Organic LETTERS

Letter

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Convenient Access to Polyfunctional Pyrazoles via a Highly Efficient and Regioselective Multicomponent Reaction

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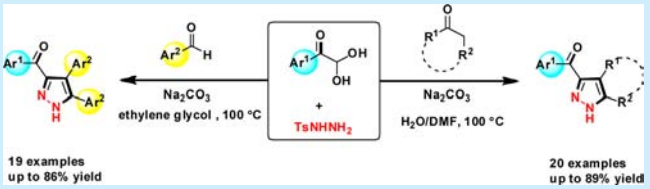
Supporting Information

ABSTRACT: A multicomponent reaction has been developed for the synthesis of polyfunctional pyrazole derivatives from readily available arylglyoxal monohydrates, tosylhydrazine, and aldehydes or ketones. This synthetic method has significant advantages in broad substrate scope, excellent regioselectivity, and simple operation.



The pyrazole moiety is widely regarded as a privileged heterocyclic skeleton with broad pharmaceutical activities, including antitumor, antifungal, and inhibitory activities toward Cyclin Dependent Kinases (CDKs) and DNA gyrase (Figure 1).[1] Substituted pyrazoles have also been utilized as useful ligands for metal catalyzed cross-coupling reactions.[2]

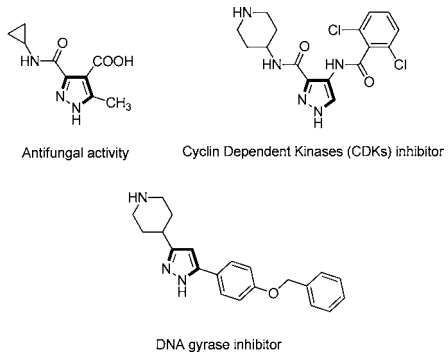
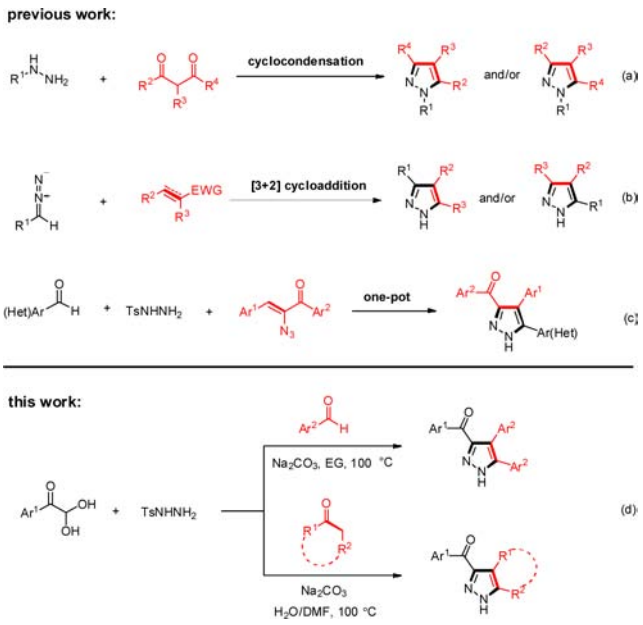


Figure 1. Some biologically active pyrazole compounds.

In the past few decades, several methods have been developed for the preparation of substituted pyrazoles.[3] The most common synthetic routes to pyrazoles are as follows: cyclocondensation between hydrazine derivatives and 1,3-dicarbonyl compounds (Scheme 1a);[4] 1,3-dipolar cycloaddition of diazo compounds with electron-deficient alkenes or alkynes (Scheme 1b);[3b,d,5] and three-component reaction of vinyl azides, aldehydes, and tosylhydrazine (Scheme 1c).[6] However, these methods are somewhat limited to harsh reaction conditions, poor regioselectivity, and narrow substrate scope. Therefore, the development of a highly efficient and regioselective method would be greatly valuable for the synthesis of polyfunctionalized pyrazoles from easily available substrates. Herein, a novel method is presented for the synthesis of polysubstituted pyrazoles from simple arylglyoxal monohydrates, tosylhydrazine, and aldehydes or ketones with excellent regioselectivity and a broad substrate scope (Scheme 1d).

Scheme 1. Strategies for the Synthesis of Pyrazole



Initially, the reaction of phenylglyoxal monohydrate (**1a**), tosylhydrazine (**2**), and benzaldehyde (**3a**) was screened in ethylene glycol at 100 °C in the presence of Cs_2CO_3. To our delight, the desired compound (4,5-diphenyl-1*H*-pyrazol-3-yl)(phenyl)methanone **4aa** was furnished in 81% yield (entry 1). Encouraged by the aforementioned results, other reaction conditions were investigated, including the choice of base,

Received: February 27, 2015
Published: March 31, 2015

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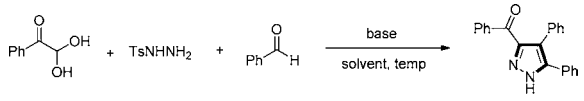
DOI: 10.1021/acs.orglett.5b00605
Org. Lett. 2015, 17, 1914−1917

solvent, and temperature. The results are summarized in Table 1. It was observed that most of the bases (Cs_2CO_3, K_2CO_3, KOH, NaOH, DABCO, DBU, and Na_2CO_3) could successfully promote the reaction (entries 1–7). Among these, Na_2CO_3 was determined optimum, and **4aa** was isolated in 85% yield (entry 7). Various solvents were screened, and the results revealed that ethylene glycol is the best choice for the reaction (entries 10–15). Unfortunately, the desired product **4aa** was not obtained in DMSO, DMF, and toluene (entries 13–15). Moreover, the yield was slightly decreased when the reaction was performed at a lower or higher temperature (entries 8 and 9).

Table 1. Optimization of the Reaction Conditions[a]



1a **2** **3a** **4aa**

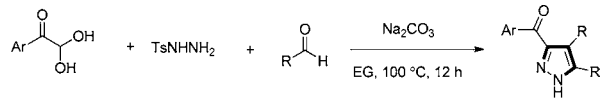
entry	solvent	base	temp (°C)	yield (%)[b]
1	EG	Cs_2CO_3	100	81
2	EG	K_2CO_3	100	75
3	EG	KOH	100	76
4	EG	NaOH	100	72
5	EG	DABCO	100	15
6	EG	DBU	100	10
7	EG	Na_2CO_3	100	85
8	EG	Na_2CO_3	80	78
9	EG	Na_2CO_3	110	82
10	EtOH	Na_2CO_3	78	71
11	*i*-PrOH	Na_2CO_3	80	73
12	H_2O	Na_2CO_3	100	66
13	DMSO	Na_2CO_3	100	–
14	DMF	Na_2CO_3	100	–
15	toluene	Na_2CO_3	100	–

[a]Reaction conditions: **1a** (0.2 mmol, 2.0 equiv), **2** (0.2 mmol, 2.0 equiv), **3a** (0.15 mmol, 1.5 equiv), base (0.8 mmol, 8.0 equiv), and solvent (3 mL) for 12 h. [b]Isolated yields. EG = ethylene glycol.

With the optimized conditions in hand, the scope of the arylglyoxal monohydrates (**1**) was investigated. The results are summarized in Table 2. The efficiency of this transformation was significantly influenced by the electronic properties of the substituents on the aromatic ring system. In general, electron-neutral (H) and halogen (2-Cl, 4-Cl, 3-Br) groups were found preferable to electron-donating (4-Me, 4-OMe, 3,4-OCH_2O) and electron-withdrawing (3-NO_2) groups in terms of isolated yields (45–85%; entries 1–8). To our delight, the arylglyoxal monohydrates with 2-thienyl, 2-benzofuryl, 1-naphthyl, and 2-naphthyl also gave the desired products successfully in moderate to good yields (68–77%; entries 9–12). Next, the scope of the aldehydes (**3**) was investigated. Yields of multisubstituted pyrazoles **4ab**–**4ah** were obtained in 55–86% yield, when using different aldehydes (entries 13–19). To our disappointment, the corresponding product **4ai** was not obtained when the substituent group R was ethyl (entry 20). A more likely reason is the instability of the alkyl diazo intermediate generated from aliphatic aldehyde with tosylhydrazine. The structure of **4ac** was further determined by X-ray crystallographic analysis (see Supporting Information).

This work aspired to obtain a diverse library of polyfunctional pyrazoles, and ketones were thus chosen for the reaction instead of aldehydes (Scheme 2). Pleasingly, arylglyoxal monohydrates (**1**) containing different functional groups (H, alkyl, halogen, electron-withdrawing (EWG), and electron-donating (EDG) groups) reacted with acetylacetone (**5a**) to provide the expected products **6aa**–**6la** in excellent yields (75–89%).

Table 2. Substrates Scope of Three-Component Reaction with Aldehydes[a]



1 **2** **3** **4**

entry	Ar	R	4	yield (%)[b]
1	Ph	Ph	**4aa**	85
2	4-MeC_6H_4	Ph	**4ba**	71
3	3-$MeOC_6H_4$	Ph	**4ca**	45
4	3,4-$(OCH_2O)C_6H_3$	Ph	**4da**	65
5	2-ClC_6H_4	Ph	**4ea**	81
6	4-ClC_6H_4	Ph	**4fa**	83
7	3-BrC_6H_4	Ph	**4ga**	80
8	3-$NO_2C_6H_4$	Ph	**4ha**	55
9	2-thienyl	Ph	**4ia**	68
10	2-benzofuryl	Ph	**4ja**	72
11	1-naphthyl	Ph	**4ka**	75
12	2-naphthyl	Ph	**4la**	77
13	Ph	4-MeC_6H_4	**4ab**	81
14	Ph	4-$MeOC_6H_4$	**4ac**	55
15	Ph	3,4-$(MeO)_2C_6H_4$	**4ad**	57
16	Ph	4-ClC_6H_4	**4ae**	84
17	Ph	4-BrC_6H_4	**4af**	86
18	Ph	2-thienyl	**4ag**	71
19	Ph	2-naphthyl	**4ah**	75
20	Ph	Et	**4ai**	0

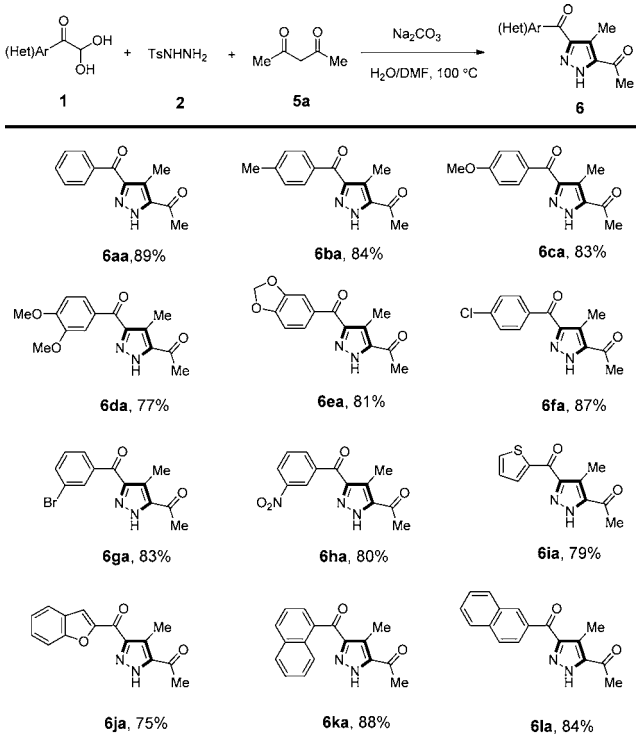
[a]Reactions were carried out with **1** (2.0 mmol, 2.0 equiv), **2** (2.0 mmol, 2.0 equiv), **3** (1.5 mmol, 1.5 equiv), and Na_2CO_3 (8.0 equiv) in ethylene glycol (20.0 mL) at 100 °C for 12 h. [b]Yields of the isolated products were shown.

Encouraged by the results achieved above, the scope of ketones was subsequently examined (Scheme 3). The steric hindrance of isopropyl (**6ac**) or *tert*-butyl (**6ad**) groups in the 1, 3-diketones was shown to significantly impair the reaction. However, the reaction occurred smoothly for other ketones regardless of differences in electronic properties, and the corresponding products were obtained in good to excellent yields (66–84%; **6ab**, and **6ae**–**6ai**). The structure of **6ah** was determined by single-crystal X-ray diffraction analysis (see SI).

To gain insight into the reaction process, control experiments were performed (Scheme 4). In the presence of Na_2CO_3, 1,2-diphenylethanone **5j**[7] was obtained with a 78% yield from benzaldehyde (**3a**) and tosylhydrazine (**2**) in ethylene glycol at 100 °C for 12 h (eq 1). It was then verified that the desired product **4aa** could be obtained in 85% yield from phenylglyoxal monohydrate (**1a**), tosylhydrazine (**2**), and 1,2-diphenylethanone **5j** under the same conditions (eq 2). The product **4aa** was also obtained in 76% yield from the reaction of 2-diazo-1-phenylethanone (**7a**), tosylhydrazine (**2**), and benzaldehyde (**3a**) at 100 °C for 12 h (eq 3). The reaction of **7a** with **5j** also afforded the desired product **4aa** in 79% yield (eq 4). These results identified that **7a** and **5j** most probably are the intermediates for this reaction. The desired product **4aa** was not obtained when using 1,2-diphenylethyne (**8a**) as the

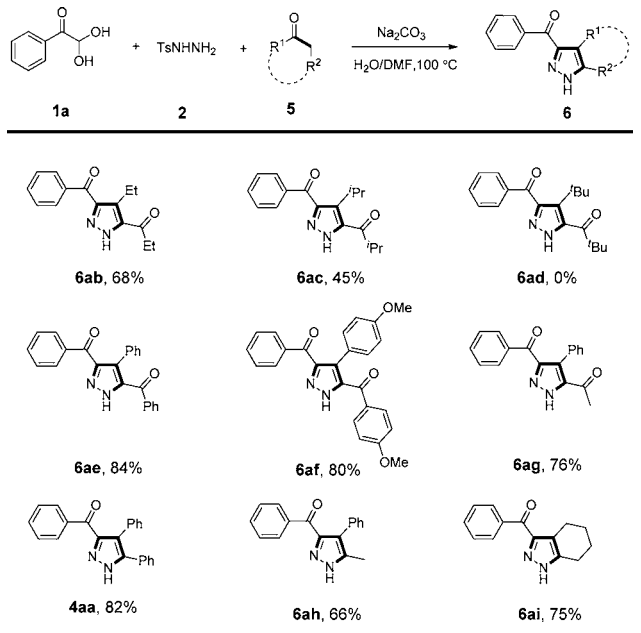
DOI: 10.1021/acs.orglett.5b00605
Org. Lett. 2015, 17, 1914–1917

Scheme 2. Scope of Arylglyoxal Monohydrates for the Reaction with Ketones[a]



[a]Reactions were performed with **1** (1.0 mmol, 1.0 equiv), **2** (1.0 mmol, 1.0 equiv), **5a** (1.5 mmol,1.5 equiv), and Na_2CO_3 (8.0 equiv) in the mixture solvent H_2O/DMF (2:1) at 100 °C for 2 h. Isolated products.

Scheme 3. Scope of Ketones[a]

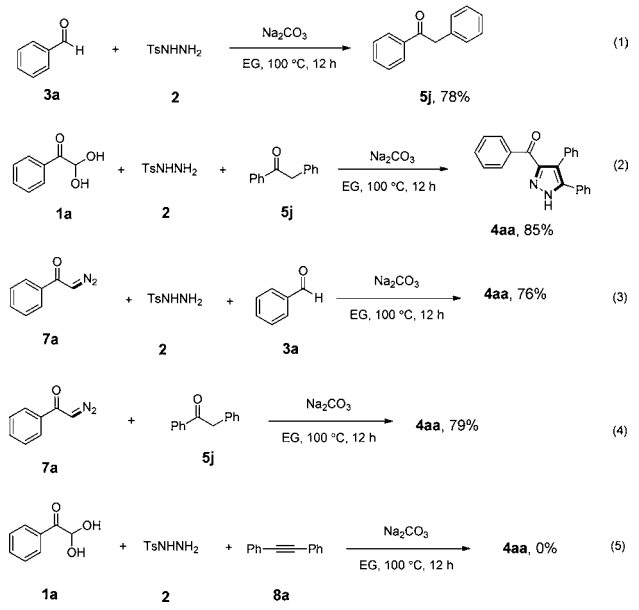


[a]Isolated products.

substrate under the same reaction conditions. This result excluded the possibility of an alkyne intermediate (**8a**) in this reaction (eq 5).[8]

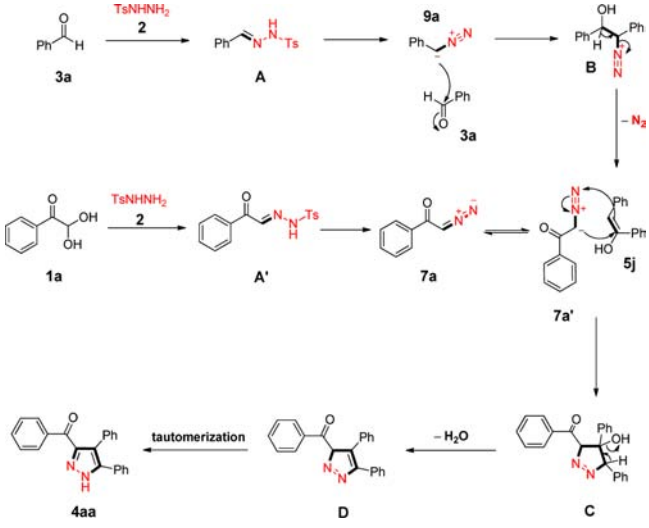
On the basis of the above-mentioned experimental results, a possible reaction mechanism for this reaction is proposed as

Scheme 4. Control Experiments



shown in Scheme 5 (**4aa** as an example). Initially, the condensation of benzaldehyde **3a** and tosylhydrazine **2** affords

Scheme 5. A Possible Mechanism



the corresponding hydrazone intermediate **A**, which subsequently transforms into intermediate **9a** in the presence of Na_2CO_3. Then, **9a** reacts with benzaldehyde **3a** to afford the intermediate **B**, which subsequently affords the compound **5j** via a 1,2-proton transfer with the departure of a molecule of N_2. Meanwhile, phenylglyoxal monohydrate **1a** reacts with tosylhydrazine **2** to furnish the hydrazone intermediate **A′** and it further converts to α-diazophenylethanone **7a**,[9] which resonates to **7a′** and reacts with **5j** via a 1,3-dipolar cycloaddition to afford intermediate **C**. Afterward, the intermedidate **C** transforms into intermediate **D** by the elimination of a molecule of H_2O. Finally, the intermediate **D** is converted to the desired product **4aa** via a tautomerization reaction.

In summary, a highly efficient and regioselective method has been developed for the synthesis of polysubstituted pyrazoles,

DOI: 10.1021/acs.orglett.5b00605
Org. Lett. 2015, 17, 1914−1917

providing easy access to a library of pyrazoles from readily available starting materials with a very simple operation. Further studies into the applications of this method are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, product characterizations, crystallographic data, and copies of the ^{1}H and ^{13}C NMR spectra are included. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to the National Natural Science Foundation of China (Grants 21272085 and 21472056) for financial support.

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DOI: 10.1021/acs.orglett.5b00605
Org. Lett. 2015, 17, 1914−1917