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可见光促进喹喔啉-2(1*H*)-酮的苯甲酰化反应

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摘要 喹喔啉酮C-3官能团化衍生物常具有突出的生物活性, 虽然人们已经成功利用过渡金属和强氧化剂催化手段获得此类化合物, 但是这些反应的条件相对苛刻. 为了发展符合"绿色化学"理念的合成方法, 其他环境友好和原子转化率高的制备方法, 光催化和电催化合成策略在喹喔啉酮C-3官能团化的应用也相继被开发出来, 成功得到了一系列芳基化、烷基化、胺化、磷酰化、磺化和酰化的3-取代喹喔啉-2(1*H*)-酮衍生物. 鉴于3-酰基喹喔啉-2(1*H*)-酮类化合物表现出的特殊生物活性, 本文将苯甲酰氯作为酰基自由基源, 利用可见光催化手段, 成功实现了苯甲酰氯对喹喔啉-2(1*H*)-酮的C-3酰基化反应, 并提出了反应可能的机理.

关键词 喹喔啉-2(1*H*)-酮, 光催化反应, 苯甲酰氯, 苯甲酰化

喹喔啉-2(1*H*)-酮是氮原子位于1和4位, 酮羰基位于2位的一类重要的苯并二嗪杂环化合物. 许多喹喔啉酮衍生物表现出很好的生物活性[1], 如抗凝血[2]、抗肿瘤[3]、抗磲啶还原酶[4]等. 喹喔啉-2(1*H*)-酮衍生物广泛存在于染料、香料和调味品等天然产物之中, 在有机合成领域也扮演着重要的角色, 因而喹喔啉-2(1*H*)-酮衍生物的合成及修饰受到重视并得到快速的发展[5~8]. 3-酰基喹喔啉-2(1*H*)-酮作为药物化学领域一类特殊的药效团, 受到人们的广泛关注. 目前, 合成3-酰基喹喔啉-2(1*H*)-酮的方法主要分为两类: 一类为传统的氧化法制备, 包括苄基喹喔啉酮的直接氧化[9]、Kornblum氧化[10]和苯二氮卓化合物的氧化环收缩[11]. 但是这类氧化反应需要提前制备喹喔啉酮的相应苄基化产物, 并且强氧化条件使得底物官能团耐受性较差. 另一类为自由基反应制备, 目前报道大多采用α-酮酸和苯甲醛作为酰基自由基源, 以合成3-酰基喹喔啉-2(1*H*)-酮. α-酮酸作为一类重要的商品化羧酸衍生物, 价格低廉, 反应活性高, 常被用作一类重要的酰基化试剂. 2017年, 胡跃飞课题[12]组利用银与过硫酸钾的共催化体系实现了α-酮酸的直接脱羧, 高效制备了喹喔啉-2(1*H*)-酮的C-3酰基化产物(图1(a1)). 随后, 赵飞课题组[13]利用α-酮酸在醋酸碘苯、加热催化的作用下产生酰基自由基, 实现了喹喔啉-2(1*H*)-酮的直接C-3酰基化, 得到了中等收率的目标产物(图1(a2)). 近年来, 喹喔啉酮类化合物的光化学官能团化反应得到了快速发展[14~16]. 2019年, 魏伟课题组[17]利用可见光催化的方法促使激发态的光敏剂与氧气产生单线态的$^1O_2$进而与α-酮酸作用产生酰基自由基, 最终获得了一系列收率良好和官能团耐受的3-酰基喹喔啉酮衍生物(图1(a3)). 水因为其特殊的物理和化学性质一直被人们视作有机化学反应良好的溶剂或反应介质. 人们既能通过光解水获取清洁的能源氢气以缓解能源紧缺问题, 又能在水相中获

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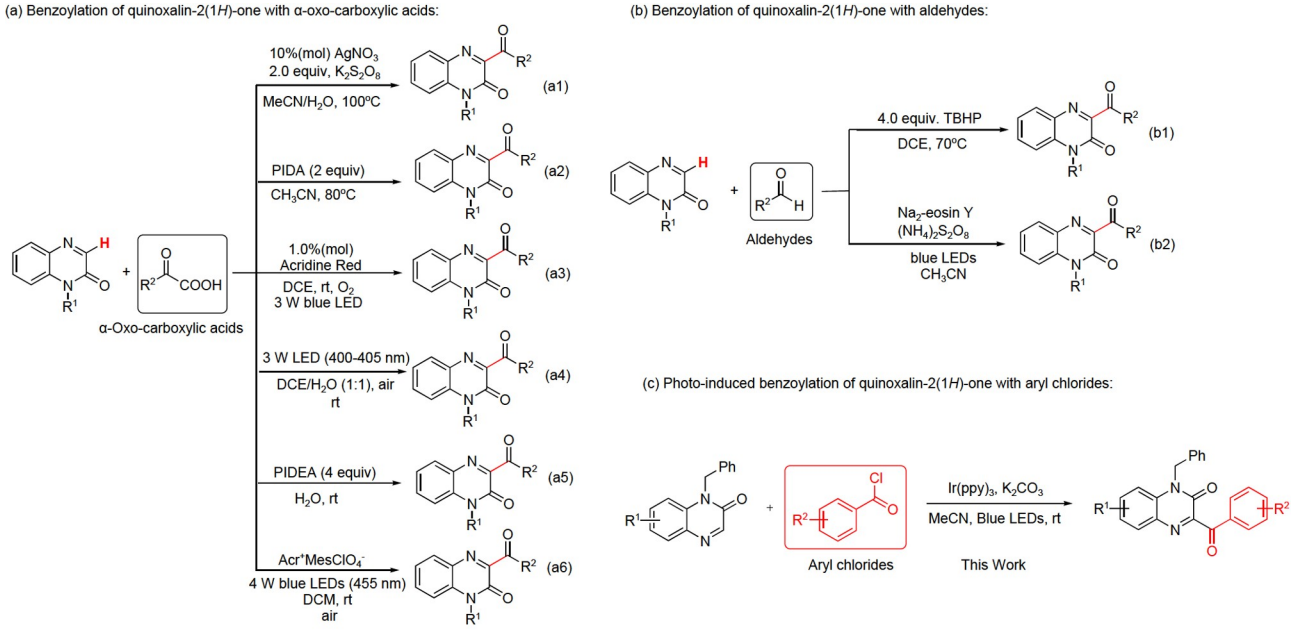

图 1 (网络版彩色)喹喔啉酮的苯甲酰化反应. (a) 喹喔啉酮与α-氧-羧酸的苯甲酰化反应; (b) 喹喔啉酮与醛的酰化反应; (c) 光促喹喔啉酮与芳基酰氯的苯甲酰化反应

Figure 1 (Color online) Benzoylation of quinoxalin-2(1*H*)-one. (a) Benzoylation of quinoxalin-2(1*H*)-one with α-oxo-carboxylic acids; (b) benzoylation of quinoxalin-2(1*H*)-one with aldehydes; (c) photo-induced benzoylation of quinoxalin-2(1*H*)-one with aryl chlorides

得有机化合物[18,19]. 2020年, 何卫民课题组[20]建立了以空气作为清洁的氧化剂, 在无光敏剂作用下, 利用可见光诱导喹喔啉-2(1*H*)-酮实现了C-3酰基化反应(图1(a4)). 而后, 宣俊课题组[21]继续选用水作溶剂, 在醋酸碘苯、光催化的作用下产生酰基自由基, 从而获得了3-酰基的产物(图1(a5)). Lee课题组[22]在有机光敏剂吖啶盐的催化下, 使用空气作为氧化剂, 选择性地合成了C-3羟基或酰基的喹喔啉酮衍生物(图1(a6)).

另外, 醛类化合物也具有价格低廉和化学性质特殊等特点, 常被视作有机合成领域重要的原料. 芳香醛类化合物也常被人们用作一类重要的自由基前体[23~27]. 2018年, 屈凌波课题组[28]在叔丁基过氧化氢(TBHP)的加热条件下实现了喹喔啉-2(1*H*)-酮与各类醛的脱氢偶联(图1(b1)). 2021年, 赵飞课题组[29]通过可见光诱导催化中性曙红Y对苯甲醛实现氢原子转移(HAT), 从而获得了各类C3酰化的喹喔啉-2(1*H*)-酮产物(图1(b2)).

芳香酰氯作为一类价格低廉、含量丰富和反应活性高的重要原料, 常被广泛应用于有机合成领域之中, 商品化的此类化合物也日益丰富, 它们的价格与芳香羧酸相当. 因此, 芳香酰氯常被人们视作一种简单易得、直接高效的芳酰基自由基源, 基于3-酰基喹喔啉-2(1*H*)-酮类化合物的特殊生物活性及其在药物开发中的潜力, 开发绿色环保、操作简便及经济适用性好的喹喔啉-2(1*H*)-酮类化合物苯甲酰基化反应, 仍然具有重要的研究意义. 本课题组[30~34]近年来一直致力于发展可见光催化的绿色合成反应, 基于喹喔啉酮类化合物的重要价值, 开发了可见光促进喹喔啉-2(1*H*)-酮的苯甲酰化反应.

1 实验

(ⅰ) 试剂与仪器. 核磁共振氢谱、碳谱和氟谱采用Bruker超导傅里叶数字化核磁共振仪(400 MHz, 德国)于室温下测定. 实验所需的无水无氧干燥溶剂大多经FLEANO溶剂纯化系统(逸峰科技)处理后得到, 实验所用其他试剂均为分析纯, 未经其他处理. 反应后处理均采用分析纯溶剂.

(ⅱ) 方法. 可见光促进喹喔啉-2(1*H*)-酮的酰基化反应一般方法: 将干燥并装有搅拌磁子的schlenk反应管、胶塞和反应所需的药品, 按照手套箱的基本操作规程, 送至充满Ar氛围的手套箱(Mikrouna Supper 1220/750)中. 精准称取光敏剂三(2-苯基吡啶)合铱($Ir(ppy)_3$, 0.004 mmol)和底物喹喔啉-2(1*H*)-酮(0.1 mmol)并添加至反应管中, 用移液枪向反应管中添加乙腈

(MeCN, 1 mL), 塞上胶塞后将反应管送出手套箱. 用微量进样器分别吸取苯甲酰氯(0.2 mmol)和*N*,*N*-二异丙基乙胺(DIPEA, 0.2 mmol)加入到反应管中, 将反应管置于20 W蓝色LED(发光二极管)光反应装置中. 通过薄层色谱法(TLC)监测直至反应完全, 反应液经过减压蒸馏浓缩, 再经柱层析分离纯化得到相应的3-酰基喹喔啉-2(1*H*)-酮.

2 结果与讨论

2.1 反应条件的筛选及优化

以1-苄基喹喔啉-2(1*H*)-酮**1a**作为模板底物, 苯甲酰氯**2a**为酰基自由基源, MeCN为反应溶剂, K_2CO_3为碱, 在蓝光的照射下, 对光催化剂进行了筛选(表1). 结果表明, 三联吡啶氯化钌($Ru(bpy)_3Cl_2$)、曙红Y(Eosin Y)、伊红Y二钠盐(Na_2Eosin Y)、亚甲基蓝(methylene blue)和罗丹明B(Rhodamine B)均不能催化当前反应进行(表1, 条目1~5). 令人高兴的是, 使用*fac*-$Ir(ppy)_3$能促进当前反应发生, 并以78%收率得到喹喔啉-2(1*H*)-酮的3-酰基化产物**3aa**(表1, 条目6). 溶剂是有机反应中重要的影响因素之一, 它不仅影响反应物的溶解性, 而且也关系到有机反应的进行. 因此, 接下来考察了不同的非质子反应溶剂. 结果表明, 除了四氢呋喃(THF)外, 该反应在二氯甲烷(DCM)、甲苯、1,4-二氧六环(1,4-dioxane)和*N*,*N*-二甲基甲酰胺(DMF)等非质子性溶剂中均获得了较好的收率(表1, 条目7~11). 在此基础上, 我们也对光敏剂的用量进行了筛选, 结果表明当*fac*-$Ir(ppy)_3$的用量从4%(mol)降低至2%(mol)时, 反应收率明显降低(表1, 条目12).

为了进一步提高该反应的收率, 我们对碱进行了筛选(表2). 当在体系中使用碳酸铯时反应收率仅为21%. 使用其他的无机碱如KOH、$NaHCO_3$和NaOAc时, 均能以中等收率得到目标产物**3aa**(表2, 条目2~5). 继而, 又尝试了部分有机碱在当前反应中的效果, 发现Et_3N和2,6-二甲基吡啶均能促进当前反应发生; 而使用DIPEA时, 反应较快, 收率可达84%(表2, 条目6~8). 另外, 当前反应中碱是必需的, 因为不加入碱时反应很慢, 且只能以低收率得到酰化产物(表2, 条目9).

2.2 反应适用性研究

在最佳的反应条件下, 对该反应进行了适用性考察(图2). 首先, 考察了含有不同取代基团的喹喔啉-

表 1 反应条件建立[a)]

Table 1 Reaction conditions optimization

1a 2a 3aa

条目	光敏剂	溶剂	时间(h)	收率(%)[b)]
1	$Ru(bpy)_3Cl_2$	MeCN	22	ND
2	Eosin Y	MeCN	22	ND
3	Na_2Eosin Y	MeCN	22	ND
4	亚甲基蓝	MeCN	22	ND
5	罗丹明B	MeCN	24	ND
6	*fac*-$Ir(ppy)_3$	MeCN	17	78
7	*fac*-$Ir(ppy)_3$	THF	22	28
8	*fac*-$Ir(ppy)_3$	DCM	22	70
9	*fac*-$Ir(ppy)_3$	甲苯	22	73
10	*fac*-$Ir(ppy)_3$	DMF	24	75
11	*fac*-$Ir(ppy)_3$	1,4-二氧六环	22	63
12[c)]	*fac*-$Ir(ppy)_3$	MeCN	17	47

a) 反应条件: **1a**(0.1 mmol), **2a**(0.2 mmol), 光敏剂(0.004 mmol), 溶剂(1 mL), K_2CO_3(0.2 mmol), 氩气氛围下置于20 W蓝光灯(442 nm)照射下反应; b) 用300~400目硅胶柱层析分离纯化获得; c) *fac*-$Ir(ppy)_3$(0.002 mmol)

表 2 反应条件优化[a)]

Table 2 Reaction conditions optimization

1a 2a 3aa

条目	碱	时间(h)	收率(%)[b)]
1	K_2CO_3	17	78
2	Cs_2CO_3	24	21
3	KOH	17	76
4	$NaHCO_3$	6	69
5	NaOAc	24	75
6	Et_3N	23	68
7	DIPEA	7	84
8	2,6-二甲基吡啶	19	73
9	无	24	39

a) 反应条件: **1a**(0.1 mmol), **2a**(0.2 mmol), *fac*-$Ir(ppy)_3$(0.004 mmol), MeCN(1 mL), 碱(0.2 mmol), 氩气氛围下置于20 W蓝光灯(442 nm)照射下反应; b) 用300~400目硅胶柱层析分离纯化获得

2(1*H*)-酮. 发现含有*N*-甲基取代的喹喔啉酮在当前反应中更为有利, 反应收率能达到95%(**3ba**). 当使用含有甲基取代的喹喔啉酮时, 反应收率略微下降(**3ca**, **da**). 含有不同卤素基团的喹喔啉酮, 无论是*N*-苄基还是*N*-甲基底物, 在当前反应中适用性都较好, 都能以高收率得到目标苯甲酰化产物(**3ea**~**ka**), 卤素原子在当前反应体系中未受影响. 值得注意的是, 当前合成方法提供了一种高效制备**3da**的方法, 该化合物被报道具有突出的抗肿瘤活性[22]. 此外, 我们还尝试了**1a**的克级反应, 能以58%收率得到产物**3aa**.

同时, 从电子效应和空间效应的角度对含有不同取代基的苯甲酰氯衍生物的适用性进行了考察(**3aa**~**ai**). 结果表明, 当苯甲酰氯的对位被取代时, 吸电子取代基底物的收率普遍高于给电子基底物的收率(**3aa**~**ae**). 此外, 对邻位和间位含有甲基和氯原子的苯甲酰氯进行了考察, 发现当前反应会受到一定程度的位阻影响, 含有邻位取代基的底物收率普遍低于其他位点取代底物的收率(**3af**~**ai**). 但是, 乙酰氯和吡啶-2-甲酰氯在当前体系下没有发生反应, 提示烷基酰氯或者杂芳基酰氯不适用于该反应.

2.3 反应机理探究

为了进一步验证该反应的机理, 我们尝试在标准条件下, 向反应体系中加入2,2,6,6-四甲基哌啶(TEMPO)作为自由基捕获剂. 发现当加入4当量的自由基捕获剂后(图3), 反应被完全抑制, 没有观察到目标产物

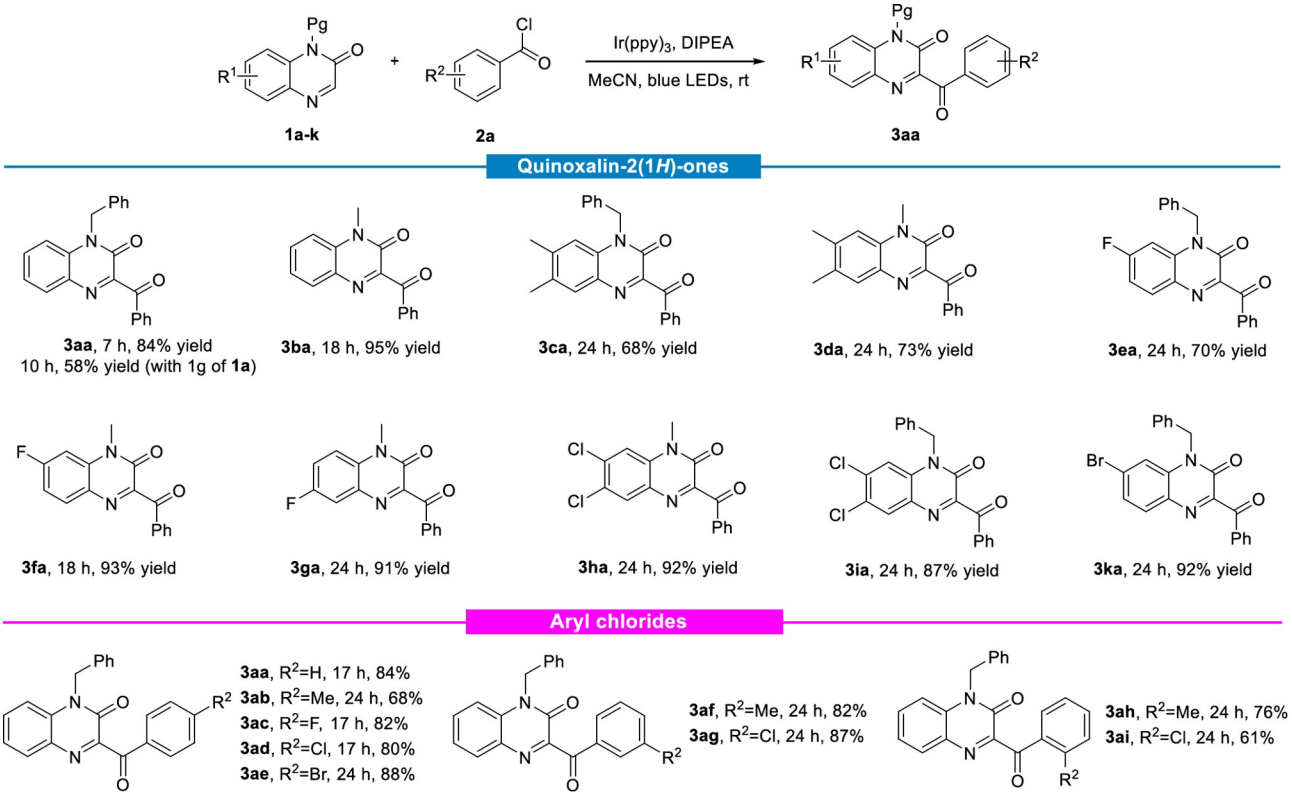

图 2 (网络版彩色)喹喔啉酮的苯甲酰化反应底物适应性考察
Figure 2 (Color online) Substrates scope studies of quinoxalin-2(1*H*)-ones and aryl chlorides

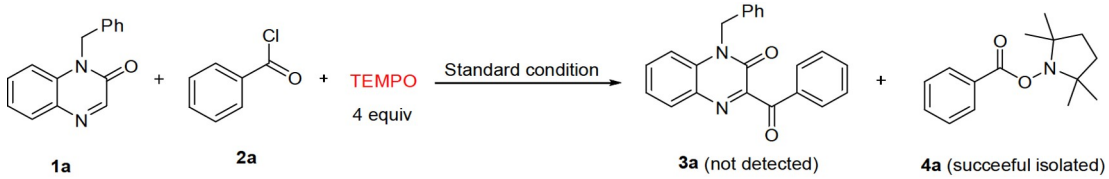

图 3 (网络版彩色)自由基捕获实验
Figure 3 (Color online) Radical traping experiment

2a生成. 并且通过柱层析分离, 获得苯甲酰基自由基与TEMPO的偶联中间体**4a**. 该实验证明当前苯甲酰化反应为自由基反应历程, 且苯甲酰基自由基是当前反应中的中间体.

为了更好地阐明反应历程, 进行了Stern-Volmer荧光淬灭实验(图4). 首先根据反应体系的浓度, 配置了浓度为0.1 mmol/L的*fac*-Ir(ppy)$_3$光敏剂溶液, 而后分别配置浓度为10 mmol/L的*N*-苄基喹喔啉酮、DIPEA和苯甲酰氯溶液, 在375 nm的激发波长下, 尝试了450~700 nm波长范围下对激发态光敏剂进行淬灭. 实验发现DIPEA并不能淬灭激发态的光敏剂, 苯甲酰氯较*N*-苄基喹喔啉酮具有明显的淬灭效果. 结合自由基捕获实验的结果, 提示了当前光促反应的能量传导主要发生于激发态光敏剂*fac*-Ir(ppy)$_3^*$与苯甲酰氯.

在以上机理探究实验的基础上, 结合相关文献[35,36]报道, 对该反应的机理作出了推测(图5). 在蓝光照射下, 光敏剂*fac*-Ir(ppy)$_3$从基态转为激发态*fac*-Ir(ppy)$_3^*$, 苯甲酰氯与激发态*fac*-Ir(ppy)$_3^*$发生单电子转移得到苯甲酰自由基**A**. 自由基中间体**A**继而与喹喔啉酮**1a**发生酰化反应得到*N*-自由基中间体**B**, 其后经1,2氢迁移得到自由基中间体**C**. 自由基中间体**C**被光敏剂氧化为中间体**D**, 最后在缚酸剂DIPEA的作用下脱质子得到酰基化产物**3aa**.

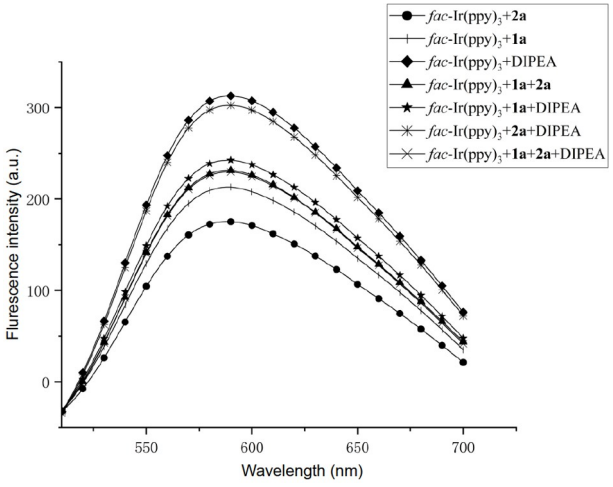

图 4 Stern-Volmer荧光淬灭实验
Figure 4 Stern-Volmer fluorescence quenching experiment

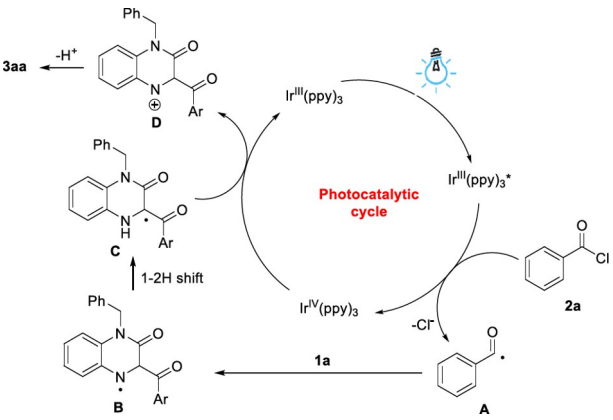

图 5 (网络版彩色)喹喔啉酮的苯甲酰化反应机理
Figure 5 (Color online) Mechanism for the benzoylation of quinoxalinone

3 结论

本文发展了一种以简单易得、价格低廉的芳基酰氯作为酰基自由基来源的光催化芳基酰基化反应. 该光催化体系能应用于含有多种取代基的喹喔啉-2(1*H*)-酮, 成功制备了一系列3-芳基酰基喹喔啉-2(1*H*)-酮衍生物. 当前反应不仅提供了一种以芳基酰氯作为酰基自由基来源的光化学反应, 也提供了绿色、高效和便捷的3-芳基酰基喹喔啉-2(1*H*)-酮衍生物制备方法.

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Summary for “可见光促进喹喔啉-2(1*H*)-酮的苯甲酰化反应”

Visible light promoted benzoylation of quinoxalinone-2(1*H*)-ones

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Quinoxalinone-2(1*H*)-ones is an important class of benzodiazine heterocyclic compounds. Many quinoxalinone derivatives exhibit good biological activities, such as anticoagulant, antitumor, and can serve as pteridine reductase inhibitors. 3-Acylquinoxaline-2(1*H*)-ones are a special class of pharmacophores in the field of medicinal chemistry and have received considerable attention. In general, the synthetic methods for 3-acylquinoxaline-2(1*H*)-ones are divided into two categories. The traditional oxidation methods include direct oxidation of benzyl quinoxaline, Kornblum oxidation and the oxidation ring contraction of benzodiazepines. This type of oxidation reaction requires the preparation of the corresponding benzylation products of quinoxalinones in advance, and they are associated with less functional groups tolerance under the strong oxidation conditions. The second method for the synthesis of 3-acylquinoxaline-2(1*H*)-ones is the radical reactions between α-keto acids and benzaldehyde as acyl radical sources to synthesize 3-acylquinoxaline-2(1*H*)-ones. Besides, α-keto acids and aldehydes have also been employed as radical sources in the preparation of 3-acylquinoxaline-2(1*H*)-ones.

Aryl chlorides are widely used as important raw material in the field of organic synthesis because of its low price, easily accessible and high reactivity. Therefore, aryl chlorides are often regarded as a simple, direct and efficient aryl radical source. In recent years, our group has been committed to the development of visible light promoted green synthesis reactions. Due to the special biological activity of 3-acylquinoxaline-2(1*H*)-ketones and its great potential in drug development, we herein report our studies on the visible light promoted benzoylation of quinoxalin-2(1*H*)-ones. The reaction conditions were studied by using 1-benzylquinoxaline-2(1*H*)-one and benzoyl chloride as reaction substrates under the irradiation with blue light. Screening of various photocatalysts revealed that *fac*-Ir(ppy)$_3$ was the most effective photocatalyst and furnished the acylation product in 78% yield. By investigating different solvents, acetonitrile was found to be optimal solvent. To further improve the yield of this reaction, different bases were screened and found *N*,*N*-diisopropylethylamine to be optimal and gave the desired product in 84% yield.

Under optimal reaction conditions, we investigated the substrate scope of current reaction. It was found that quinoxalinone containing *N*-methyl substitution was more favorable in the present reaction condition, and the products were obtained in up to 95% yield. When quinoxalinone with methyl substitutions was used, the reaction yield decreased slightly. Quinoxalinones containing different halogen groups successfully participated in the current reaction, gave the desired benzoylation products in high yields, and the halogen atoms remained unaffected. On the other hand, we investigated the applicability of benzoyl chloride derivatives containing different substituents from the perspective of electronic and steric hindrance effects. The results showed that the yields of substrates with electron-withdrawing substituents on *para*-position are generally higher than that with electron-donating groups. In addition, benzoyl chlorides containing methyl and chlorine atoms in the *ortho* and *meta*-positions were investigated, and it was found that the current reaction is slightly affected by steric hindrance.

In order to further verify the mechanism of the present reaction, we added TEMPO as a free radical scavenger to the reaction system under standard conditions. A completele inhibition was observedindicating that the current benzoylation reaction proceeds with radical reaction process, and the benzoyl radical is an intermediate in the current reaction.

In conclusion, a photo induced aryl acylation reactions using aryl chlorides as acyl radical source was developed. The photocatalytic system could be applied to the acylation of quinoxaline-2(1*H*)-ones containing a variety of substituents, and a series of 3-arylacylquinoxaline-2(1*H*)-one derivatives have been successfully prepared. The current reaction not only provides a photochemical reaction with aryl chlorides as acyl radical source, but also provides a green, efficient and convenient method for the preparation of 3-arylacylquinoxaline-2(1*H*)-one derivatives.

quinoxaline-2(1*H*)-one, photo reduced reaction, benzoyl chloride, benzoylation

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