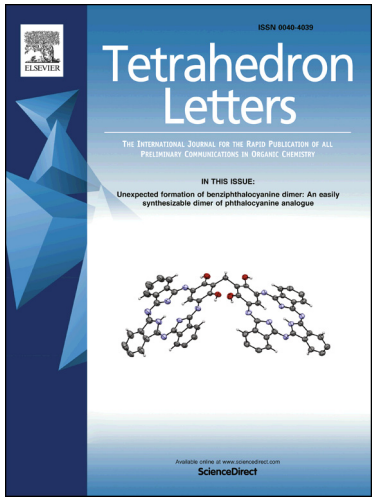

A Four-Step Tandem Synthesis of 3,5-Diaroyl-4-arylpyrazoles from 1,3-Diaryl-propane-1,3-diketones

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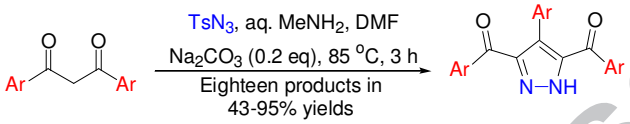

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A Four-Step Tandem Synthesis of 3,5-Diaroyl-4-arylpyrazoles from 1,3-Diarylpropane-1,3-diketones

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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 Figure 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.

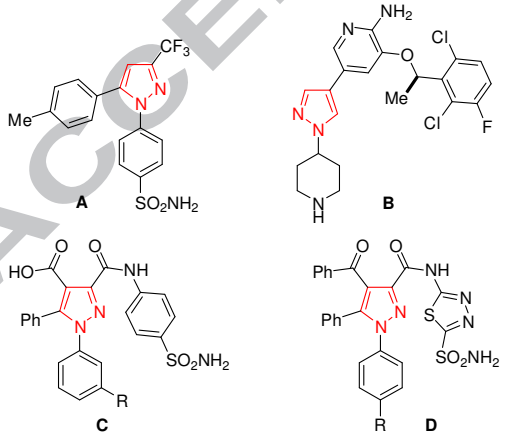
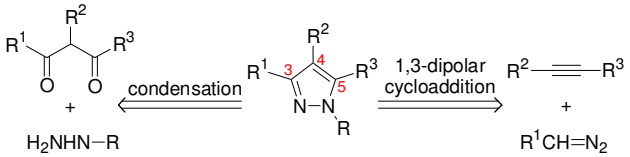


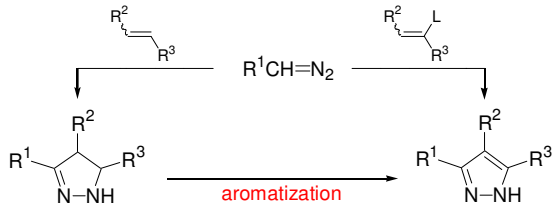
Figure 1. Some bioactive pyrazole derivatives.

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.



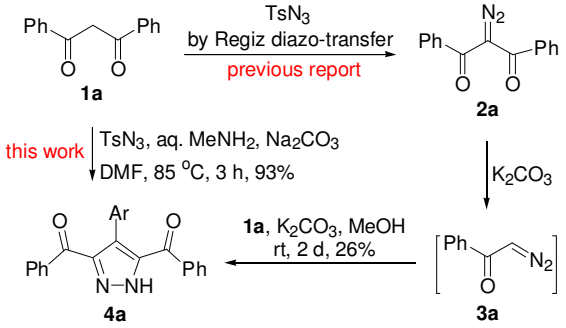
Scheme 1. Two practical methods for the synthesis of pyrazoles.

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]



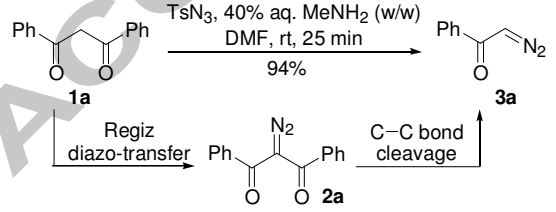
Scheme 2. 1,3-Dipolar cycloaddition with different alkenes.

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 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-diarylpropane-1,3-diones **1**, TsN_3, aqueous $MeNH_2$ and Na_2CO_3 in DMF at 85 °C for 3 h.



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

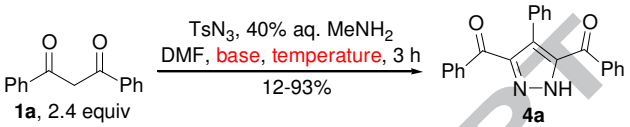
In fact, the previous reported two-step procedure[6] for the conversion of **1a** into **4a** involved three well-studied reactions: (a) Regitz diazo-transfer of **1a**; (b) C–C bond cleavage of **2a**; and (c) 1,3-dipolar cycloaddition between **1a** and **3a**. Investigation showed that they are all 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**.



Scheme 4. 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).

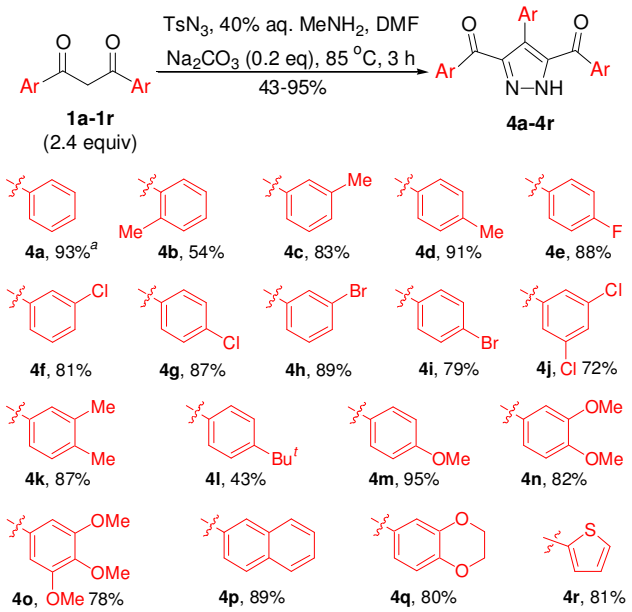
Table 1. Conditional tests for the tandem synthesis of **4a**.[a]



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



[a]The isolated yields were obtained for all products.

Scheme 5. Tandem synthesis of the desired products **4a-4r**.

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 can not be converted into the corresponding α-diazoketones.[12] As shown in Figure 2, the structure of the product **4e** was confirmed by single crystal X-ray diffraction analysis.[15]

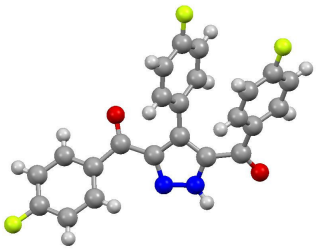
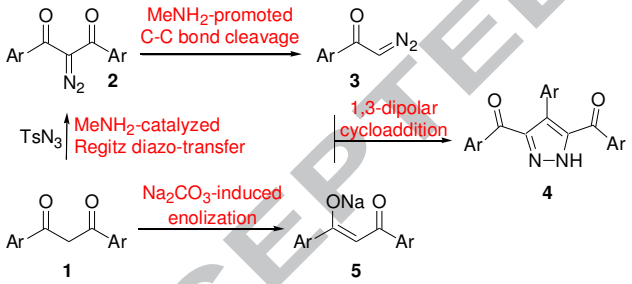


Figure 2. The structure of **4e**.

Based on the above results, a possible pathway was proposed for this tandem reaction. As shown in Scheme 6, the substrate **1** initially carried out a $MeNH_2$-catalyzed Regitz diazo-transfer to give product **2**. A $MeNH_2$-mediated C–C bond cleavage of **2** then occurred to form product **3**. Meanwhile, the excess substrate **1** was enolized in presence of Na_2CO_3 to yield reactive specie **5**. Finally, the target product **4** was produced by a dipolar cycloaddition between **3** and **5**. Since **1** was used twice as a substrate to form the intermediate **3** and the reactive specie **5**, respectively, this procedure actually is a four-step tandem procedure.



Scheme 6. A proposed pathway for the tandem synthesis of **4**.

In conclusion, a novel method was developed for the synthesis of 3,5-diaroyl-4-arylpyrazoles by simply stirring the mixture of 1,3-diarylpropane-1,3-diones, TsN_3, aqueous $MeNH_2$ and Na_2CO_3 in DMF at 85 °C for 3 h. It was a novel four-step tandem reaction, in which the 1,3-diarylpropane-1,3-diketone was used twice as a substrate. Although both aqueous $MeNH_2$ and Na_2CO_3 were used as bases, each of them has its specific duties and responsibilities without interferences.

Acknowledgments

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14. **A typical procedure for preparation of 3,5-dibenzoyl-4-phenylpyrazole (4a).** To a stirred solution of 1,3-diphenylpropane-1,3-dione (**1a**, 269 mg, 1.2 mmol) and Na_2CO_3 (10.6 mg, 0.1 mmol) in DMF (2 mL) was added tosyl azide (98.6 mg, 0.5 mmol) and $MeNH_2$ (40% aqueous solution, 46.6 mg, 0.6 mmol) successively. After the mixture was stirred at 85 °C (oil bath) for 3 h (monitored by TLC), it was quenched with water. The resultant mixture was extracted with CH_2Cl_2 and the combined layers were dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by a flash chromatography [silica gel, 15% EtOAc in petroleum ether (60–90 °C)] to give 164 mg (93%) of product **4a** as a white solid, mp 148–150 °C (lit.[6] 154 °C). ^{1}H NMR (400 MHz) δ12.3 (s, 1H), 7.78 (bs, 4H), 7.41–7.39 (m, 2H), 7.26–7.23 (m, 4H), 7.15–7.12 (m, 2H), 7.07–7.02 (m, 3H); ^{13}C NMR (100 MHz) δ 133.0, 130.6, 130.4, 130.0, 128.0, 127.7, 127.6, 127.4.

    The products **4b–4r** were prepared by the similar procedure.
15. CCDC 1565073 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supplementary Material

Supplementary data associated with this article can be found, in the online version, at

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Highlights

1. A tandem method for synthesis of 3,4,5-trisubstituted pyrazoles was developed.
2. It was performed by simply stirring the mixture of all reactants together.
3. Two bases were used, but each of them has its specific duties and responsibilities.
4. A novel four-step tandem pathway was proposed.