develop skeletally diverse heterocyclic scaffolds through multi-component reaction in an eco-friendly synthetic protocol has been demonstrated. The scaffold shows reactivity similar to active methylene compounds generally employed in MCRs.

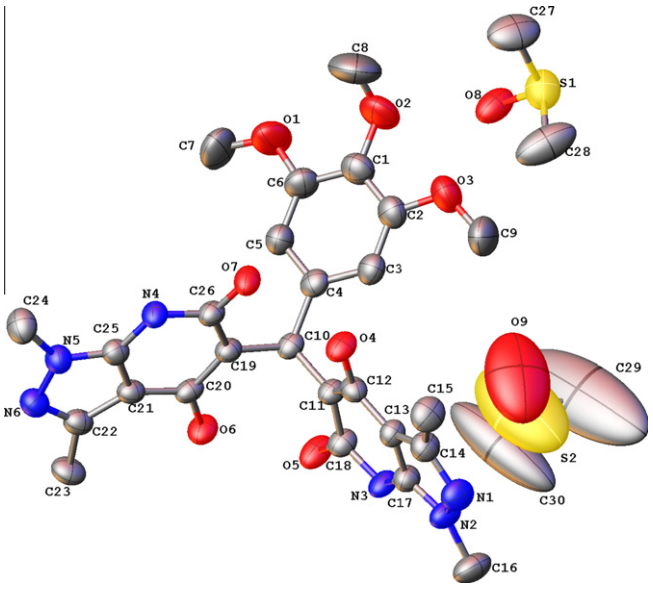


**Figure 3.** Crystal structure of **9d** DMSO solvate (the solvent molecule is disordered).

## Acknowledgment

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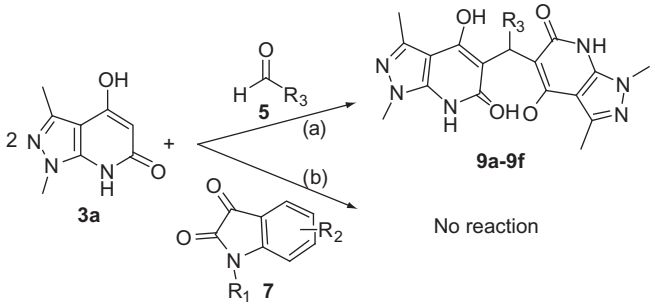
## Supplementary data

Supplementary data (general experimental procedure, complied spectroscopic data of new compounds and scanned copies of spectra) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.04.013.

**Table 5**
Pseudo three-component reaction (reaction 2)[a]




| Entry | $R_3$ **5** | Time (h) | Product **9** | Yield[b] (%) |
|---|---|---|---|---|
| 1 | 4′-Me-$C_6H_4$ | **6** | **9a** | 90 |
| 2 | 4′-MeO-$C_6H_4$ | **6** | **9b** | 88 |
| 3 | 2′-MeO, 3′-MeO-$C_6H_3$ | **6** | **9c** | 70 |
| 4 | 3′,4′,5′-$(MeO)_3$-$C_6H_2$ | **6** | **9d** | 60 |
| 5 | 2′-Furanyl | **6** | **9e** | 77 |
| 6 | 2′-Thiophenyl | **6** | **9f** | 85 |
| 7 | Isatin **7** | **12** | — | No reaction |

[a] (a) and (b): The reactions were carried out with 4-hydroxy-1,3-dimethyl-1*H*-pyrazolo[3,4-*b*]pyridine-6(7*H*)-one (2 mmol), aldehyde/isatin (1 mmol), piperidine (10 mol %), and water (10 mL) at 30 °C.
[b] Yields of isolated products.

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19. Crystallographic data (excluding structure factors) for **6k**, **8a,** and **9d** in this Letter have been deposited with Cambridge Crystallographic Data Centre as supplementary publication number CCDC 836901,836902 and 836903, respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].