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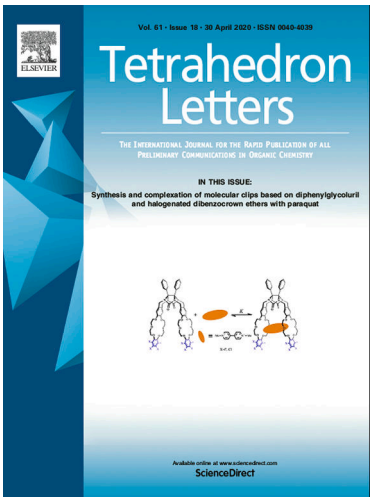

Direct decarboxylative C-H 3-arylation of quinoxalin-2(H)-ones with aryl acyl peroxides leading to 3-arylquinoxalin-2(1H)-ones

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Direct decarboxylative C-H 3-arylation of quinoxalin-2(H)-ones with aryl acyl peroxides leading to 3-arylquinoxalin-2(1H)-ones

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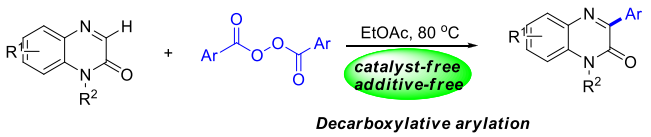
ABSTRACT

A facile and direct decarboxylative C-H 3-arylation of quinoxalin-2(H)-ones with aryl acyl peroxides has been developed for the synthesis of 3-arylquinoxalin-2(1H)-ones under simple heating conditions. The present methodology provides a simple and highly efficient approach to various 3-arylquinoxalin-2(1H)-ones in high yields without the use of any catalyst and additives.

Quinoxalin-2(1H)-ones are extremely valuable organic compounds, which have been extensively employed in synthetic chemistry, pharmaceutical industry, and materials.[1] In particular, 3-arylquinoxalin-2(1H)-ones as an important structural motif is frequently found in various biologically active compounds and pharmaceutical molecules, which possess a wide range of biological activities.[2] Consequently, many synthetic methods have been developed to access 3-arylquinoxalin-2(1H)-ones. The traditional methods mainly involve the oxidative cyclization of aryl-1,2-diamines with alkynes,[3] the condensation/cyclization of aryl-substituted precursors,[4] and the Heck/Suzuki coupling of 3-haloquinoxalin-2(1H)-ones with arylboronic acids or arenes.[5] However, these reactions usually encounter some limitations such as the extra steps to prepare starting materials, complex operations, or harsh reaction conditions. In recent years, the direct C-H functionlization of quinoxalin-2(1H)-ones has became as a highly attractive protocol for the synthesis of 3-substitued quinoxalin-2(1H)-ones.[6] In this context, the C-H arylation of quinoxalin-2(1H)-ones with various arylating reagents including arylboronic acids,[7] diaryliodonium salts,[8] arylhydrazines,[9] arylamines,[10] arenes[11] and aryl diazonium salts[12] have been developed. Nevertheless, most these well developed protocols still require the use of transition metal reagents, excess oxidants, or additive (i.e. strong acids and hypervalent iodine reagents). Thus, the development of facile and efficient strategy for the C-H arylation of quinoxalin-2(1H)-ones is still greatly demanded.



Scheme 1. Decarboxylative reaction for 3-arylation of quinoxalin-2(H)-ones.

Recently, decarboxylative C-H 3-alkylation of quinoxalin-2(H)-ones to synthesize 3-alkylquinoxalin-2(H)-ones using carboxylic derivatives such as phenyliodine(III) dicarboxylates[13] and N-hydroxyphthalimide esters[14] as the alkyl radical precursors have been reported. Aryl acyl peroxides are cheap and readily available carboxylic acid derivatives, which can generate oxygen-centered radicals (acyloxyl radicals)[15] and carbon-centered radicals (aryl radicals)[16] under transition-metal catalysis and/or heating conditions. To the best of our knowledge, the utilization of aryl acyl peroxides as the arylating reagents *via* decarboxylative C-H 3-arylation of quinoxalin-2(1H)-ones is still unexplored. Herein, we wish to report a facile and efficient strategy for the synthesis of 3-arylquinoxalin-2(1H)-ones *via* direct decarboxylative C-H 3-arylation of

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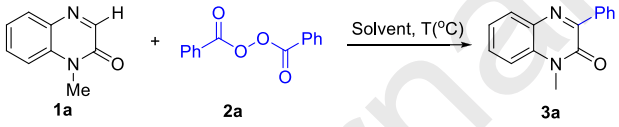
simple heating conditions (Scheme 1). The present method provides an attractive approach to construct a series of 3-arylquinoxalin-2(1H)-ones in high yields with good functional group tolerance by not requiring of any external catalyst and additives.

Initially, N-methyl-3-phenylquinoxalin-2(1H)-one **1a** and benzoyl peroxide (BPO) **2a** were employed as the model substrates to optimize the reaction conditions. When the reaction of **1a** and **2a** was performed in DME at 80°C for 24h, the desired product N-methyl-3-phenylquinoxalin-2(1H)-one **3a** was obtained in 23% yield (Table 1, entry 1). Subsequently, a number of solvents were tested and the results showed that the reaction medium had a great influence on the reaction efficiency (Table 1, entries 2-9). As shown in Table 1, DCE, CH_3CN and EtOAc gave the product **3a** in good yields (Table 1, entries 2,3,5). Other solvents such as DME, THF, EtOH, and DMF only generated the product **3a** in relatively lower yields (Table 1, entries 4-7). None of product was detected in DMSO and H_2O (Table 1, entries 8 and 9). Among the above solvents examined, ethyl acetate gave the best outcome in this reaction, delivering the desired product **3a** in 88% yield (Table 1, entry 3). The reaction efficiency was also greatly affected by the temperature, and the increase or decrease of the reaction temperature all resulted in a lower yield of **3a** (Table 1, entries 10 and 11). No reaction was observed when the model reaction was carried out at room temperature (Table 1, entry 12). Finally, the addition of metal catalyst such as $Cu(OAc)_2$ or $FeCl_3$ did not improve the reaction efficiency.

Table 1

Screening of the reaction conditions.[a]



Entry	Solvent	T(°C)	Yield(%)[b]
1	DME	80°C	23
2	DCE	80°C	76
3	CH_3CN	80°C	80
4	THF	80°C	7
5	EtOAc	80°C	88
6	EtOH	80°C	13
7	DMF	80°C	18
8	DMSO	80°C	0
9	H_2O	80°C	0
10	EtOAc	90°C	87
11	EtOAc	60°C	64
12	EtOAc	25°C	0
13	EtOAc	80°C	86[c]
14	EtOAc	80°C	85[d]

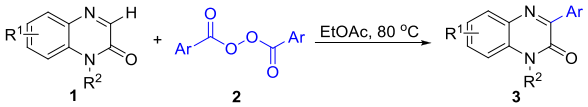
[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), solvent (4 mL), 25-90°C, 24h.

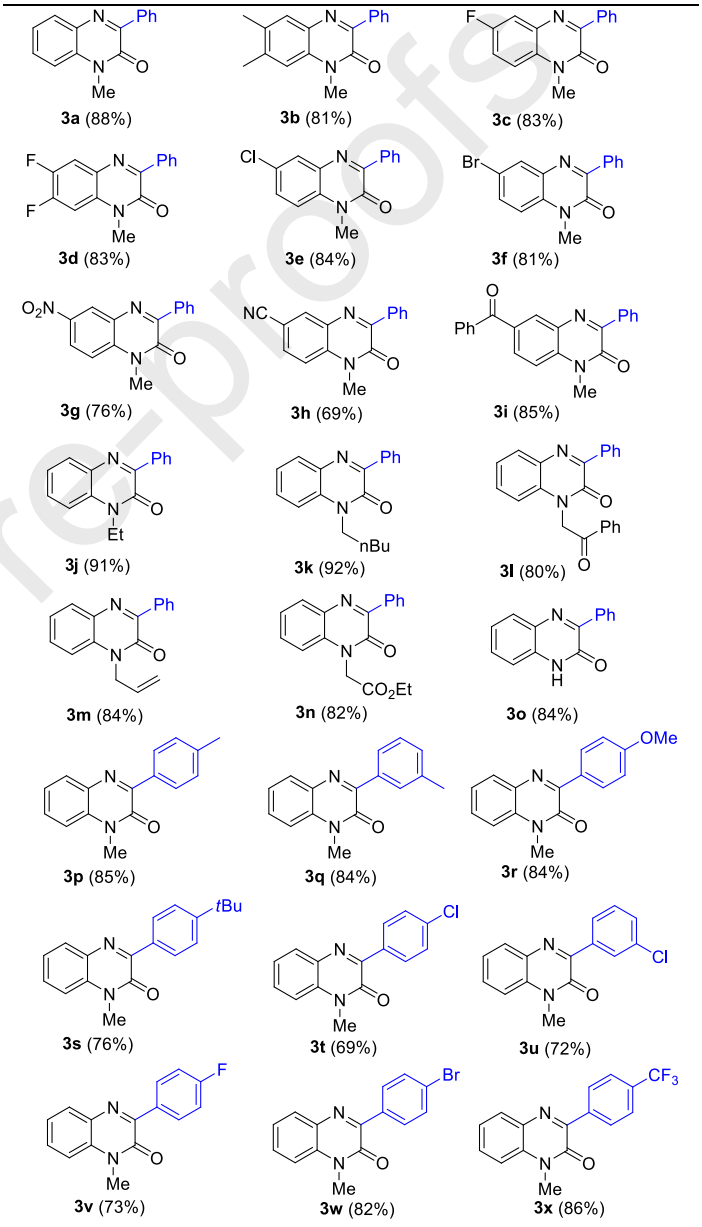
[b] Isolated yields based on **1a**.

[d] $FeCl_3$ (5 mol%).

Table 2

Substrate scope.[a,b]





[a] Reaction condition: **1** (0.2 mmol), **2** (0.3 mmol), EtOAc (4 mL), 80°C, 24 h.

[b] Isolated yields based on **1**.

With the optimal reaction conditions in hand, the scope and generality of this decarboxylative arylation of quinoxalin-2(1H)-ones and aryl acyl peroxides was

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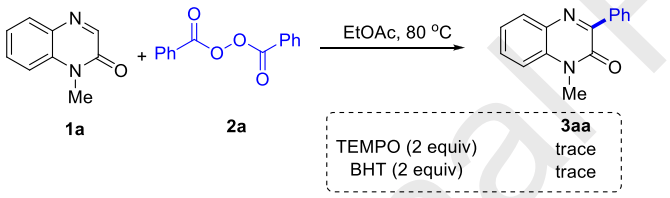
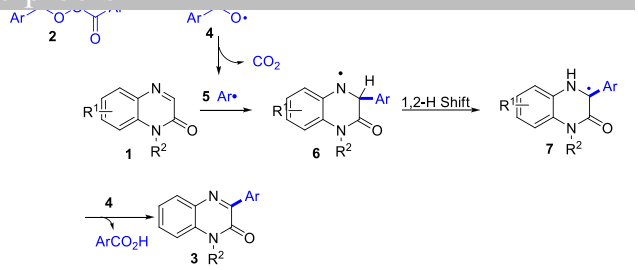
donating and electron-withdrawing groups on the phenyl ring were suitable for this procedure, yielding the products **3b**-**3i** in good yields. Notably, a series of functional groups such as halogen, nitro, cyano, and carbonyl groups were well tolerated, facilitating the further transformations. The effect of various N-protected groups on the reactions was also examined. A series of quinoxalin-2(H)-ones with ethyl, pentyl, allyl substituents at the nitrogen atom and other alkyl substituents bearing keto and ester functionalities reacted efficiently with BPO **2a** and delivered the corresponding products **3j**–**3n** in high yields. It was found that the N-free protected quinoxalin-2(1*H*)-one was also suitable for the direct C-H arylation reaction to give the desired product **3o** in 84% yield. Next, the scope of different substituted aryl acyl peroxides was examined. As shown in Table 2, a series of aryl acyl peroxides containing electron-donating (methyl, alkoxy) or electron-withdrawing groups (F, Cl, Br, trifluoromethyl) on the phenyl ring underwent the reaction smoothly to produce the corresponding products **3p**-**3x** in good yields. Moreover, when alkyl diacyl peroxide such as dilauroyl peroxide was investigated in our reaction system, only a trace amount of desired product was detected.

Radical inhibiting experiments were carried out to elucidate the possible reaction mechanism. When radical-inhibiting reagent such as TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) or BHT (2,6-di-tert-butyl-4-methylphenol) was separately added in the present reaction system, the model reaction of **1a** and **2a** was significantly inhibited. This result suggested that the present decarboxylative arylation might involve a radical pathway (Scheme 2).



Scheme 2. Control experiments.

On the basis of these results and previous reports,[8-12,16] a possible reaction pathway was proposed as shown in Scheme 3. Initially, aryl acyl peroxide **2** was decomposed to aroyloxyl radical **4** under the heating conditions. Aroyloxyl radical **4** was further converted into aryl radical **5** along with the release of CO_2. Then, the selective addition of aryl radical **5** to C3-position of quinoxalin-2(1*H*)-one **1** giving carbon radical intermediate **6**, which underwent a 1,2-hydrogen shift process to generate intermediate **7**. Finally, the hydrogen abstraction of the intermediate **7** by aroyloxyl radical **4** produced the desired product **3**.



Scheme 3. Possible mechanism.

In summary, a facile and efficient protocol has been developed for the synthesis of 3-arylquinoxalin-2(1*H*)-ones *via* direct decarboxylative C-H 3-arylation of quinoxalin-2(H)-ones with aryl acyl peroxides. The present transformation can be efficiently conducted under catalyst- and additive-free conditions, which provides a simple and highly attractive approach to a series of 3-arylquinoxalin-2(1*H*)-ones in good to excellent yields with favorable functional group tolerance. Further investigation of the detailed reaction mechanism and synthetic application are ongoing in our lab.

Acknowledgements

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Graphical Abstract

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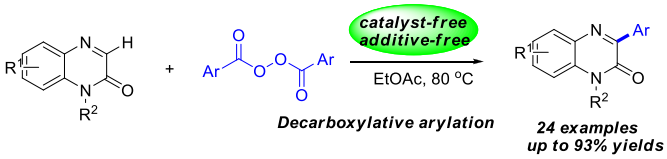
A simple and direct decarboxylative C-H 3-arylation of quinoxalin-2(H)-ones with aryl acyl peroxides for the synthesis of 3-arylquinoxalin-2(1H)-ones has been developed under catalyst- and additive-free conditions.



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