Organocatalysis

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Organocatalytic Oxidative Annulation of Benzamide Derivatives with Alkynes**

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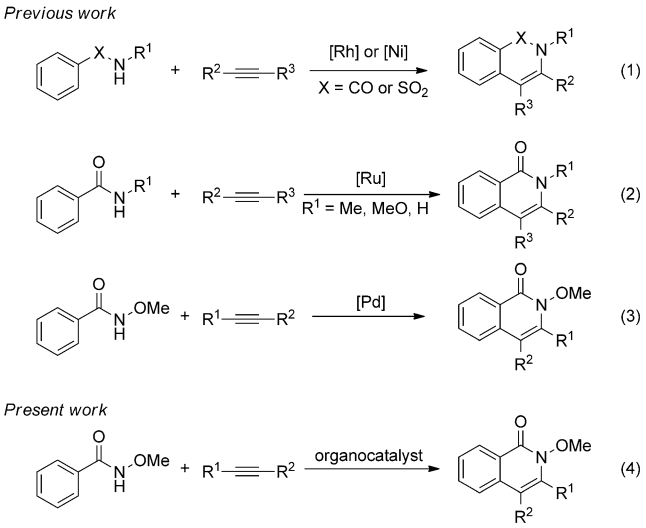
Abstract: *Organocatalytic annulation by functionalization of benzamide derivatives with alkynes has been developed. We report a new approach of cycloaddition under mild reaction conditions using simple catalysts, such as iodobenzene and peracetic acid, as oxidant. Those novel, mild reaction conditions provided a straightforward synthesis of isoquinolones with fast reaction rate. Notable selectivity in annulation of unsymmetrically disubstituted alkynes was demonstrated.*

C–H bond functionalization has emerged over the last few decades and represents an attractive strategy to enhance molecular complexity. C–H bond functionalization catalyzed by transition metals is an intensively investigated area of great significance.[1] Methods of direct coupling between non-functionalized compounds represent an environmentally benign and economically attractive synthetic strategy to the desired products. However, these methods are limited. The development of new efficient, direct oxidative cross-coupling methods is highly demanded.[1]

Isoquinoline and isoquinolones represent important heterocyclic scaffolds with broad ranges of biological activities.[2] Several attractive synthetic routes to isoquinolones were developed using transition-metal-catalyzed processes in last years.[3–8] Impressive annulation with alkynes was first developed by Fagnou and co-workers employing rhodium catalyzed directed C–H activation.[3a] Interestingly, Rovis′ group independently demonstrated the annulation of benzamide with alkynes and alkenes through rhodium-catalyzed C–H functionalization [Scheme 1, Eq. (1)].[4a] Recently, the Ackermann and Wang groups reported an efficient ruthenium catalyzed approach to annulation of benzamine and alkyne [Scheme 1, Eq. (2)].[5] Very recently, palladium-catalyzed synthesis of isoquinolones has been developed by Huang and co-workers [Scheme 1, Eq. (3)].[6] Typically, transition-metal-catalyzed annulations require high temperature, external oxidant and long reaction time. It is notable that metal-free approaches to annulation of benzamide derivatives with alkynes have never been reported. Moreover, a mild, efficient and organocatalytic synthesis of isoquinolones by annulation of alkynes and benzamide is demanded. Herein we report the discovery of the first metal-free annulation of alkynes by cascade C–C and C–N bond formation under organocatalytic reaction conditions [Scheme 1, Eq. (4)].



Scheme 1. Annulation of benzamide and benzenesulfonamide derivatives with alkynes

We began our studies[9] on annulation using *N*-methoxybenzamide (**1a**) and diphenylacetylene (**2a**) as starting materials in presence of (diacetoxyiodo)benzene (PIDA) as a oxidant in 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) at room temperature (Table 1).[10] To our delight, the product of annulation **3a** was isolated with 40% yield.[11] Furthermore, the use of $PhI(OCOCF_3)_2$ did not provide the desire product at all (Table 1, entries 1–2). Encouraged by the initial result, we tested organocatalytic conditions using iodobenzene as catalyst in presence of oxidants such as *m*-CPBA. The application of substoichiometric amounts of iodobenzene resulted in formation of product **3a** with higher yield (Table 1 entry 3). In the screening of various oxidants, peracetic acid was found as best oxidant to provide isoquinolone **3a** in 68% yield (Table 1 entries 3–6). HFIP was the best solvent giving the desired product of annulation. The formation of product **3a** was not observed using EtOAc, $CHCl_3$, MeOH, and DCE as solvents (Table 1, entries 7–11; see also the Supporting Information). The application of CF_3CH_2OH as a solvent resulted in reduced yield of the desired product **3a**. We next investigated different aryl iodides as potential catalysts (Table 1, entries 12–15). Of the tested compounds, iodobenzene delivered the best result for the synthesis of annulated

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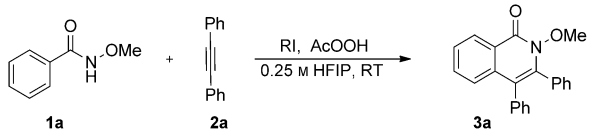
Table 1: Optimization of organocatalytic isoquinolone synthesis.[a]



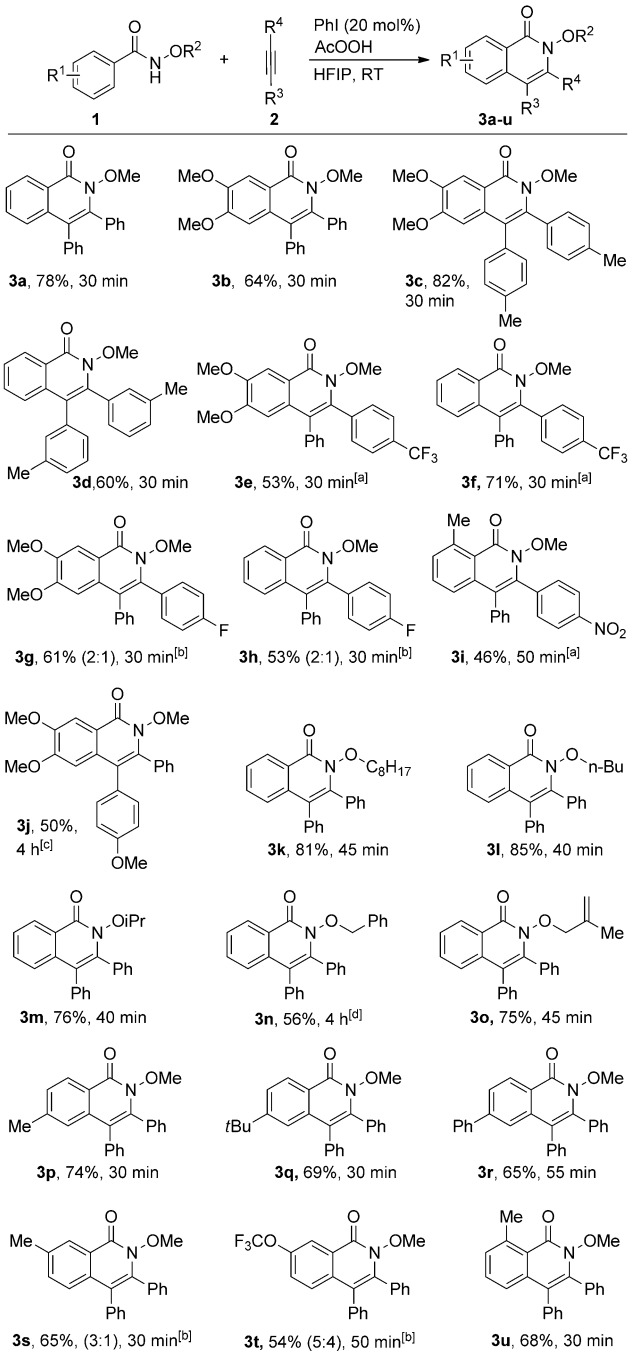
1a 2a 3a

Entry	Solvent	RI	Oxidant	Yield [%][b]
1	HFIP	–	$PhI(OAc)_2$	40
2	HFIP	–	PIFA	n.d.
3[c]	HFIP	PhI	*m*-CPBA	52
4	HFIP	PhI	AcOOH	68
5	HFIP	PhI	DTHP	n.d.
6	HFIP	PhI	H_2O_2	n.d.
7	CF_3CH_2OH	PhI	AcOOH	44
8	HFIP/CH_2Cl_2 (1:1)	PhI	AcOOH	41
9	$CHCl_3$	PhI	AcOOH	n.d.
10	MeOH	PhI	AcOOH	n.d.
11	$ClCH_2CH_2Cl$	PhI	AcOOH	n.d.
12	HFIP	4-MeO-C_6H_4I	AcOOH	5
13	HFIP	4-Me-C_6H_4I	AcOOH	20
14	HFIP	4-NO_2-C_6H_4I	AcOOH	n.d.
15[d]	HFIP	**A**	AcOOH	64
16[e]	HFIP	PhI	AcOOH	73
17[e,f]	HFIP	PhI	AcOOH	78
18[g,e]	HFIP	PhI	AcOOH	55

[a] Reaction conditions: **1a** (0.15 mmol), **2a** (0.18 mmol), RI (20 mol%) and oxidant (2 equiv) in solvent (1.0 mL) and open flask for 30 min. [b] Yield of isolated product after column chromatography. [c] *m*-CPBA (1.5 equiv) used. [d] 2,2′-Diiodo-4,4′,6,6′-tetramethyl-1,1′-biphenyl (**A**) (10 mol%) was used. [e] 1.5 equiv of AcOOH [f] AcOOH acid was added portion wise in 15 min. [g] PhI (15 mol%) was used. n.d. = not detected.

product. The yield of product was increased when peracetic acids was added portion-wise. It was found that the optimal amount of peracetic acid is 1.5 equivalents and catalyst loading is 20 mol% (Table 1, entries 16–18; see also the Supporting Information). Under optimized conditions, the desired product **3a** was obtained with 78% yield in 30 min (Table 1, entry 17).

With optimal reaction conditions, we next explored the scope of reaction with a variety of substituted alkynes (Scheme 2). Annulations of alkyne-bearing electron-withdrawing and electron-donating groups worked well and afforded the cyclized products in good yield. Symmetrically disubstituted diphenyl acetylenes react well and provided the desired products in 60–82% yield (Scheme 2, **3b–d**). Notably, the application of *N*,3,4-trimethoxybenzamide as coupling partner allowed selective formation of one regioisomer (Scheme 2; **3b**, **3c**). A variety of functional groups such as trifluoromethyl-, fluoro-, nitro-, and methoxy- were tolerated under the developed mild organocatalytic reaction conditions (Scheme 2, **3e–j**). Unsymmetrical diphenylacetylenes substituted with methoxy-, nitro- and trifluoromethyl groups, regioselectively delivered single regioisomers which was unapproachable by analogous transition-metal-catalyzed processes (Scheme 2; **3e**, **3f**, **3i**, **3j**). Nevertheless, the application of diphenylacetylenes substituted with weak electronic-effect groups, for example fluorine, led to formation of regioisomer mixtures (Scheme 2, **3g**, **3h**).



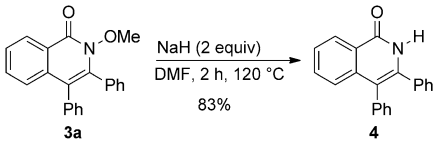
Scheme 2. Scope of the organocatalyzed annulation. Reaction conditions: **1** (0.15 mmol), **2** (0.18 mmol), 20 mol% PhI and AcOOH (1.5 equiv) in HFIP at room temperature. [a] 25 mol% of PhI was used. [b] Major isomer is shown. [c] $PhI(OAc)_2$ (1.5 equiv) used instead of PhI and AcOOH. [d] Catalyst **A** (10 mol%), CF_3CO_2H (5 equiv) and AcOOH (2 equiv) were used in 1,2-dichloroethane (2 mL).

After investigation of the scope of alkynes, different substituents on the nitrogen atom of benzamides were tested in annulation with diphenylacetylene. We observed that a broad range of alkoxy groups can be employed under organocatalytic reaction conditions providing products in 56–85% yield (Scheme 2, **3k–o**). It is notable that a double bond is tolerated under the oxidative reaction conditions

(Scheme 2, **3o**). Unfortunately, an application of *N*-alkyl and *N*-aryl benzamides in the annulation did not allow the formation of desired products. Therefore, the presence of alkoxy groups on the nitrogen atom of benzamides is essential for a successful organocatalytic annulation.

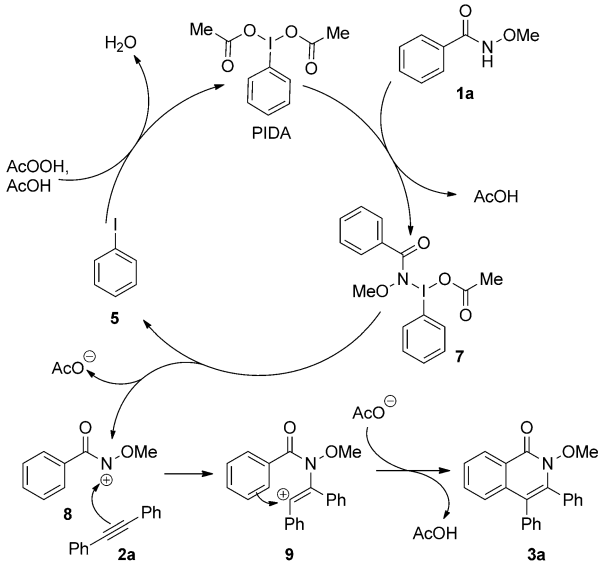
We next turned our attention to the different benzamides substituted in aromatic part (Scheme 2, **3p**–**u**). In general, *ortho*-, *meta*-, and *para*-substitutions were tolerated. Nevertheless, the utilization of *meta*-substituted derivative resulted in formation of a mixture of regioisomers (Scheme 2, **3s**, **3t**). Benzamides with electron-donating and electron-neutral substituents allowed formation of desired isoquinolones while electron-withdrawing groups suppressed the formation of annulated products.

The products could be straightforwardly deprotected by cleavage of the N–O bond to provide substituted isoquinolin-1(2*H*)-ones.[6] For example, the treatment of **3a** with sodium hydride gave the desired product **4** with 83% yield (Scheme 3).



Scheme 3. Deprotection of isoquinolone **3a**.

Based on preliminary investigations, a mechanism is proposed in Scheme 4. Initially, iodobenzene (**5**) is oxidized under the reaction conditions to form PIDA. The reaction of PIDA with **1a** generates an intermediate **7** through ligand exchange on hypervalent iodine. After that, the nitrenium ion **8** and iodobenzene (**5**) are generated by disproportionation of intermediate **7**. The nitrenium ion **8** is trapped by alkyne **2a** forming a carbenium ion **9**. Following intermolecular Friedel–Crafts process resulted in the desired isoquinolone **3a** (Scheme 4).



Scheme 4. Proposed mechanism of organocatalyzed annulation of benzamide.

In conclusion, we have described an iodobenzene-catalyzed regioselective annulation of *N*-alkoxybenzamide derivatives with readily available alkynes. Simple organocatalysts offer a novel straightforward approach for the synthesis of isoquinolones. The desired products formed smoothly at ambient temperature in short times using peracetic acid as the oxidant. A notably high regioselectivity was described in annulation of unsymmetrical diarylacetylenes demonstrating that the developed organocatalytic approach is superior to transition-metal-catalyzed reactions.

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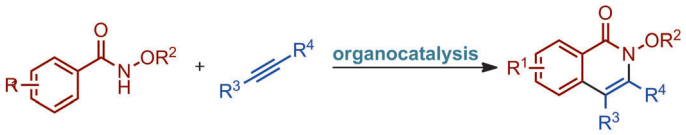
Communications

Organocatalysis

S. Manna,
A. P. Antonchick* _____ ■■■■–■■■■

Organocatalytic Oxidative Annulation of Benzamide Derivatives with Alkynes



Annulation without hesitation: *N*-alkoxybenzamides convert into isoquinolones smoothly and rapidly under organocatalytic conditions. The annulation of unsymmetrical diarylacetylenes proceeds with a high regioselectivity. The transformation is based on the hypervalent-iodine mediated generation of nitrenium ions.