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Efficient Multicomponent Strategy to Pentacyclic Pyrazole-Fused Naphtho[1,8-*fg*]-isoquinolines through Cleavage of Two Carbon−Carbon Bonds

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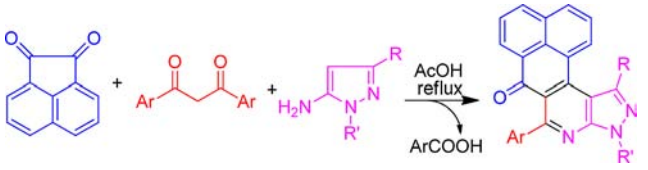
ABSTRACT



Multicomponent reactions of acenaphthylene-1,2-dione with diaroylmethanes and electron-rich pyrazol-5-amines have been discovered. A series of new and polyfunctionalized pentacyclic pyrazole-fused naphtho[1,8-*fg*]isoquinolines were regioselectively synthesized. The reactions were easy to perform simply by mixing three common reactants in AcOH. During these reaction processes, the insertion of active methylene of diaroylmethane into the sp^2-sp^2 C−C bond of the cyclohexa-2,5-dienone ring was readily achieved and two C−C bonds were cleaved under transition-metal-free conditions.

Efficient and rapid construction of structurally complex and functionally diverse multicyclic skeletons is a challenging theme in organic, medicinal, and combinatorial chemistry.[1] In light of this, multicomponent reactions (MCRs) for use in total syntheses of natural products or natural-like structures were one of the key tools that enabled the multiring-junction frameworks to be predicted by controlling the reaction process.[2,3] These reactions can avoid time-consuming and costly processes for purification of various precursors and isolation of intermediates.[4] They also form an ideal platform for rapid generation of both complexity and diversity in a collection of compounds with predefined functionality, e.g., ligands for catalysis or bioactive compounds. Therefore, the design of efficient MCRs involving C−C bond cleavage is a challenge in organic chemistry. However, to the best of our knowledge, the utilization of a multicomponent strategy combined with double C−C bond cleavages for the

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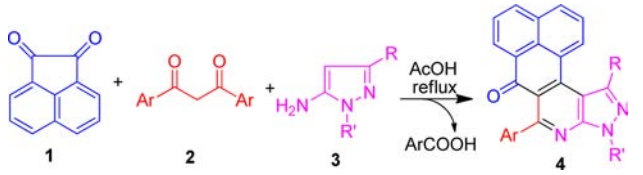
construction of a pentacyclic pyrazole-fused naphthoisoquinoline skeleton has not been achieved so far.

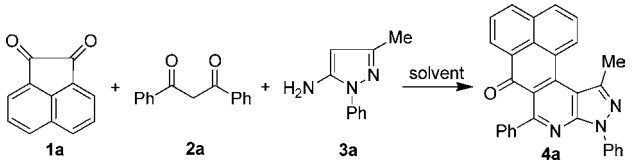
Recently, our group and others have developed various multicomponent reactions that can provide easy access to important polyfunctionalized ring structures of chemical and pharmaceutical interest.[5−7] During our continuous efforts on the development of useful multicomponent reactions,[5] herein, we report the challenging ring expansion and annulation of acenaphthylene-1,2-dione with diaroylmethanes and electron-rich pyrazol-5-amines yielding multifunctionalized pentacyclic pyrazole-fused naphthoisoquinolines (Scheme 1). A great aspect of the present multicomponent insertion reactions is shown by the fact that *the formation of two new six-membered rings (cyclohexaenone and pyridine rings) and four σ-bonds was readily achieved via a metal-free ring expansion reaction in an intermolecular manner and in a one-pot operation; the cyclopentenedione ring was converted into the corresponding cyclohexadienone unit by the insertion of the active methylene of diaroylmethane into the sp^2-sp^2 C−C bond of the cyclopentenedione ring under transition-metal-free conditions.*

Scheme 1. Synthesis of Pentacyclic Pyrazole-Fused Naphtho-[1,8-*fg*]isoquinolines



An initial reaction using acenaphthylene-1,2-dione (**1a**), dibenzoylmethane (**2a**), and 3-methyl-1-phenyl-1*H*-pyrazol-5-amine (**3a**) as a simple model substrate was investigated to establish the feasibility of the strategy and to optimize the reaction conditions (Table 1). Different solvents such as AcOH, HCOOH, trifluoroacetic acid (TFA), EtOH, MeOH, toluene, DMF, 1,2-dichloroethane (DCE), and CH_3CN were explored. The results are listed in Table 1. As shown in Table 1, the reaction scarcely proceeded in nonprotonic solvents, such as DMF, DCE, and CH_3CN. A poor yield (19%) of product **4a** was observed using toluene as solvent. Also, the reaction failed to generate the desired product **4a** in the weak protic solvents such as EtOH and MeOH. AcOH and HCOOH at 70 °C gave similar outcomes (Table 1, entries 9 and 10), while a 23% yield of **4a** was obtained in TFA (Table 1, entry 12). Subsequently, the reaction temperatures were elevated in both AcOH and HCOOH to observe the variation of yields of **4a**. Gratifyingly, it was found that the reaction worked efficiently in AcOH under reflux conditions, which afforded the corresponding product **4a** in 74% yield (Table 1, entry 7), while the lower yield (50%) of product **4a** was isolated in HCOOH under reflux conditions (Table1, entry 11). It was determined that acetic acid can serve not only as a suitable medium but also as an adequate Brønsted acid promoter for this multicompoent reaction.

Table 1. Optimization of Reaction Conditions for the Multicomponent Reactions



entry	solvent	temp (°C)	yield (%)[a]
1	DMF	150	trace
2	DCE	reflux	trace
3	CH_3CN	reflux	trace
4	toluene	reflux	19
5	EtOH	reflux	trace
6	MeOH	reflux	trace
7	AcOH	reflux	74
8	AcOH	80	45
9	AcOH	70	38
10	HCOOH	70	35
11	HCOOH	reflux	50
12	TFA	70	23

[a] Isolated yield.

We next explored the scope of this cascade reaction of acenaphthylene-1,2-dione **1**, diaroylmethanes **2**, and electron-rich pyrazol-5-amines **3** under the optimized conditions (AcOH, reflux). The results are summarized in Table 2. It was found that the nitrogen-tethered substituents on the pyrazole ring **3** did not hamper the reaction process. Several different *N*-substituents **3d**−**3e** bearing electron-withdrawing or -donating groups were tried and found to be suitable for this cascade reaction. *N*-Methyl substituted pyrazol-5-amine **3f** and **3g** underwent the cyclization to afford corresponding pentacyclic pyrazole-fused naphthoisoquinolines **4f** and **4g** in 77% and 75% yields, respectively. Moreover, reactions of methyl, phenyl, and cyclopropyl substituents at the 3-position of pyrazol-5-amines with acenaphthylene-1,2-dione **1** and diaroylmethanes **2** all worked well to afford the desired products in moderate yields. *p*-OMePh and *p*-ClPh diaroylmethanes were also examined in the meantime. As expected, the reactions proceeded smoothly to give the corresponding products in moderate to good yields. Indeed, the protocol

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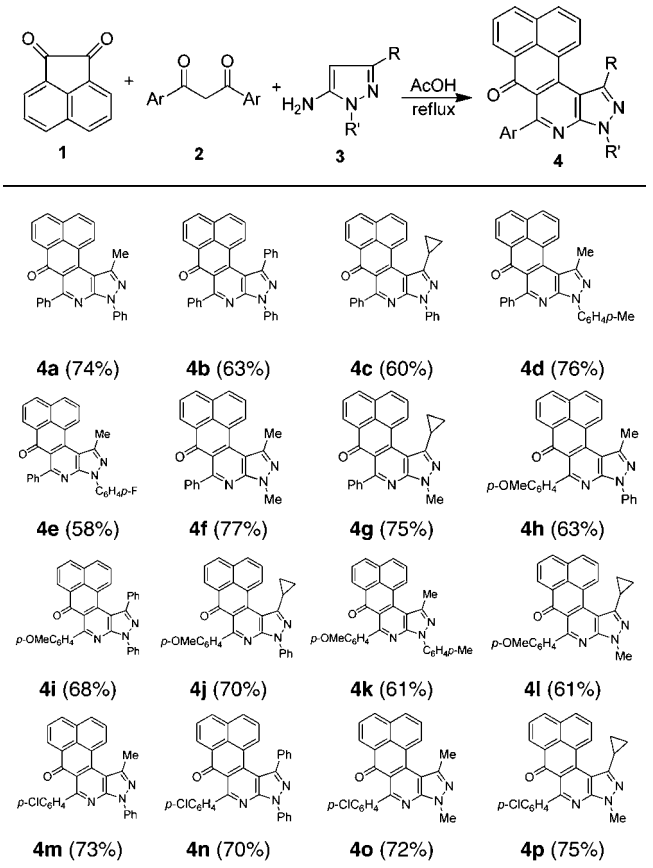
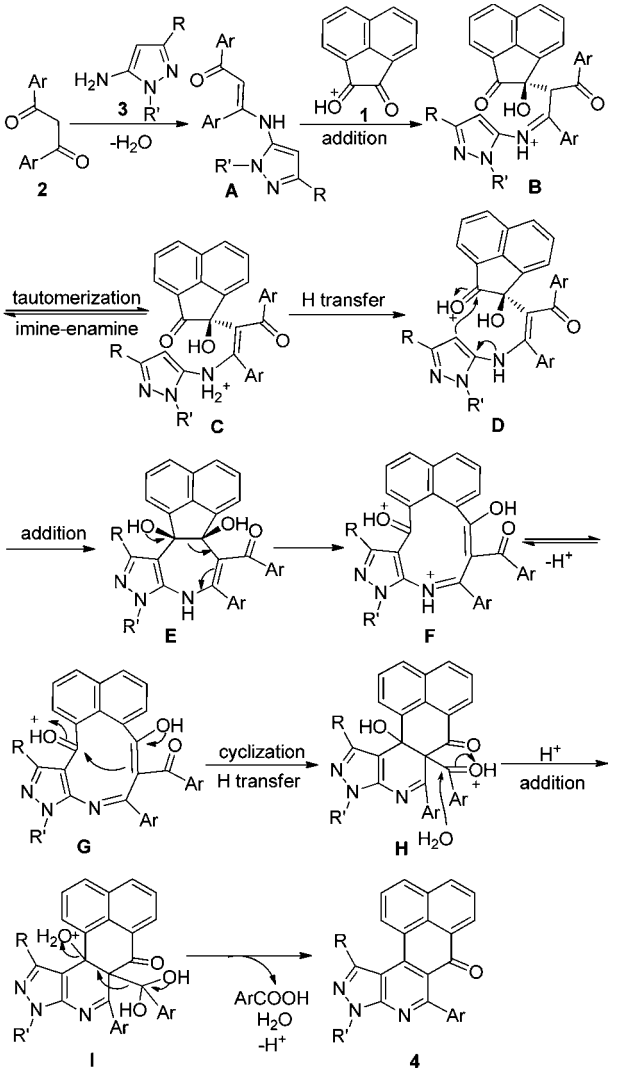
Table 2. Scope Investigation for the Reaction of **1** with **2** and **3**



provides an unusual route for the generation of complex pentacyclic pyrazole-fused naphtho[1,8-*fg*]isoquinolines, which are difficult to synthesize by other methods. Moreover, it also provides a new example of metal-free insertion in an economical and atom-efficient manner, which was generally catalyzed by transition metals.[8−10]

A plausible mechanism for this three-component reaction is postulated in Scheme 2. The reaction involves ring

Scheme 2. Proposed mechanism for the products **4**



closure cascade reactions that consist of initial enamine **A** formation from **2** and **3**, intermolecular nucleophilic addition (**A** to **B**), tautomerization and H transfer (**B** to **D**), subsequent intramolecular addition (**D** to **E**), ring opening of acenaphthylene-1,2-diols through C−C bond cleavage (**E** to **G**), a second intramolecular cyclization (**G** to **H**), and a third nucleophilic addition (**H** to **I**) and subsequent elimination to final product **4** *via* a second C−C bond cleavage.

In all cases, the complexity of the resulting products from this new reaction illustrates the remarkable regioselectivity of the sequence starting from very common starting materials. In most cases, the products can precipitate out after cold water was poured into the reaction mixture. The structural elucidation and the attribution of regioselectivity were unequivocally determined by NMR spectroscopic analysis and X-ray diffraction of a single crystal of pyrazolo[3,4-*c*]isoquinolines **4a** (Figure 1). During these processes, up to two new rings and four σ-bonds were formed accompanied by cleavage of two C−C bonds of acenaphthylene-1,2-dione and diaroylmethanes. *The insertion of the active methylene of diaroylmethane into*

(8) For selected examples of insertion of arynes, see: (a) Yoshida, H.; Terayama, T.; Ohshita, J.; Kunai, A. *Chem. Commun.* **2004**, 1980. (b) Tambar, U. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2005**, *127*, 5340. (c) Okuma, K.; Okada, A.; Koga, Y.; Yokomori, Y. *J. Am. Chem. Soc.* **2001**, *123*, 7166. (d) Tambar, U. K.; Ebner, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2006**, *128*, 11752. (e) Huang, X.; Xue, J. *J. Org. Chem.* **2007**, *72*, 3965. (f) Yoshida, H.; Mimura, Y.; Ohshita, J.; Kunai, A. *Chem. Commun.* **2007**, 2405. (g) Yoshioka, E.; Kohtani, S.; Miyabe, H. *Org. Lett.* **2010**, *12*, 1956. (h) Biswas, K.; Greaney, M. F. *Org. Lett.* **2011**, *13*, 4946.

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(10) For selected examples of insertion of carbine, see: (a) Yoshioka, E.; Kohtani, S.; Miyabe, H. *Angew. Chem., Int. Ed.* **2011**, *50*, 6638. (b) Zhou, L.; Ye, F.; Zhang, Y.; Wang, J. *J. Am. Chem. Soc.* **2010**, *132*, 13590. (c) Devine, S. K. J.; Van Vranken, D. L. *Org. Lett.* **2008**, *10*, 1909. (d) Khanna, A.; Maung, C.; Johnson, K. R.; Luong, T. T.; Van Vranken, D. L. *Org. Lett.* **2012**, *14*, 3233. (e) Doyle, M. P.; Duffy, R.; Ratnikov, M.; Zhou, L. *Chem. Rev.* **2010**, *110*, 704.

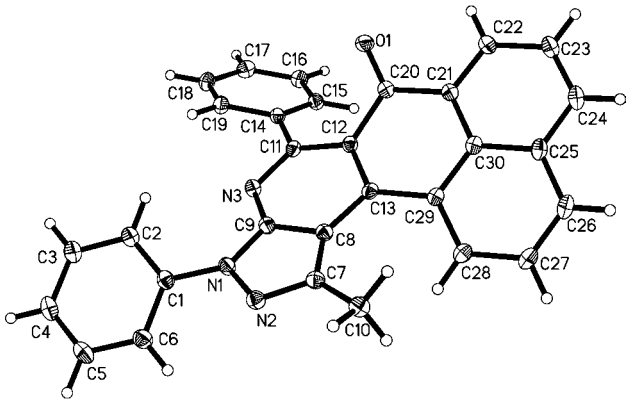

Figure 1. X-ray structural of **4a**.

the sp^2–sp^2 C–C bond of the cyclopentenedione ring was simultaneously achieved under transition-metal-free conditions (Table 2). This observation is very interesting and useful in organic chemistry.

In conclusion, we have successfully established the first insertion-based three-component reactions of acenaphthylene-1,2-dione that led to new structures of the pentacyclic pyrazole-fused naphthoisoquinoline skeleton with high regioselectivity. The present work provides an attractive strategy for the synthesis of structurally diverse naphthoisoquinoline derivatives. Other features of this tactic include mild conditions, convenient one-pot operations, and excellent regioselectivity. Due to the easy availability of the starting materials and potential utilities of products, this method could be useful in organic synthesis and medicinal chemistry.

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Supporting Information Available. Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.