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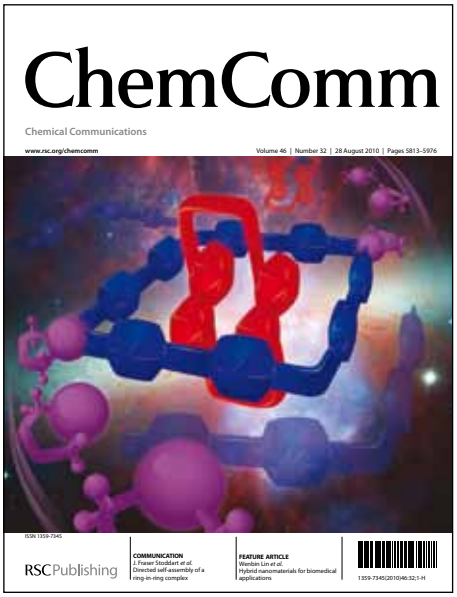

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Unexpected isocyanide-based cascade cycloaddition reaction with methyleneindolinone

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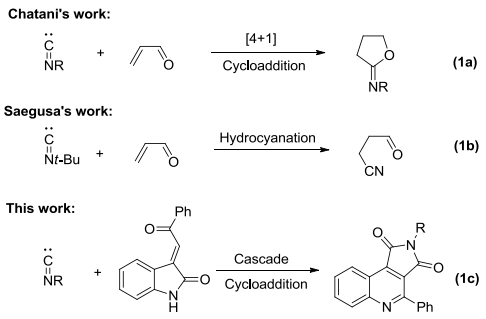
An unprecedented cascade reaction of isocyanide and methyleneindolinone has been established, which represents a novel and different reaction fashion compared with traditional ones. This present transformation involves the ring-opening of methyleneindolinone and the construction of two other new rings simultaneously in an atom-economic manner.

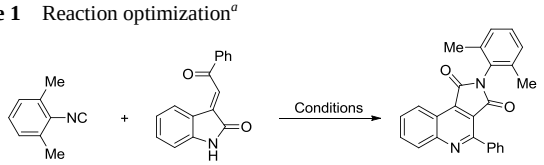
In the past decades, isocyanides have proved themselves to be irreplaceable one-carbon building blocks in modern organic chemistry.[1] Accordingly, it has witnessed a rapid progress in various carbon-carbon and carbon-heteroatom bond-forming reactions involving isocyanides. Among them, the isocyanide-based multicomponent reactions (IMCR) have been extensively investigated and become a powerful tool towards diversity-oriented syntheses.[2] Moreover, much efforts have also been devoted to the transition-metal-catalyzed insertion reactions involving isocyanides.[3] In these above-mentioned transformations, the exceptional reactivity of isocyanides plays a significant role since they can function both as nucleophile



Scheme 1 Reactions of isocyanide and α,β-unsaturated carbonyl compounds.

and electrophile on the same carbon atom.[4] On the other hand, the unique features of isocyanide had also make themselves widely applied in the syntheses of various heterocycles.[5] In such cases, isocyanide-based efficient syntheses to heteroaryl rings such as indole,[6] oxazole,[7] pyrrole[8] and imidazole[9] have been well documented. In the past years, we have focused much attention on cycloaddition reactions involving isocyanides to synthesize carbocycles and heterocycles.[10a-10d] More recently, we have also disclosed the Diels-Alder cycloaddition reaction of aryne and methyleneindolinone to construct fused oxindole.[10e] As a continuation, we are also interested in exploring the reactivity of methyleneindolinone with isocyanide.

Table 1 Reaction optimization[a]



Entry	Catalyst[a]	Solvent	Temp/°C	Yield (%)[b]
1	$BF_3 \cdot Et_2O$	Toluene	80	45
2	$AlCl_3$	Toluene	80	17
3	$FeCl_3$	Toluene	80	trace
4	$BiCl_3$	Toluene	80	trace
5	$RuCl_3 \cdot H_2O$	Toluene	80	20
6	$NiCl_2 \cdot 6H_2O$	Toluene	80	8
7	$Pd(OAc)_2$	Toluene	80	-[c]
8	$Zn(OTf)_2$	Toluene	80	NR
9	AgOTf	Toluene	80.	NR
10	$Yb(OTf)_3$	Toluene	80	trace
11	$Sc(OTf)_3$	Toluene	80	trace
12	TsOH	Toluene	80	28
13	HCl	Toluene	80	33
14	TfOH	Toluene	80	21
15	$BF_3 \cdot Et_2O$	THF	reflux	56
16[d]	$BF_3 \cdot Et_2O$	THF	reflux	65
17	$BF_3 \cdot Et_2O$	CH_3CN	reflux	trace
18	$BF_3 \cdot Et_2O$	DCM	reflux	20

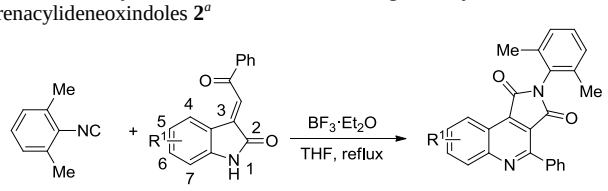
[a] 20 mol% catalyst was used. [b] Isolated yield of product. [c] A complex mixture was observed. [d] 40 mol% catalyst was employed.

It is already known that the cycloaddition reactions of isocyanide to α,β-unsaturated carbonyl compounds have been well documented.

Chatani reported the first catalytic [4+1] cycloaddition reaction of isocyanide and α,β-unsaturated ketones leading to γ-lactone derivatives (Scheme 1, equation **1a**).[11] Saegusa also demonstrated that an efficient and unique hydrocyanation reaction took place when *tert*-butyl isocyanide was mixed with unsaturated carbonyl compounds or acetals in the presence of $TiCl_4$ (Scheme 1, equation **1b**).[12] However, our experiments showed that when methyleneindolinone was employed as α,β-unsaturated carbonyl compounds to react with isocyanides, a quite different cascade cycloaddition reaction took place.

In our initial experiments, cycloaddition reactions of 2,6-dimethylphenyl isocyanide **1a** and arenacylideneoxindoles **2a** in toluene was used as standard protocol. In the presence of $BF_3{\cdot}Et_2O$, as shown in Table 1, the reaction of **1a** and **2a** essentially led to the formation of unexpected product **3a** in 45 % yield (Table 1, entry 1). Encouraged by this experimental result, we investigated a variety of catalysts. However, the replacement of $BF_3{\cdot}Et_2O$ with several metal chlorides only resulted in very low yield (Table 1, entries 3-6). Further experiments also demonstrated that metal triflates were also unfavorable for the formation of compound **3a** (Table 1, entries 8-11). In addition, the employment of Brønsted acid such as TsOH and HCl also demonstrated somewhat low efficiency compared with $BF_3{\cdot}Et_2O$ (Table 1, entries 12-14). To our delight, the screening of solvents further indicated that the present reaction took place more efficiently in THF as the solvent (Table 1, entries 15-18).

Table 2 Cycloaddition reaction using isocyanide **1a** and arenacylideneoxindoles **2**[a]

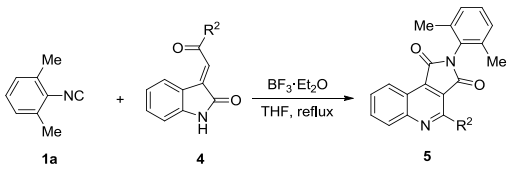


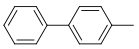
Entry	R^1	Product	Yield (%)[b]
1	H	**3a**	65
2	5-fluoro	**3b**	51
3	5-chloro	**3c**	82
4	5-bromo	**3d**	72
5	5-methyl	**3e**	57
6	5-methoxy	**3f**	68
7	5,7-dimethyl	**3g**	50
8	4-chloro	-	NR
9	6-bromo	**3h**	41
10	7-bromo	**3i**	75

[a] The reaction of **1a** (1.2 mmol) and **2** (1.0 mmol) was carried out in the presence of $BF_3{\cdot}Et_2O$ (40 mol %) in 10 mL THF under reflux unless otherwise noted. [b] Yield of product after silica gel chromatography.

Once the optimized reaction condition has been established, we turned our attention to the reaction scope. As shown in Table 2, changing the substituent of substrate **2** on the aromatic ring at position 5, 6 and 7 was first carried out. In such cases, both electron-withdrawing (Table 2, entries 2-4 and entries 9-10) and –donating substituents (Table 2, entries 5-7) on the aryl ring all worked well to produce the cycloadducts **3** in satisfactory yields and all new compounds were characterized by ^1H NMR, ^{13}C NMR, and HRMS spectra. Moreover, the structure of **3a** and **3f** were determined by X-ray crystallographic analysis. No reaction occurred when 4-substituted substrate **2** was used (Table 2, entry 8), presumbly due to the steric hindrance.

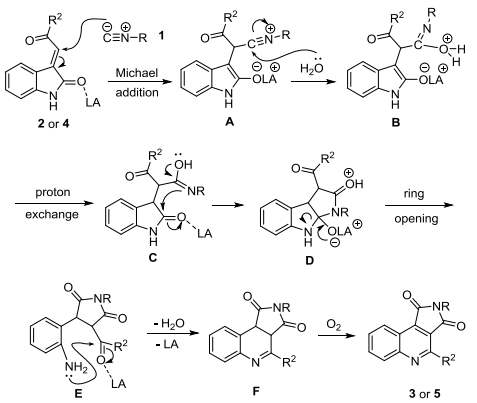
Table 3 Cycloaddition reaction using isocyanide **1a** and arenacylideneoxindoles **4**[a]



Entry	R^2	Product	Yield (%)[b]
1	4-FC_6H_4	**5a**	71
2	2-ClC_6H_4	**5b**	81
3	3-ClC_6H_4	**5c**	65
4	4-ClC_6H_4	**5d**	60
5	4-BrC_6H_4	**5e**	57
6	2-MeC_6H_4	**5f**	40
7	3-MeC_6H_4	**5g**	69
8	4-MeC_6H_4	**5h**	54
9		**5i**	38
10	3-$MeOC_6H_4$	**5j**	85
11	4-$MeOC_6H_4$	**5k**	73
12	4-$NO_2C_6H_4$	**5l**	67
13	Me	**5m**	70

[a] The reaction of **1a** (1.2 mmol) and **4** (1.0 mmol) was carried out in the presence of $BF_3{\cdot}Et_2O$ (40 mol %) in 10 mL THF under reflux unless otherwise noted. [b] Yield of product after silica gel chromatography.

To further demonstrate the versatility of this process, a feasibility investigation of substrate **4** by varing the substituents bearing carbonyl group was also carried out (Table 3). To our delight, treatment of the isocyanide **1a** and various substituted **4** essentially afforded desired compounds **5** in all cases (Table 3). Substrate with aliphatic substituent was also employed to form product **5** in satisfactory yield (Table 3, entry 13). The structure of compound **5b** was further confirmed by single crystal X-ray analysis. Most importantly, the present cycloaddition strategy represents the first example of synthesis of functionalized quinoline from isocyanide and methyleneindolinone. Taking the broad range of significant biological activities of quinolines into account, the present strategy is quite desirable.[13]



Scheme 2 Proposed mechanism.

The mechanistic proposal for the present cascade cycloaddition reaction is outlined in Scheme 2. The beginning of the present process involves the isocyanide nucleophilic attack towards the reactive double bond at the position 3. Accordingly, the intermediate **A** was trapped by water to generate **B**.[14] Subsequent proton transfer

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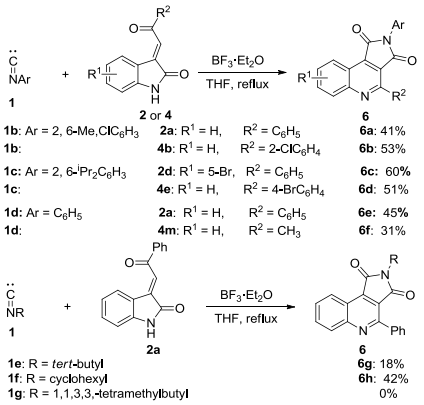
and intramolecular nucleophilic attack essentially leads to the unusual ring-opening process. The reactive intermediate **E** experiences the cyclization process followed by oxidative aromatization to give the unusual quinoline **3** or **5.**[15] It is interesting to note that no intermediate **F** was ever detected from the reaction mixtures, presumably due to the facile dehydrogenative oxidation. The control experiment also showed that no reaction occurred when the reaction was conducted with rigorous exclusion of water and oxygen.



Scheme 3 Experiments with other isocyanides.

To further explore the scope and limitation of the present cyclization strategy, we attempted to briefly investigate the cycloaddition reaction with other isocyanides. Aromatic isocyanides **1b**, **1c** and **1d** with arenacylideneoxindoles **2** or **4** worked well to yield the desired products from **6a** to **6f**. Aliphatic isocyanide **1e** and **1f** also experienced the corresponding cascade reaction to afford the quinoline derivatives **6g** and **6h** (Scheme 3). No desired compound was isolated when 1,1,3,3,-tetramethylbutyl isocyanide **1g** was used. In this case, no reaction occurred under the standard conditions.

In conclusion, we have described the cycloaddition reactions of isocyanides and methyleneindolinones to generate quinolines. This unprecedented process involves the opening of one ring and the efficient construction of other two new rings in one step. The present strategy also opens a convergent and powerful pathway for the construction of polycyclic skeletons. Furthermore, this method is also distinguished by its convenient experimental set-up and excellent atom economy. Further experiments with broader substrates scope are currently underway in our lab.

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Electronic Supplementary Information (ESI) available: [Experimental details and spectroscopic and analytical data for all new compounds. CIF files of compounds **3a**, **3f**, **5b**, CCDC 945280, 945281 and 945282.]. See DOI: 10.1039/c000000x/

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