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Dehydrogenative etherification homocoupling of heterocyclic *N*-oxides

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ABSTRACT

A novel approach was developed for the dehydrogenative etherification homocoupling of heterocyclic *N*-oxides in the presence of silver oxide and PyBroP. Various substrates were well tolerated and the desired products were obtained in moderate to good yields. Generally, this reaction features excellent functional group compatibility, broad substrate scope and good regioselectivity.

Introduction

Quinoline heterocycles are ubiquitous core structures in medicinal chemistry, the agrochemical industry, and materials science.[1] As an important class of *N*-heterocycle, the direct functionalization of quinolines has attracted extensive attention from synthetic chemists,[2] and in recent years, there have been many attempts regarding their direct functionalization. Various modifications have been reported at the C2-position of quinolines, such as halogenation, amination, alkylation, arylation, alkenylation, cyanation, and acylation.[3] Among quinoline derivatives, the homodimers of electron-deficient *N*-heterocycles are important and useful compounds. They are widely used in light-emitting materials,[4] for marking biomacromolecules in bioanalysis,[5] as ligands in transition metal catalyzed synthesis,[6] and as substructures in a wide variety of biologically active compounds.[7] Remarkably, a series of quinoline derivatives with potential anti-prostate cancer biological activities have been reported by Li and co-workers, which have similar structures to *O*-tethered dimeric quinolines (Fig. 1).[8] Malathi,[9] Małgorzata,[10] and Zhao[11] have reported the synthesis of *O*-tethered dimeric quinolines using quinolin-2 (1*H*)-ones as precursors, but which suffers from relatively low yields, requires multiple steps, and utilises strong bases (Scheme 1). Additionally, there are few literature reports regarding the direct synthesis of homodimers of electron- deficient *N*-heterocycles *via* homocoupling of the corresponding *N*-heterocycles. Herein, we report the reaction of quinoline *N*-oxides with silver oxide in acetonitrile to afford the corresponding homodimers which are connected by an ether bond at the C2 position. The phosphonium salt PyBroP (bromotri (1-pyrrolidinyl) phosphonium hexafluorophosphate)[12] is utilised as a nucleophile to activate the homocoupling reaction.

Initially, quinoline *N*-oxide **1a** was chosen as a model substrate for optimization of the reaction parameters due to its widespread use in C—H functionalization reactions (Table 1). To our delight, excellent conversion of **1a** was achieved in the reaction utilising PyBroP (3 equiv.), potassium carbonate (2 equiv.) and acetonitrile at 25 °C for 12 h under an air atmosphere. The corresponding dimeric product **2a** was isolated in 38% yield (Entry 1). To improve the yield of the quinoline homodimer, different additives were examined. Silver oxide was demonstrated as a favorable additive, compared to potassium carbonate, sodium carbonate, cesium carbonate and silver carbonate, affording the desired product **2a** in 80% yield (Entry 5). A number of solvents such as DCE, CH_2Cl_2, THF, $CHCl_3$ and DMF were examined, however none could match the efficiency of CH_3CN (Entries 14–18). Temperatures lower or higher than 50 °C resulted in reduced yields of **2a** (Entries 7 and 13). Finally, different amounts of PyBroP and silver oxide were examined for the formation of **2a**; the optimal loading was determined as PyBroP (2 equiv.) and silver oxide (1 equiv.) (Entries 8–12).

With the optimized reaction conditions in hand, we then explored the scope of quinoline *N*-oxides amenable to the

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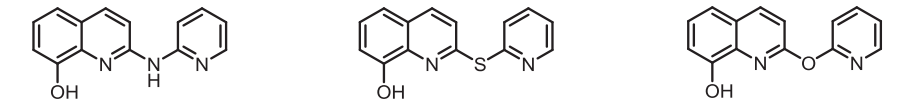
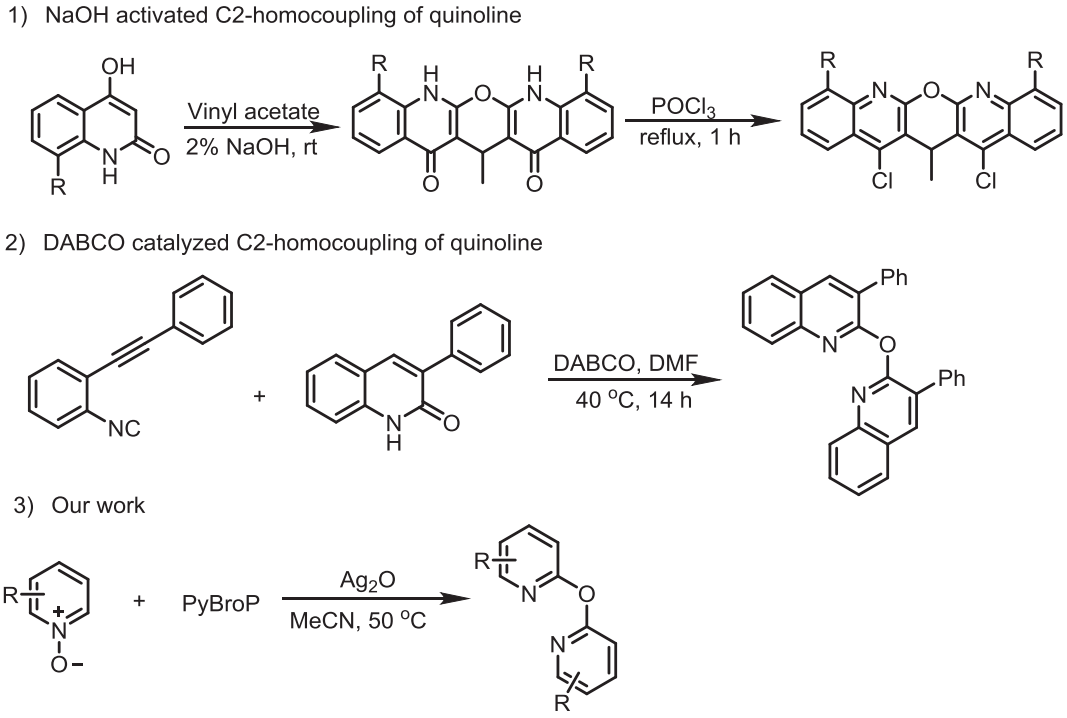
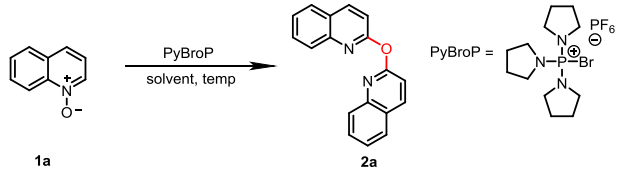


Fig. 1. Structures related to *O*-tethered dimeric quinolines.



Scheme 1. Synthesis of *O*-tethered dimeric quinolines.

Table 1
Reaction Conditions Optimization.[a]



Entry	PyBroP (equiv.)	Additive (equiv.)	Temp (°C)	Solvent	Yield **2a** (%)[b]
1	3	K_2CO_3 (2)	25 °C	CH_3CN	38
2	3	Cs_2CO_3 (2)	25 °C	CH_3CN	48
3	3	Na_2CO_3 (2)	25 °C	CH_3CN	51
4	3	Ag_2CO_3 (2)	25 °C	CH_3CN	61
5	3	Ag_2O (2)	25 °C	CH_3CN	80
6	2	Ag_2O (2)	25 °C	CH_3CN	78
7	2	Ag_2O (1)	25 °C	CH_3CN	77
8	2	Ag_2O (1)	50 °C	CH_3CN	86
9	3	Ag_2O (2)	50 °C	CH_3CN	86
10	3	Ag_2O (1)	50 °C	CH_3CN	86
11	2	Ag_2O (0.5)	50 °C	CH_3CN	69
12	1	Ag_2O (1)	50 °C	CH_3CN	72
13	2	Ag_2O (1)	70 °C	CH_3CN	83
14	2	Ag_2O (1)	50 °C	CH_2Cl_2	51
15	2	Ag_2O (1)	50 °C	DCE	46
16	2	Ag_2O (1)	50 °C	THF	56
17	2	Ag_2O (1)	50 °C	$CHCl_3$	37
18	2	Ag_2O (1)	50 °C	DMF	24

[a] Reagents and conditions: quinoline *N*-oxide (0.2 mmol), PyBroP, Ag_2O, solvent (2.0 mL), under air in a sealed tube, 12 h.
[b] Isolated yield.