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Tandem Access to Acridones and their Fused Derivatives: [1 + 2 + 3] Annulation of Isocyanides with Unsaturated Carbonyls

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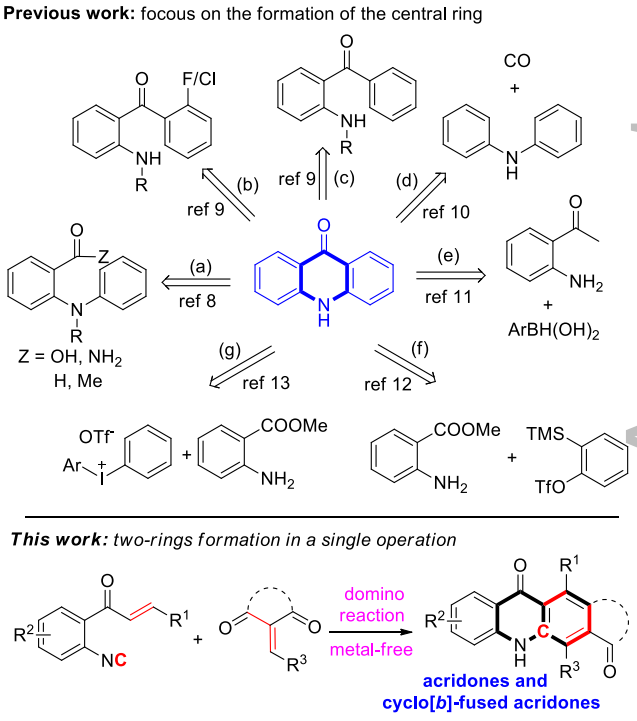
Abstract: A wide range of acridones and their cyclo[*b*]-fused derivatives are efficiently constructed by a double annulation of *o*-enoyl arylisocyanides with *α*, *β*-unsaturated carbonyls under simple metal-free condition. This protocol is general, efficient and practical, featuring the successive formation of two rings by a one-pot domino transformation. A tandem process involing an isocyanide-based [1 + 4] cycloaddition, an aminofuran-based intramolecular [4 + 2] cycloaddition, ring opening and aromatization is proposed for the transformation.

Keywords: [1 + 2 + 3] annulation; acridones; isocyanides; tandem reaction; unsaturated carbonyls

Introduction

Acridones and their fused frameworks[1] are prominent moieties in many natural products,[2] anticancer drugs,[3] anti-malarials[4] and biomaterials.[2a,5] Moreover, the acridones are also served as useful building blocks for the construction of organic semiconductors,[6] dyestuffs and fluorescent labels.[7] As a consequence, great effort has been devoted to developing new protocols for their preparation. Up to now, the synthetic methods mainly rely on (i) the intramolecular cyclization of the corresponding *N*-arylsubstituted acids, amides, and ketones (Scheme 1, path a)[8] as well as 2-aminobenzophenones (Scheme 1, path b and c),[9] (ii) the palladium/copper co-catalyzed oxidative carbonylation of diphenylamines with CO (Scheme 1, path d);[10] and Cu(II)-mediated cascade reaction of o-amino acetophenones and phenylboronic acids (Scheme 1, path e);[11] (iii) the annulation of anthranilic acid derivatives with aryne or aryliodonium (Scheme 1, path f[12] and g[13]). Despite these achievements, most of the existing synthetic approaches focus on the closure of the central pyridone ring from two preformed benzenoids. Therefore, the development of conceptually new methodologies is still highly demanded.



Scheme 1. The synthesis of acridones.

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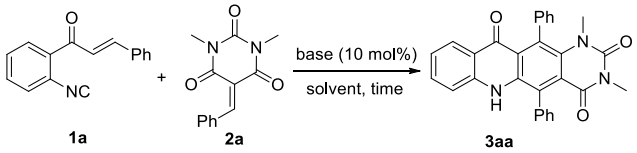
Functionalized isocyanides, as versatile building blocks, have been widely applied in synthesis of *N*-containing heterocycles.[14] During the past decade, our research group has been working on the double annulation of functionalized isocyanides, such as active methylene isocyanides,[15] trifluoromethylated isocyanides[16] *o*-alkenylarylisocyanides,[17] and *o*-enoyl arylisocyanides,[18] as a novel strategy for the efficient construction of polycyclic azaheterocycles. Last year, we developed a formal [1 + 2 + 3] annulation of *o*-alkenylaryl isocyanides with unsaturated ketones as a new strategy for the expeditious synthesis of carbazole derivatives.[19] In this domino process, an aminofuran intermediate was in situ generated and converted to carbazoles via a facile intramolecular Diels-Alder reaction of furan (*IMDAF*). While the *IMDAF* reaction has been proven to be useful for the construction of complex frameworks for years,[20] a domino process involving the generation and transformation of furan intermediate is still appealing due to its high synthetic efficiency and ready availability of starting materials. Herein, we expand the [1 + 2 + 3] annulation to *o*-enoyl arylisocyanides, whereby a wide range of polysubstituted acridone derivatives have been efficiently synthesized from readily available isocyanides and *α,β*-unsaturated carbonyls (Scheme 1, bottom). This domino transformation allows the successive formation of two rings under metal-free conditions in a single operation, which represents a new synthetic strategy for acridone synthesis.

Results and Discussion

In 2018, we prepared various *o*-enoyl arylisocyanides from readily available 1-(2-aminophenyl)prop-2-en-1-ones, and used them as versatile synthons for the efficient synthesis of phenanthridines.[18] Herein, we chose *o*-cinnamoyl arylisocyanide **1a** and 5-benzylidene dimethylbarbituric acid **2a** as model substrates to screen the reaction conditions (Table 1). As expected, when a mixture of arylisocyanide **1a** (0.25 mmol) and **2a** (1.2 equiv.) in 1,4-dioxane was stirred at 130 °C, the acridone product **3aa** was obtained in 21% yield (Table 1, entry 1). There was no significant improvement of the yield of **3aa** when changing the reaction temperature and the solvent (Table 1, entries 2-5). To our delight, the yields of **3aa** was increased to 78% when using DABCO (10 mol%) as the catalyst (Table 1, entry 6). DBN and DBU were found to be less effective than DABCO in terms of yields (Table 1, entries 7-8). Increasing or decreasing the loading of DABCO led to a slightly lower yield of **3aa** (Table 1, entries 9-10). Hence, the optimal conditions were determined as treatment of the reaction mixture with 10 mol% DABCO at 130 °C in 1,4-dioxane (Table 1, entry 6).

Table 1. Screening of reaction conditions.[a,b]



Entry	Solvent	Base	T (°C)	T (h)	**3aa**
1	1,4-dioxane	--	130	7	21%
2	1,4-dioxane	--	90	7	14%
3	1,4-dioxane	--	150	7	22%
4	DMF	--	130	7	10%
5	DCE	--	130	18	20%
6	***1,4-dioxane***	***DABCO***	***130***	***5***	***78%***
7	1,4-dioxane	DBN	130	5	74%
8	1,4-dioxane	DBU	130	5	71%
9[c]	1,4-dioxane	DABCO	130	5.5	63%
10[d]	1,4-dioxane	DABCO	130	3	74%

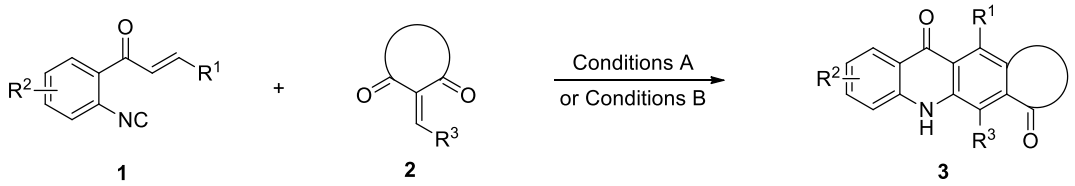
[a]Reaction conditions: **1a** (0.25 mmol), **2a** (0.3 mmol), base, solvent (2 mL).
[b] Yields of isolated products.
[c] DABCO (5 mol%) was added.
[c] DABCO (20 mol%) was added.

With the optimal conditions in hand (Table 1, entry 6), the scope of *o*-enoyl arylisocyanides **1** was first surveyed. Fortunately, most of the desired acridone products were obtained in moderate to good yields (Table 2). In the double annulation, various *o*-enoyl arylisocyanides **1** bearing diverse R^1 groups such as phenyl (**1a**), electron-rich aryls (**1b, 1c, 1g-i**), electron-deficient aryls (**1d-f**) and heteroaryls (**1j**) were all effective substrates. The reactions were proceeded smoothly, when the R^2 groups of isocyanides were electron-deficient groups such as 5-chloro, 4-chloro and 4-bromo (**1k-m**). Notably, the steric effect of substituents on the benzene ring of isocyanides **1** has no obvious influence on product yields.

Furthermore, the scope of *α,β*-unsaturated diketones **2** was investigated under identical conditions. Firstly, we made a study for the scope of 5-substituted vinyl dimethylbarbituric acids. As depicted in Table 2, a wide range of R^3 groups on vinyl dimethylbarbituric acids such as phenyl (**2a**), electron-rich aryls (**2b, 2c**), electron-poor aryls (**2d, 2e, 2g**) and *β*-naphthyl group (**2i**) were compatible and various acridones **3** were prepared in good yields in the cascade reaction.[21] More steric hindrance of the substituent was unfavourable to the reaction (**2f**). By contrast, the vinyl dimethylbarbituric acids **2** bearing heteroaryl and aliphatic groups at *β*-position gave lower yields of acridones **3ah** and **3aj**. Moreover, this tandem reaction was proved to be of high practical and was amenable to gram scale up under the same reaction condition (**3ai**). In addition, using unprotected vinyl barbituric acid **2k** as substrate, acridone derivative **3ak** was constructed with moderate yield. Furtherly, *β*-benzylidene 5/7-membered cyclic 1,3-diketones (**2l** and **2n**) were also

transformed smoothly into the corresponding acridones with high yields (**3al** and **3an**). It was worth mentioning that the three component reaction of dimedone, benzaldehyde and *o*-cinnamoyl arylisocyanide **1a** was feasible for the synthesis of **3am** in moderate yield. Additionally, a three component double [1 + 2 + 3] annulation of diketone **2o** with isocyanide **1a** was successfully developed for the highly efficient construction of the polysubstituted diacridone **3ao** in 81% yield.

Table 2. Scope of isocyanides and cyclic *α,β*-unsaturated carbonyls[a,b]



1 **2** **3**

1a-m

R^2 = H, R^3 = Ph

3ba, R^1 = 4-MeC_6H_4, 56%
3ca, R^1 = 4-$MeOC_6H_4$, 59%
3da,R^1 = 4-ClC_6H_4, 60%
3ea, R^1 = 4-BrC_6H_4, 56%
3fa, R^1 = 2-ClC_6H_4, 75%
3ga, R^1 = 2-MeC_6H_4, 64%
3ha, R^1 = 3-MeC_6H_4, 74%
3ia, R^1 = β-naphthyl, 84%
3ja, R^1 = 2-thienyl, 70%

R^1 = Ph, R^3 = Ph

3ka, R^2 = 5-Cl, 87%
3la, R^2 = 4-Cl, 66%
3ma, R^2 = 4-Br, 66%

2l[c] **3al**, 82%

2m[c,d] **3am**, 56%

2n[c] **3an**, 91%

2a-j

3aa, R^3 = C_6H_5, 78%
3ab, R^3 = 4-MeC_6H_4, 84%
3ac, R^3 = 4$MeOC_6H_4$, 90%
3ad, R^3 = 4-ClC_6H_4, 74%
3ae, R^3 = 4-BrC_6H_4, 78%
3af, R^3 = 2-ClC_6H_4, 40%
3ag, R^3 = 3-ClC_6H_4, 64%
3ah, R^3 = 2-thienyl, 34%
3ai, R^3 = β-naphthyl, 91% (82%)[e]
3aj, R^3 = cyclohexyl, 24%

2k **3ak**, 42%

2o **3ao**, 81%

[a]Unless noted, the reactions were carried out under conditions A. Conditions A: **1a** (0.25 mmol), **2a** (0.3 mmol), DABCO (0.025 mmol), 1,4-dioxane (2 mL), 130 °C.
[b] Yields of isolated products.
[c] Conditions B: 1) **1a** (0.25 mmol), **2a** (0.3 mmol), DABCO (0.025 mmol), 1,4-dioxane (2 mL), 130 °C, stirring for 5 h; 2) Tf_2O (30 mol%), 130 °C, stirring for 0.5 h.
[d] Three-component reaction, dimedone (0.3 mmol), benzaldehyde (0.3 mmol) and isocyanide **1a** (0.25 mmol).
[e] 1.25 g of **3ai** was obtained.

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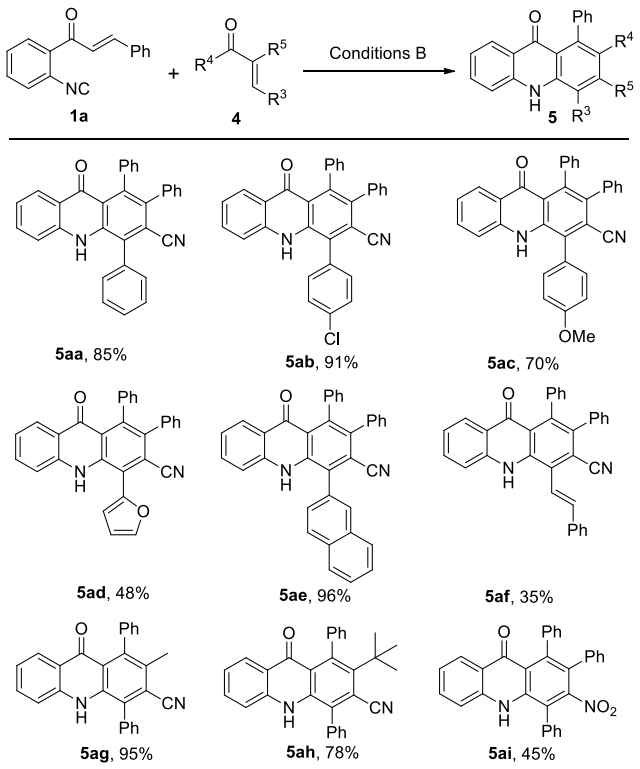
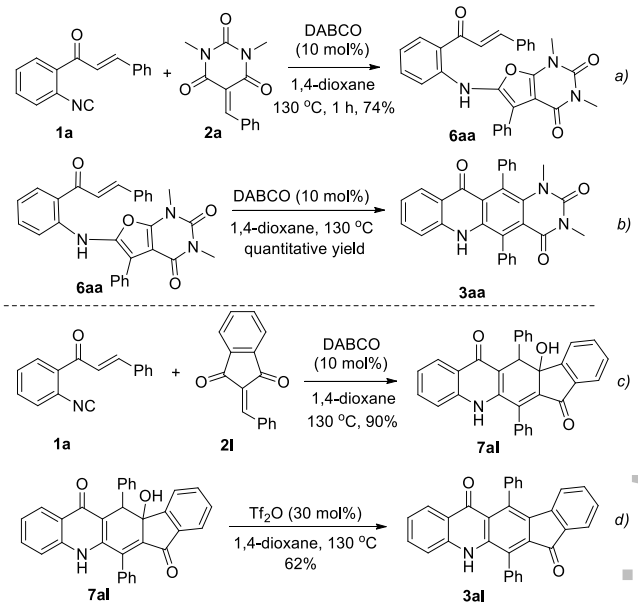
Subsequently, the scope of acyclic *α,β*-unsaturated compounds **4** was examined for the efficient synthesis of polyfunctionalized acridones (Table 3). The reaction of isocyanide **1a** with a wide range of acyclic *α,β*-unsaturated compounds **4** resulted the tricyclic frameworks bearing various R^4 groups (phenyl, methyl and *tert*-butyl), R^5 groups (cyano, and nitro) and R^3 groups, such as phenyl (**5aa**, **5ag-5ai**), *para*-substituted aryl (**5ab**, **5ac**), *β*-naphthyl group (**5ae**). The acridone derivatives **5** were generally obtained in good to high yields, except heteroaryl- and styryl-substituted **5ad** and **5af**. These results indicated that the electronic and steric effects have no obvious influence on the [1 + 2 + 3] annulation, which is also suitable for the efficient preparation of polysubstituted acridones.

Table 3. Scope of non-cyclic *α,β*-unsaturated compounds.[a,b]



[a]Conditions B: 1) **1a** (0.25 mmol), **2a** (0.3 mmol), DABCO (0.025 mmol), 1,4-dioxane (2 mL), 130 °C, stirring about 5 h; 2) Tf_2O (30 mol%), 130 °C, stirring about 0.5 h.
[b]Yields of isolated products.

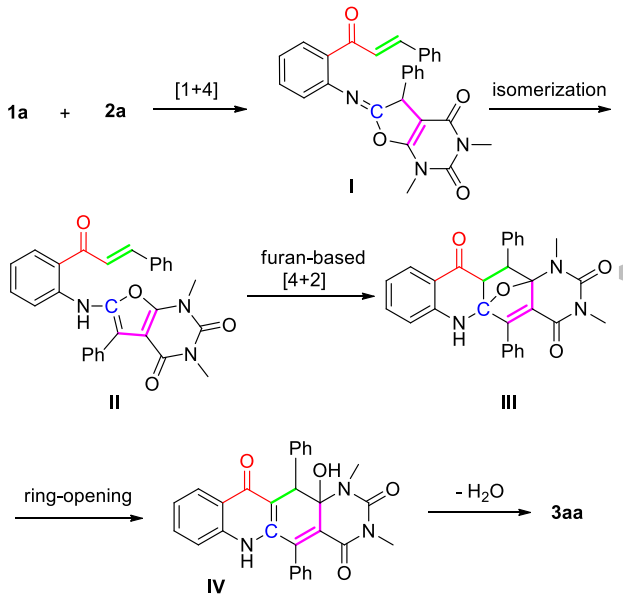
In order to understand the mechanism of this double annulation, control experiments were conducted. When *o*-cinnamoyl arylsocyanide **1a** and 5-vinyl dimethylbarbituric acid **2a** were treated with DABCO (10 mol%) in 1,4-dioxane at 130 °C for 1 h, the cyclization aminofuran **6aa** was isolated in 74% yield (Scheme 2a). Next, it was found that the acridone **3aa** was obtained quantitatively from aminofuran **6aa** under the optimized condition (Scheme 2b). Moreover, *o*-cinnamoyl arylsocyanide **1a** and 2-benzylidene-1,3-indandione **2l** gave the 11*b*-hydroxy-11*b*,12-dihydro-indeno[1,2-*b*]acridone



Scheme 2. Control Experiments

7al in 90% yield (Scheme 2c). The aromatization product **3al** was achieved after treating with Tf_2O (30 mol%) in 1,4-dioxane at 130 °C (Scheme 2d). These results clearly showed that aminofuran and hydroxydihydroacridone are the possible intermediates. Therefore, the [1 + 2 + 3] annulation strategy involves the [1 + 4] annulation of isocyanides with *α,β*-unsaturated compounds followed by an intramolecular Diels-Alder reaction, rearrangement and dehydration sequence.

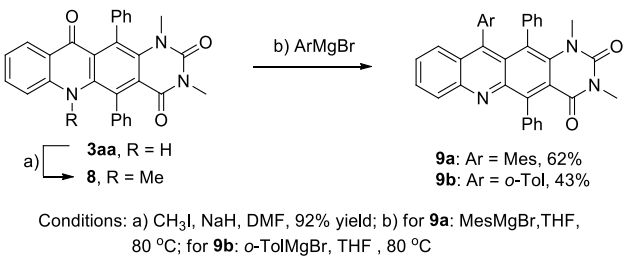
Based on the experimental results and our previous research,[19] a possible mechanism for the synthesis of acridone derivatives **3** and **5** is proposed (see Scheme 3, exemplified with the formation of **3aa**). At the beginning, a [1 + 4] annulation, initiated by nucleophilic addition of isocyanide **1a** on to *β*-carbon



Scheme 3. Proposed mechanism

of Michael acceptor **2a** and followed by cyclization, takes place to form the intermediate **I**. Then an aminofuran intermediate **II** is generated through isomerization of **I**. Subsequently, an intramolecular Diels-Alder reaction of furan (IMDAF) proceeds smoothly to produce the oxygen-bridged tetracyclic intermediate **III**, from which an oxabicyclic ring-opening reaction happens to give the hydroxylated intermediate **IV**. Finally, the acridone **3aa** is obtained via dehydration. The role of DABCO is not very clear at this stage, it probably promotes both the IMDAF and the dehydration steps. In some cases (conditions B in Tables 2 and 3), trifluoromethanesulfonic anhydride is used to promote the dehydration reaction.

9-aryl acridine framework is often found in electrically/photochemically active catalysts[22]. As shown in Scheme 4, 9-aryl acridine derivatives were conveniently prepared from acridone **3aa** in two steps. Treatment of **3aa** with iodomethane afforded *N*-methyl acridone **8** in quantitative yield, then 9-aryl acridines **9a**[23] and **9b** were obtained in moderate yields through a cascade addition/elimination/ demethylation sequence, respectively.



Scheme 4. The synthesis of 9-aryl acridines

Conclusion

In conclusion, a novel base-catalyzed [1 + 2 + 3] annulation of *o*-enoyl arylisocyanides and *α,β*-unsaturated carbonyls has been successfully developed for the efficient construction of polysubstituted and cyclo[*b*]-fused acridones. The domino transformation features the formation of three bonds and two rings in a single operation from readily available starting materials under metal-free condition. On the basis of control experiments, an isocyanide-based [1 + 4] cycloaddition and an aminofuran-based [4 + 2] cycloaddition cascade account for the mechanism. In addition, the synthetic potential of the resulting acridones was demonstrated by the convenient preparation of the valuable 9-aryl acridine derivatives. Further studies on the [1 + 2 + 3] annulation are ongoing in our research group.

Experimental Section

General procedure for the synthesis of 3 (with **3aa** as an example): To a mixture of isocyanide **1a** (0.25 mmol, 58.25 mg) and *α,β*-unsaturated ketone **2a** (0.3 mmol, 73.2 mg) in 1,4-dioxane (2 mL) was added DABCO (0.025 mmol, 2.8 mg) and set in a pre-heated (130 °C) metal block. After the reaction was finished as indicated by TLC (reaction time, 4~5 h), the reaction mixture was cooled to room temperature and concentrated in vacuo. Purification of the crude product with flash column chromatography (silica gel; DCM : EtOAc = 300:7-250:7) to give acridone **3aa** (87.5 mg, 78% yield) as a yellow solid.

Acknowledgements

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