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A four-step tandem synthesis of 3,5-diaroyl-4-arylpyrazoles from 1,3-diaryl-propane-1,3-diketones

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ABSTRACT

A novel four-step tandem procedure was developed for efficient synthesis of 3,5-diaroyl-4-arylpyrazoles by simply stirring the mixture of 1,3-diarylpropane-1,3-diketones, TsN_3, aqueous $MeNH_2$ and Na_2CO_3 in DMF at 85 °C for 3 h.

Pyrazoles are an important heterocyclic family due to their wide spectrum of biological properties.[1] As shown in Fig. 1, both structures of celecoxib (**A**)[2a] and crizotinib (**B**)[2b] contain a pyrazole unit. The former is used as a COX-2 selective nonsteroidal anti-inflammatory drug and the latter is an anti-cancer drug for treatment of some non-small cell lung carcinoma. Recently, 3,4,5-trisubstituted pyrazoles **C**[3a] were reported as potent inhibitors of carbonic anhydrase isoforms and **D**[3b] demonstrated the antiproliferative activities.

Pyrazole scaffold is a five-membered heterocycle containing two nitrogen atoms. A number of methods have been developed for the synthesis of pyrazole derivatives and two practical methods were mainly employed.[1d,4] As shown in Scheme 1, one is the condensation between hydrazines and 1,3-dicarbonyls; the other is 1,3-dipolar cycloaddition between diazo compounds and alkynes.

The 1,3-dipolar cycloaddition usually has higher regioselectivity and is more suitable for the synthesis of 3,4,5-trisubstituted pyrazoles because two substituents (R^2 and R^3) conveniently come from the alkynes. However, this method seriously suffered from the limited scope of alkynes. As shown in Scheme 2, although alkenes are excellent dipolarophiles for most 1,3-dipolar cycloadditions, only a few of them bearing a good leaving group (such as NO_2 or Br) can be used as alternatives of alkynes for such purpose.[5] When the normal alkenes were used, at least one more step for aromatization was required.[6]

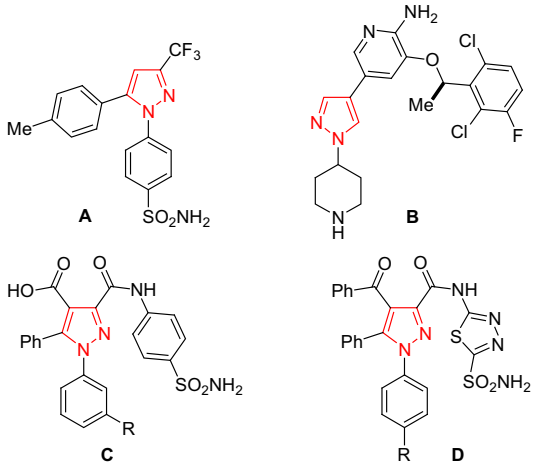

Fig. 1. Some bioactive pyrazole derivatives.

However, several interesting 1,3-dipolar cycloadditions[6,7] between aldehydes/ketones and diazo compounds drew our attention, in which the carbonyl group was *in situ* converted into enol or enamine in the presence of a base, such as a secondary amine or a carbonate. It was interesting to observe that 1,3-diphenylpropane-1,3-dione (**1a**) were converted into 3,5-dibenzoyl-4-phenylpyrazole (**4a**) in two separated steps, but with low efficiency (Scheme 3).[6] Herein, we would like to report that the same

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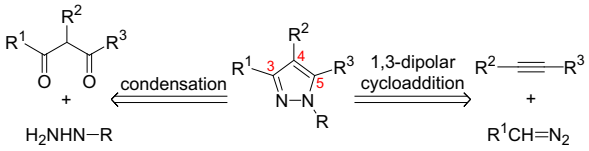
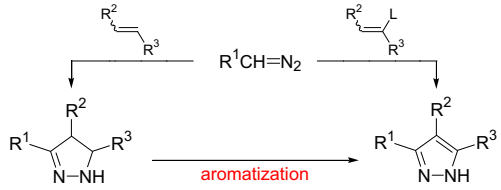
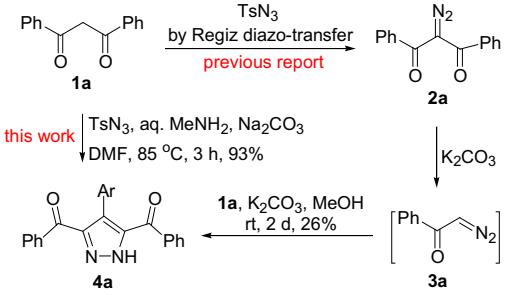


Scheme 1. Two practical methods for the synthesis of pyrazoles.



Scheme 2. 1,3-Dipolar cycloaddition with different alkenes.

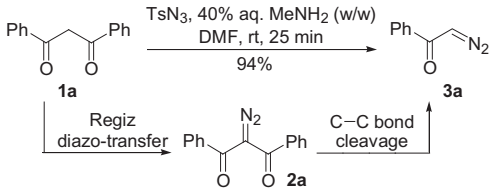


Scheme 3. Synthesis of 3,5-dibenzoyl-4-phenylpyrazole (**4a**).

conversion can be completed in one step with high efficiency. Further experiments proved that this is a general four-step tandem procedure, by which a series of 3,5-diaroyl-4-aryl-pyrazoles **4** were synthesized efficiently by simply stirring the mixture of 1,3-diaryl-propane-1,3-diones **1**, TsN_3, aqueous $MeNH_2$ and Na_2CO_3 in DMF at 85 °C for 3 h.

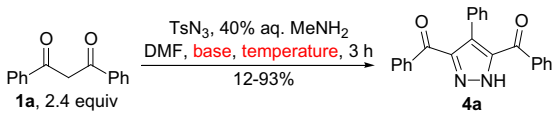
In fact, the previous reported two-step procedure[6] for the conversion of **1a** into **4a** involved three well-studied reactions: (a) Regitz diazo-transfer of **1a**; (b) C–C bond cleavage of **2a**; and (c) 1,3-dipolar cycloaddition between **1a** and **3a**. Investigation showed that they are all base-catalyzed reactions and the best catalyst for each reaction is tertiary amines,[8] alkali hydroxides[9,10] and alkali carbonates,[7a,11] respectively. Unfortunately, these three reactions have not become a tandem reaction because no one base or bases could be shared efficiently by each of them. For example, the previous conversion of **2a** into **4a** actually is a two-step tandem reaction including a formation of **3a** by C–C bond cleavage of **2a**. It had a low efficiency just because K_2CO_3 is not an efficient base for C–C bond cleavage of **2a**. Luckily, we recently found that the compound **3a** could be obtained in almost quantitative yield when the mixture of substrate **1a** and TsN_3 was treated by aqueous $MeNH_2$ in DMF.[12] As shown in Scheme 4, since the diazo compound **2a** was confirmed to be an intermediate, this procedure offered a highly efficient two-step tandem synthesis of **3a** from **1a**.

This result also strongly implied that the pyrazole **4a** may be synthesized by this procedure when excess **1a** is employed. Thus, we were encouraged to test the tandem synthesis of **4a** from **1a** as shown in Table 1. To our disappointment, the desired **4a** was obtained in 12% yield when the mixture of **1a** (2.4 equiv), TsN_3 and aq. $MeNH_2$ (40%, w/w) was stirred at room temperature for 3 h (entry 1). The yield of **4a** was significantly improved at 85 °C (entry 2), but it still was not acceptable. Considering $MeNH_2$ is not a good base for enolization of **1a**, the second base was used. Compared to the amines (entries 3–6) and alkali hydroxides (entry 7), the alkali carbonates (entries 8–10) gave the best results. The highest yield of **4a** was obtained in the presence of 0.2 equiv of Na_2CO_3 (entry 10).



Scheme 4. Two-step tandem synthesis of **3a** from **1a**.

Table 1
Conditional tests for the tandem synthesis of **4a**.[a]



Entry	Base (equiv)	Temp (°C)	Time (h)	**4a** yield (%)[b]
1	–	rt	3	12
2	–	85	3	42
3	Et_3N (0.2)	85	3	50
4	DABCO (0.2)	85	3	68
5	pyrolidine (0.2)	85	3	71
6	DBU (0.2)	85	3	80
7	KOH (0.2)	85	3	83
8	Cs_2CO_3 (0.2)	85	3	85
9	K_2CO_3 (0.2)	85	3	91
10	**Na_2CO_3 (0.2)**	**85**	**3**	**93**
11	Na_2CO_3 (0.2)	75	8	93
12	Na_2CO_3 (0.2)	95	3	90
13	Na_2CO_3 (0.1)	85	3	88
14	Na_2CO_3 (0.3)	85	3	93

[a] The solution of **1a** (1.2 mmol), TsN_3 (0.5 mmol), aq. $MeNH_2$ (40%, w/w, 0.6 mmol) and a base in DMF (2 mL) was stirred under the given temperatures and times.
[b] Isolated yields.

To generalize this tandem reaction, different substrates were tested. As shown in Scheme 5, all tested substrates **1a**–**1r** gave the desired products **4a**–**4r** smoothly under the optimized conditions.[14] The steric effects were clearly observed in the group of products **4b**–**4d**, in which the *ortho*-substituents (**4b**) led to lower yields and longer reaction times. Their electronic effects were completely same as the synthesis of α-diazoketones **3**.[12] The product **4r** was synthesized smoothly from the corresponding heteroaryl substrates **1r**. In a 3-gram scale synthesis, **4a** was obtained in 95% yield after purification by a flash chromatography. However, the strong electron-withdrawing group substituted 1,3-diaryl-1,3-diketones and 1,3-dialkyl-1,3-diketones proved to be unsuitable substrates for this tandem synthesis, because the former usually are inaccessible substrates[13] and the later cannot be converted into the corresponding α-diazoketones.[12] As shown in Fig. 2, the structure of the product **4e** was confirmed by single crystal X-ray diffraction analysis.[15]