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Dimerization of heteroaromatic *N*-oxides under metal-free conditions[†]

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A novel procedure for the dimerization of heteroaromatic N-oxides under transition-metal-free conditions has been developed. The protocol is effective and convenient. The biheteroaromatic mono N-oxides products were obtained in up to 93% yield.

Biheteroaromatic N-oxides have found wide application as structure motifs in pharmaceuticals, functional materials and organic synthesis as ligands.1 Conventional strategies to build such a structure typically involve multistep reaction sequences,² or transition-metal-catalyzed coupling-reactions of a heteroaryl halide or pseudohalide with a heteroaryl organometallic reagent³ (Scheme 1, path a). These approaches always require harsh reaction conditions, or transition metals, most of which are expensive and non environmentally benign. The removal of harmful transition-metal contamination is often costly and difficult in pharmaceuticals.⁴ Therefore an environmentally benign and practical access to construct biheteroarmatic N-oxide compounds is highly desired. Recently, the dimerization of quinoline N-oxide was achieved under organocatalytic reaction conditions by Kondo group.5 However, an organosilicon additive is required and the biquinoline N-oxide is obtained in lower yield. Then, they developed a similar procedure using onium amide bases in situ generated.6 To the best of our knowledge, one-pot protocol to synthesize biquinoline N-oxide under transition metals and catalysts free conditions has not been reported so far. Herein, we disclosed an efficient, simple method to construct the biheteroaromatic mono *N*-oxides under metal-free conditions (Scheme 1, path b).

At the outset of the study, we chose quinoline *N*-oxide (1a) as a model substrate to screen the reaction parameters (Table 1). Firstly, the reaction was carried out in the presence of 10 mol% $Pd(OAc)_2$ and 2.0 equiv. of ^tBuOLi in toluene at 120 °C for 20 h. The desired product 2a was isolated in 56% yield (entry 1). Encouraged by this result, we further optimized the reaction conditions. Surprisingly, 87% yield could be obtained in the absence of $Pd(OAc)_2$ (entry 2). We found that reducing reaction time was beneficial for the reaction, as the yield of 2a was improved to 91% (entry 3). For this process, examination of the amount of ^tBuOLi indicated that 1.5 equiv. of ^tBuOLi was optimal (entries 3–6). Base screening disclosed that ^tBuOLi was superior to others (entries 4, 7–11). Investigation of different solvents showed that toluene was the best suitable solvent (entries 4, 12–17). Furthermore, decreasing the temperature of the reaction brought a significant decrease in the yields (entries 18–20). Finally, the optimal conditions for the dimerization were identified to be ^tBuOLi (1.5 equiv.) as the base and toluene as the solvent at 120 °C for 3 hours.

Having established the optimal reaction conditions in hand, we investigated the generality and scope of substrates for this transition-metal-free transformation. The results in Table 2 demonstrated that this reaction had a good functional group tolerance. The reaction of quinoline *N*-oxide and its derivatives with moderate electron-withdrawing group, such as Br and Cl, readily proceeded smoothly and provided the desired products in 75–93% yields (**2a–2e**). When Br group at 3-position of



Scheme 1 Dimerization of heteroaromatic *N*-oxides through different methods.

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Table 1 Optimization of reaction conditions^a



Entry	Catalyst	Bases (equiv.)	Solvents	Yield ^b (%)
1 ^c	$Pd(OAc)_{2}(10\%)$	^t BuOLi (2.0)	Toluene	56
2^{c}		t BuOLi (2.0)	Toluene	87
3	_	t BuOLi (2.0)	Toluene	91
4	_	t BuOLi (1.5)	Toluene	93
5	_	^t BuOLi (2.5)	Toluene	93
6	_	t BuOLi (1.0)	Toluene	81
7	_	^t BuONa (1.5)	Toluene	58
8	_	K_2CO_3 (1.5)	Toluene	0
9	_	$K_{3}PO_{4}(1.5)$	Toluene	0
10	_	Cs_2CO_3 (1.5)	Toluene	0
11	_	DBU (1.5)	Toluene	0
12	_	^t BuOLi (1.5)	DMSO	nd ^d
13	_	t BuOLi (1.5)	THF	0
14	_	^t BuOLi (1.5)	DMF	40
15	_	t BuOLi (1.5)	CH ₃ CN	0
16	_	^t BuOLi (1.5)	Dioxane	72
17	_	^t BuOLi (1.5)	DCE	Trace
18^e	_	^t BuOLi (1.5)	Toluene	81
19 ^f	_	t BuOLi (1.5)	Toluene	75
20 ^g	_	t BuOLi (1.5)	Toluene	72
		()		

^{*a*} Reaction conditions: **1a** (0.5 mmol), solvent (2.5 mL), 3 h at 120 °C. ^{*b*} Isolated yields. ^{*c*} 20 h. ^{*d*} nd is not detected. ^{*e*} 110 °C. ^{*f*} 100 °C. ^{*g*} 90 °C.

quinoline *N*-oxide was also well tolerated and the product was obtained in 75% yield (2e), indicating that this reaction was not sensitive significantly to steric hindrance in the substrate. Electron-rich substrates, such as methyl, methoxyl groups substituted on the aromatic rings, provide the dimerization products in moderate yields (2f and 2g). However, when the pyridine rings were substituted by methyl or methoxyl groups, the dimerization products were obtained in 49%, 28% and 34% yields, respectively (2h–2j). Good yield was afforded when the reaction system was applied to quinoxaline *N*-oxide (2k). In addition, pyridine *N*-oxide derivatives were also shown to be possible substrates and gave the desired products in moderate to good yields (2l–2n).

The controlled experiment was carried out to see if the dimerization was achieved *via* a nucleophilic addition-elimination process⁵⁻⁷ (Scheme 2). When benzoxazole was employed in the reaction, the corresponding products **2a** and **2o** could be given in 40% and 41% (based on **1a**) yields, respectively, which suggested that benzoxazole carbanion was generated by the aid of base and served as an external nucleophile.

A possible mechanism for this dimerization of quinoline *N*-oxide was proposed and described as follows (Scheme 3): (i) deprotonation of quinoline *N*-oxide *in situ*-generated carbanion **A** firstly by ^tBuOLi. (ii) Subsequently, the intermediate **B** was formed by attacking at the α -position of another quinoline

Table 2 Substrate scope for the dimerization of heteroaromatic *N*-oxides using ^tBuOLi as the base^{a,b}



 a Reaction conditions: 1 (0.5 mmol), solvent (2.5 mL), 3 h, 120 °C. b Isolated yields. c 130 °C.



Scheme 2 Controlled experiment.



Scheme 3 Proposed reaction mechanism

N-oxide. (iii) The final product **2a** was generated with concomitant release of the LiOH.

In conclusion, a mild and efficient method for the dimerization of heteroaromatic *N*-oxides under metal-free conditions has been developed. A broad range of 2,2'-biheteroaromatic mono *N*-oxides were obtained in up to 93% yield. Further efforts on the reaction mechanism will be studied in the future research.

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