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Multicatalytic One-Pot Reaction of 1-(2-Alkynylphenyl)ketoximes for Generation of Indole Derivatives

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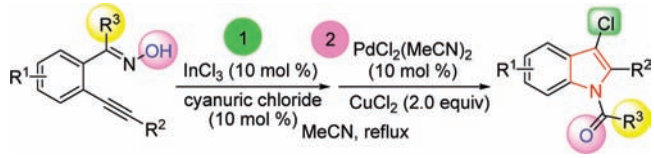
ABSTRACT



Multicatalytic one-pot Beckmann rearrangement/intramolecular cyclization/halogenation reaction of 1-(2-alkynylphenyl)ketoxime is reported, leading to the expected indole derivatives in good yield.

The tandem reaction has been recognized as an attractive strategy for molecular complexity generation.[1] As part of a program in our laboratory for natural product-like compound construction,[2,3] we identified that 2-alkynylbenzaldoxime was a useful building block for N-heterocycle generation via tandem reactions.[3] On the other hand, it is well-known that the Beckmann rearrangement of ketoximes is a fundamental and commonly used tool for amide formation.[4] Many catalytic methods have appeared for the transformation recently.[5] For instance, Yamamoto and co-workers reported that 2,4,6-trichloro-1,3,5-triazine (cyanuric chloride) was an effective organocatalyst (cocatalyzed by HCl or $ZnCl_2$) for the Beckmann rearrangement under reflux in acetonitrile or nitromethane.[5h] Encouraged by these results, we envisioned that 1-(2-alkynylphenyl)ketoxime might be utilized as a

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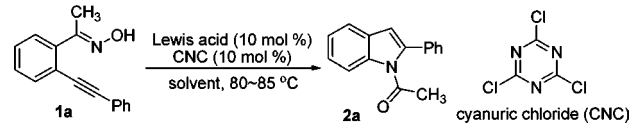
substrate in tandem reactions as well. We anticipated that after a Beckmann rearrangement of 1-(2-alkynylphenyl)-ketoxime 2-alkynylanilide would be afforded. Thus, the intramolecular cyclization would occur in the presence of suitable catalyst to generate an indole scaffold,[6,7] which is a core structure in both natural products and therapeutic agents.[8]

As described, two separate catalytic systems are necessary in the above two steps. Recently, a strategy involving two or more catalysts in one pot to cooperatively catalyze a chemical reaction has been demonstrated, which broadens the reaction scope within organic synthesis.[9,10] The proposed tandem Beckmann rearrangement−intramolecular cyclization reaction of 1-(2-alkynylphenyl)ketoxime led us to envision the possibility to incorporate two catalytic systems to achieve the indole synthesis. 1-(2-Alkynylphenyl)ketoxime could be synthesized easily according to the literature method.[11] To validate our hypothesis, we carried out the initial studies using (*E*)-1-(2-(2-phenylethynyl)phenyl)ethanone oxime **1a** as the substrate (Table 1).

As mentioned above, 2,4,6-trichloro-1,3,5-triazine (cyanuric chloride) has been demonstrated as an effective organocatalyst in the presence of acid cocatalyst for the Beckmann rearrangement.[5h] Thus, at the outset, the reaction was catalyzed by cyanuric chloride (10 mol %) and $CuCl_2$ (10 mol %) (Table 1, entry 1). However, the reaction was complicated. Similar results were observed when $Cu(OTf)_2$ or CuI was utilizied as a replacement of $CuCl_2$ (Table 1, entries 2 and 3). We were gratified to find that the desired product **2a** was obtained in 25% isolated yield when the reaction was catalyzed by cyanuric chloride (10 mol %) and $PdCl_2$ (10 mol %) (Table 1, entry 4). Higher yield of indole **2a** was generated when $PdCl_2(MeCN)_2$ was used in the reaction (Table 1, entry 5). However, when the reaction was cocatalyzed by cyanuric chloride and $InCl_3$ (Table 1, entry 6), only the Beckmann rearrangement product was furnished with 90% yield. We reasoned that the palladium catalyst was mainly beneficial for the intramolecular cyclization process. In addition, we noticed that in Yamamoto's report an additional acid catalyst would facilitate the Beckmann rearrangement. Therefore, $ZnCl_2$ or $InCl_3$ was added in the cyanuric chloride, and a $PdCl_2(MeCN)_2$ cocatalzyed tandem reaction of (*E*)-1-(2-(2-phenylethynyl)phenyl)ethanone oxime **1a** (Table 1, entries 7 and 8) occurred. With an expectation to achieve increased efficacy, we improved the experimental procedure: cyanuric chloride with $ZnCl_2$ or $InCl_3$ was added in the reaction first. After consumption of (*E*)-1-(2-(2-phenylethynyl)phenyl)ethanone oxime **1a**, $PdCl_2(MeCN)_2$ was then added. To our delight, the desired product **2a** was generated in 41% and 80% yield, respectively. A blank experiment indicated that only a trace amount of product was afforded without the addition of cyanuric chloride (data not shown in Table 1). Further screening of solvents showed that the reaction worked the most effectively in MeCN. Inferior results were observed when the reaction was performed in other solvents (Table 1, entries 9−11). A trace amount of product **2a** was detected when the reaction occurred at room temperature (Table 1, entry 12). Lower yield was isolated when the amount of catalysts was reduced to 5 mol % (Table 1, entry 13).

With the optimal conditions in hand, we thus examined the scope of the multicatalytic one-pot Beckmann rearrangement/intramolecular cyclization reactions of 1-(2-alkynylphe-

Table 1. Initial Studies for the Multicatalytic One-Pot Reaction of 1-(2-Alkynylphenyl)ketoxime **1a**



entry	Lewis acid	solvent	yield (%)[a]
1	CNC, $CuCl_2$	MeCN	complicated
2	CNC, $Cu(OTf)_2$	MeCN	complicated
3	CNC, CuI	MeCN	complicated
4	CNC, $PdCl_2$	MeCN	25
5	CNC, $PdCl_2(MeCN)_2$	MeCN	35
6	CNC, $InCl_3$	MeCN	−[b]
7	CNC, $PdCl_2(MeCN)_2$, $ZnCl_2$	MeCN	41
8	*CNC, $PdCl_2(MeCN)_2InCl_3$*	*MeCN*	*80*
9	CNC, $PdCl_2(MeCN)_2$, $InCl_3$	DMF	35
10	CNC, $PdCl_2(MeCN)_2$, $InCl_3$	toluene	trace
11	CNC, $PdCl_2(MeCN)_2$, $InCl_3$	DCE	51
12[c]	CNC, $PdCl_2(MeCN)_2$, $InCl_3$	MeCN	trace
13[d]	CNC, $PdCl_2(MeCN)_2$, $InCl_3$	MeCN	60

[a] Isolated yield based on 1-(2-alkynylphenyl)ketoxime **1**. [b] Beckmann rearrangement product was obtained in 90% yield. [c] The reaction was performed at room temperature. [d] In the presence of 5 mol % of catalysts.

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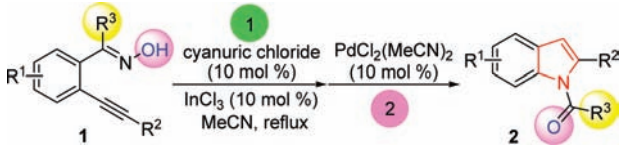
Table 2. Multicatalytic One-Pot Beckmann Rearrangement/Intramolecular Cyclization Reactions of 1-(2-Alkynylphenyl)-ketoximes



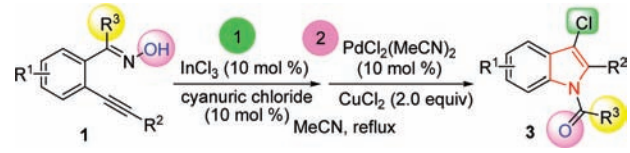
entry	R^1	R^2	R^3	yield (%)[a]
1	H	C_6H_5	CH_3	80 (**2a**)
2	H	4-$CH_3C_6H_4$	CH_3	74 (**2b**)
3	H	4-$CH_3OC_6H_4$	CH_3	62 (**2c**)[b]
4	H	*n*-C_4H_9	CH_3	62 (**2d**)
5	H	cyclopropyl	CH_3	53 (**2e**)
6	H	$SiMe_3$	CH_3	–[c] (**2f**)
7	H	C_6H_5	CH_3CH_2	74 (**2g**)
8	H	4-$CH_3C_6H_4$	CH_3CH_2	70 (**2h**)
9	H	4-$CH_3OC_6H_4$	CH_3CH_2	60 (**2i**)
10	H	*n*-C_4H_9	CH_3CH_2	53 (**2j**)
11	H	C_6H_5	C_6H_5	–[d] (**2k**)
12	5-Cl	C_6H_5	CH_3	52 (**2l**)
13	5-CH_3	C_6H_5	CH_3	66 (**2m**)
14	5-CH_3	4-$CH_3C_6H_4$	CH_3	70 (**2n**)

[a] Isolated yield based on 1-(2-alkynylphenyl)ketoxime **1**. [b] A byproduct was formed concomitantly. [c] The reaction was complex. [d] Only the Beckmann rearrangement product was isolated.

nyl)ketoximes. The results are shown in Table 2. This multicatalytic one-pot reaction was found to be workable for 1-(2-alkynylphenyl)ketoximes with electron-withdrawing and -donating substituents on the aromatic backbone. Reactions employing the substrates with an alkyl group (*n*-butyl or cyclopropyl substituent) attached to the C≡C triple bond proceeded smoothly as well to generate the desired products in good yields (Table 2, entries 4, 5, and 10). However, the reaction was complex when R^2 was replaced by the trimethylsilyl group (Table 2, entry 6). It should be noted that a byproduct was formed concomitantly when R^2 was changed as the 4-methoxyphenyl group (Table 2, entry 3). For the substrate with the phenyl group (R^3) attached to the oxime, no desired product was detected, and only the Beckmann rearrangement product was isolated (Table 2, entry 11).

To broaden the utility of this tandem reaction, we conceived that an additional step for halogenation was possible. Thus, further investigation by adding copper(II) chloride was explored for the tandem reaction of (*E*)-1-(2-(2-phenylethynyl)phenyl)ethanone oxime **1a**.[12] Finally, we realized that the reaction worked efficiently in the presence of 2.0 equiv of $CuCl_2$, which led to the desired 3-chloroindole **3a** in 66% yield (Table 3, entry 1). A similar result was

Table 3. Synthesis of 3-Chloroindoles via Multicatalytic One-Pot Reactions of 1-(2-Alkynylphenyl)ketoximes



entry	R^1	R^2	R^3	yield (%)[a]
1	H	C_6H_5	CH_3	66 (**3a**)
2	H	C_6H_5	CH_3CH_2	70 (**3b**)
3	H	4-$CH_3C_6H_5$	CH_3CH_2	61 (**3c**)
4	5-Cl	C_6H_5	CH_3	50 (**3d**)
5	5-CH_3	C_6H_5	CH_3	70 (**3e**)
6	5-CH_3	4-$CH_3C_6H_4$	CH_3	63 (**3f**)

[a] Isolated yield based on 1-(2-alkynylphenyl)ketoxime **1**.

generated when R^3 was replaced by an ethyl group (Table 3, entry 2). Other 1-(2-alkynylphenyl)ketoximes with a chloro, methyl group attached on the aromatic ring were examined as well, and all reactions worked well to give the desired product **3** in reasonable yield.

In conclusion, we have developed a novel approach to indole derivatives via a multicatalytic one-pot Beckmann rearrangement/intramolecular cyclization/halogenation reaction of 1-(2-alkynylphenyl)ketoxime. The starting materials are easily accessible, and the final product could be further elaborated via known palladium-catalyzed cross-coupling reactions. Using 1-(2-alkynylphenyl)ketoxime as a substrate in other tandem reactions is under investigation currently.

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Supporting Information Available: Experimental procedures, characterization data, and ^1H and ^{13}C NMR spectra of compounds **2** and **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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