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α,β-Functionalization of Saturated Ketones with Anthranils via Cu-Catalyzed Sequential Dehydrogenation/Aza-Michael Addition/Annulation Cascade Reactions in One-Pot

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An efficient method to access functionalized quinolines from the readily available saturated ketones and anthranils have been explored. This one-pot cascade reaction involves the in situ generation of α,β-unsaturated ketones by the copper catalysed dehydrogenation of saturated ketones followed by the aza-Michael addition of anthranils and subsequent annulation.

The direct functionalizations of saturated ketones via in situ generation of α,β-Unsaturated ketones by catalytic dehydrogenation, have received much attention in the recent past.[1-3] The aforementioned protocol overcomes the problem of troublesome preparation and isolation of α,β-unsaturated ketones due to their poor stability and high reactivity.[3] Generally, the synthesis of α,β-unsaturated ketones required multiple steps[4,5] and equimolar amount of reagents such as 2-iodoxybenzoic acid (IBX) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). [6,7] However, in recent past the transition metals such as palladium, ruthenium, iridium, copper and nickel catalyzed oxidation of saturated carbonyl compounds to the corresponding α-β unsaturated carbonyl compounds has become an attractive and atom economical alternative to these methods.[2] Subsequently, the α,β unsaturated carbonyl compounds that are produced in situ, undergoes various organic transformations such as arylation, amination and conjugate addition to produce *β*-functionalized ketones.[1e-1f, 8] Considering the synthetic potential of α,β-unsaturated ketones and in frame of our own research interest in copper catalyzed heterocycle synthesis,[9] we became interested in exploring the annulation of α,β-unsaturated carbonyl compounds with anthranils. In general, anthranils serves as versatile synthetic intermediates, readily engaging in various transition metals catalyzed C-C and C-N bond forming reactions to get value added products. The direct C–H amination[10] and annulations[11] reactions by anthranil have drawn considerable attention in organic transformations (Fig-1, eq-1). We envisioned that the coupling of *in situ* generated α,β-unsaturated ketones with anthranils might produce quinolines via amination followed by annulation (Fig-1, eq.-2).

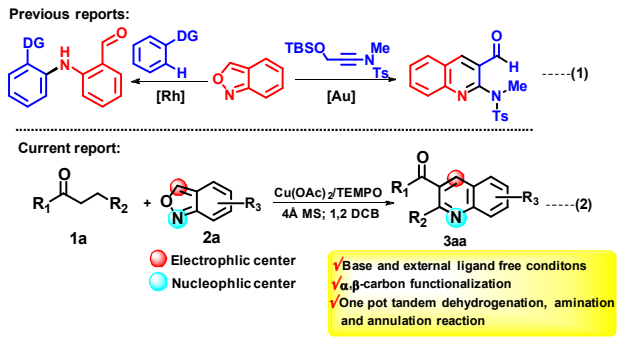

Figure 1. Use of anthranil in amination and annulation reactions (eq-1) along with present study (eq.2).

Wide abundance of quinoline framework in pharmaceuticals and natural products make it privileged scaffold, and therefore considerable efforts have been made to develop efficient and operationally simple methods for their synthesis.[12-14] The classical methods for quinoline synthesis involve the Skraup, Combes, Conrad–Limpach and Friedlander reactions.[15] Lately, metal catalyzed tandem cyclization and multi-component coupling reactions have been developed for the synthesis of functionalized quinolines.[16] Although these protocols are effective, most of them suffer from several shortcomings, such as elaborately designed starting materials and copious waste generation. Therefore, a direct access to quinolines from simpler starting materials remains an important research objective. In turn to test our hypothesis, we chose the readily available propiophenone (**1a**) and anthranil (**2a**) as model substrates for the proposed reaction cascade. Our initial efforts in reacting propiophenone (**1a,** 1.0 mmol), anthranil

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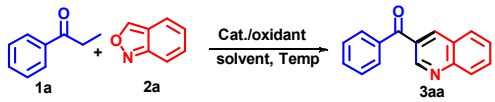
(**2a,** 1.1 mmol) in the presence of CuI (10 mol%), bipyridyl (10 mol%) and TEMPO (1.0 mmol) in DME (4.0 mL) at 110 °C for 12 hrs, under argon atmosphere did not yield any desired product (Table 1, entry-1). Use of different copper catalysts such as $Cu(OTf)_2$ and $CuSO_4$ also failed to induce the reaction (entries 2-3). However, when CuBr (10 mol%) was employed as a catalyst, 3-keto quinoline was obtained, albeit in a poor yield (14%) (entry-4). Further, the isolated yield of **3aa** was improved to 65% when $Cu(OAc)_2$ was used as catalyst

Table 1. Optimization studies.[a]



Entry	Catalyst (10 mol%)	Oxidant (1.0 equiv)	Solvent	Temp/ [°C]	Yield (%)[b]
1	CuI	TEMPO	DME	110	trace[a]
2	$Cu(OTf)_2$	TEMPO	DME	110	n.o [a]
3	$CuSO_4$	TEMPO	DME	110	n.o [a]
4	CuBr	TEMPO	DME	110	14%[a]
5	$Cu(OAc)_2$	TEMPO	DME	110	65%[a]
6	$Cu(OAc)_2$	TEMPO	DME	110	86%[c]
7	$Cu(OAc)_2$	TEMPO	Toluene	110	69%[a]
8	$Cu(OAc)_2$	TEMPO	Dioxane	110	49%[a]
9	$Cu(OAc)_2$	TEMPO	DMSO	110	31%[a]
10	$Cu(OAc)_2$	TEMPO	DMF	110	52%[a]
11	$Cu(OAc)_2$	TEMPO	NMP	110	24%[a]
12	$Cu(OAc)_2$	TEMPO	1,2 DCB	110	92%[a]
13	$Cu(OAc)_2$	TEMPO	1,2 DCB	110	92%[d]
14	$Cu(OAc)_2$	--	1,2 DCB	110	0%[e]
15	$Cu(OAc)_2$	TBHP	1,2 DCB	110	n.o[d]
16	$Cu(OAc)_2$	TBPB	1,2 DCB	110	n.o[d]
17	$Cu(OAc)_2$	$K_2S_2O_8$	1,2 DCB	110	n.o[d]
18	$Cu(OAc)_2$	TEMPO	1,2 DCB	110	40%[f]
19	$Pd(OAc)_2$	TEMPO	1,2-DCB	110	n.o
20	$NiBr_2$	TEMPO	1,2-DCB	110	n.o
21	$CoCl_2$	TEMPO	1,2-DCB	110	n.o
22	$Cu(OAc)_2$	TEMPO	1,2-DCB	130	80%[g]
23	$Cu(OAc)_2$	TEMPO	1,2-DCB	90	55%[h]

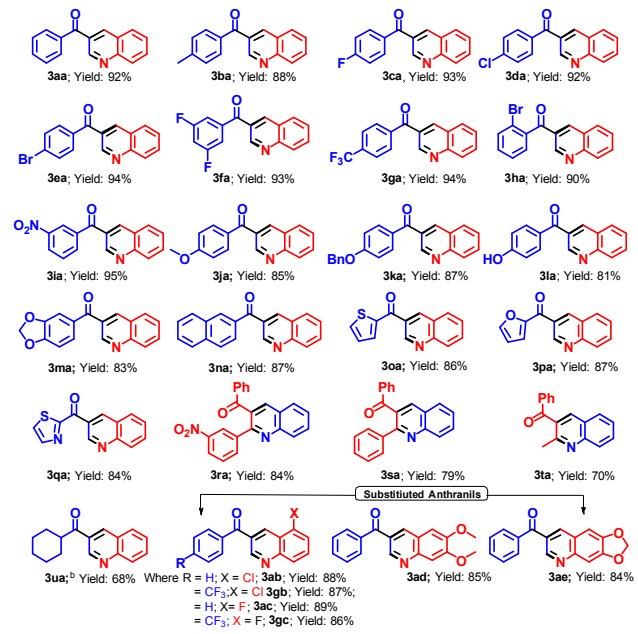
[a]Reaction was performed using **1a** (1.0 mmol), **2a** (1.1 mmol), Cu catalyst (0.10 mmol), bpy (0.10 mmol), TEMPO (1.0 mmol) solvent (4 mL) 110 °C, N_2 atmosphere 12h. [b]isolated yields. [c]4 Å MS was added, [d]No bipyridyl (bpy) added. [e]no oxidant. [f](0.5 mmol) of TEMPO was used., [g]Run at 130 °C, [h]Run at 90 °C. n.o = not obtained.

(entry-5). At this stage, the structure of **3aa** was well characterized using different spectroscopic techniques and the spectral data of **3aa** was exactly matching with previously reported compound.[17] The ultimate proof was obtained by single-crystal X-ray diffraction of one of the derivative **3af** (vide infra). Since this reaction represents an efficient and mild route to pharmaceutically valuable quinoline derivative, we systematically carried out extensive optimization of the reaction conditions (Table 1).

As water is expected as the byproduct, the use of 4 Å molecular sieves improved the yield to a greater extent (86%) (entry-6). Among the various solvents screened, 1,2-dichlorobenzene (DCB) was found to be the best for the overall formation of **3aa** (92%) (entry 12), whereas toluene, 1,4-dioxane, DMSO, DMF and NMP furnished the desired 3-keto quinoline (**3aa**) in low yields (entries 7-11). Interestingly, the absence of ligand 2,2'-bipyridyl did not affect the reaction as the product **3aa** was obtained in excellent yield (entry-13). This can be reasoned that anthranil itself might be acting as ligand under these catalytic conditions. Role of oxidant was also investigated by performing the reaction in absence of TEMPO but, the desired quinoline **3aa** was not obtained (entry-14). Further, several oxidants such as *tert*-butyl hydroperoxide (TBHP), *tert*-butyl perbenzoate (TBPB) and $K_2S_2O_8$, were also tested for this transformation but none of them could promote the reaction (entries 15-17). Attempts to use lower amount of TEMPO resulted significant decrease in the yield of corresponding **3aa** (entry-18). Switching the metal catalyst from Cu(II) to Pd (II), Ni (II) and Co (II) did not produce the desired product **3aa** (entries19-21). Increasing the reaction temperature from 110 to 130 °C furnished low yield of the desired **3aa** (entry-22). A dramatic fall in the yield (55%) of **3aa** was observed when reaction was performed at 90 °C instead of 110 °C (entry-23).

After having optimized reaction conditions in hand (Table-1 entry 13), the substrate scope of this one pot tandem reaction with respect to various propiophenones (**1a-1u**) and anthranils

Table-2 Substrate scope of the present study[a]



[a]Reaction conditions: **1a** (1.0 mmol), **2a** (1.1 mmol), $Cu(OAc)_2$ (0.1 mmol), TEMPO (1.0 mmol), 4 Å MS, 1,2-dichlorobenzene (4 mL), 110 °C, N_2 atmosphere, 12 h. [b]Reaction was run for 24 h, Yield indicates the yields of the isolated product.

(**2a-2g**) were investigated. The reaction was found to be compatible with various ketones bearing aromatic, heteroaromatic and aliphatic groups (**1a-1u**). As shown in table 2, the propiophenones containing electron withdrawing (EWGs) or electron donating groups (EDGs) at different position of phenyl ring readily delivered the desired quinolines in good yields (**3b-3m**) whereas it is worth mentioning that propiophenones bearing EWGs provided better yields comparatively. Various functional group such as fluoro (**1c**), chloro (**1d**), bromo (**1e** & **1h**), trifluoromethyl (**1g**), nitro (**1i**), alkoxy (**1j**), aryloxy (**1k**) and hydroxyl (**1l**) were well tolerated under these catalyitc conditions and furnished corresponding 3-keto quinolines in excellent yields. The method was further

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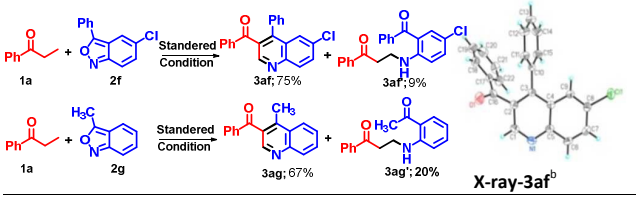
extended to the heteroaromatic ketones such as 2-propionylthiophene (**1o**), 2-propionylfuran (**1p**) and 2-propionyl thiazole (**1q**) and excellent yields of the desired products (**3oa-3qa**) were obtained. Furthermore, β-substituted ketones (**1r-1t**), also participated in this reaction and gave slightly lower yields of corresponding 2-substiituted-3-ketoquinolines (**3ra-3ta**). The aliphatic carbonyl compound such as 1-cyclohexylpropan-1-one (**1u**) took longer time (24 h) to complete the reaction and gave inferior yield (68%) of the desired product (**3ua**). The various substituted anthranils (**2b-2e**) worked well and furnished the corresponding 3-ketoquinolines (**3ab-3ae**) in excellent yields.

3-substitiuted anthranils (**2f and 2g**) expectedly took longer time (24 h) for the completion of the reaction and furnished the desired products **3af** and **3ag** in 75% and 67% yields along with uncyclized **3af'** and **3ag'** in 9% and 20% yields respectively (scheme-1). This discrimination in the yields of desired **3af** and **3ag** can be explained by electron withdrawing and electron donating nature of phenyl and methyl groups respectively. The structure of **3af** was unambiguously confirmed by single crystal X-ray diffraction data analysis.

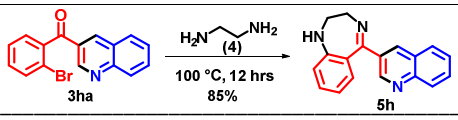
Scheme-1. Quinoline synthesis with 3-substitiuted anthranils (2f-2g)[a]



[a]Reaction conditions: **1a** (1.0 mmol), **2f** (1.1 mmol), $Cu(OAc)_2$ (0.1 mmol), TEMPO (1.0 mmol), 4Å MS, 1,2-dichlorobenzene (4 mL), 110 °C, N_2 atmosphere, 24 h; [b]ORTEP diagram of **3af** [18]

This initial success propelled us to investigate the synthetic utility of current methodology in the synthesis of biologically valuable targets (scheme-2). The (2-bromophenyl)(quinolin-3-yl)methanone

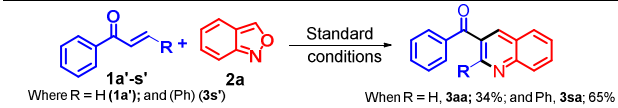
Scheme-2- Efficient synthesis of biologically important substituted benzodiazepine.[19]



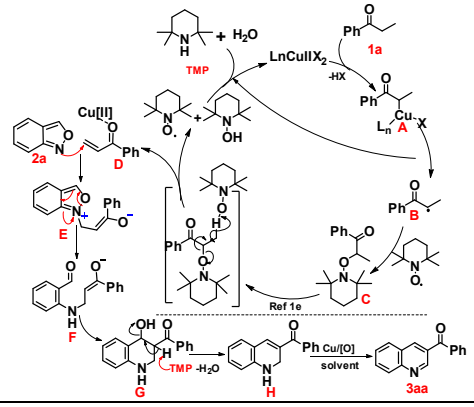
(**3ha**) produced from the reaction of 2′-bromopropiophenone (**2h**) and anthranil (**2a**) under optimized standard condition, enabled to prepare 2,3-dihydro-5-(3-quinolinyl)-1*H*-1,4-benzodiazepine (**5**), an important fungicide,[19] efficiently executed by heating **3ha** with ethylenediamine (**4**) in 85% yield.

To probe the reaction mechanism some controlled experiments were conducted (for more details please see the SI). When anthranil (**2a**) was treated with chalcones (**1a'** & **1s'**) under optimized reaction conditions, furnished the desired **3aa** and **3sa** but in low yields (scheme 3). This result demonstrates that the reaction is going through enone intermediate.

Scheme 3: Reaction of anthranil (**2a**) with chalcones (**1a'** & **3s'**):



Based on our controlled experiments (please see the SI) and literature report[1e] the mechanism as shown in scheme-4 was proposed. First $Cu(OAc)_2$ enolizes saturated ketone (**1a**) to give complex **A** which undergoes homolytic bond cleavage to generate Cu(I) species and intermediate **B** which on reaction with TEMPO produced α-TEMPO-substituted ketone **C.** Another molecule of TEMPO then abstracted β-hydrogen of intermediate **C,** resulting in elimination of TEMPOH from **C** to form desired α,β-unsaturated ketone **D.** Cu(I) species gets oxidized by TEMPO or TEMPOH to regenerate Cu(II) species. The nitrogen atom of anthranil then attacks at β-position of enone (**D**) to give intermediate **E.** The polarized N-O bond of intermediate **E** gets cleaved to produce intermediate **F**, which eventually undergoes intramolecular cyclization followed by TMP mediated dehydration to produce the dihydroquinolene **H**. Finally, the intermediate **H** undergoes to copper catalyzed aerobic oxidation[20] to give the desired **3aa**.



Scheme-4. Plausible reaction mechanism

Conclusions

In conclusion, we have developed a ligand and base free, catalytic procedure for 3-keto quinolines from readily available saturated ketones and anthranils using $Cu(OAc)_2$ *via* one pot tandem sequential dehydrogenation, aza-Michael addition and annulation reactions. The reaction is compatible with various ketones and substituted anthranils. As a result, a series of quinolines were prepared in excellent yields. Considering the wide availability of starting materials, broad substrate scopes and operational simplicity, the present method provides an attractive and novel protocol for the synthesis of the 3-substitiuted quinolines.

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18 X-ray data and ORTEP depiction of compound **3af** (CCDC **1525857**), please see the ESI.

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Table of Content

α,β-Functionalization of Saturated Ketones with Anthranils via Cu-Catalyzed Sequential Dehydrogenation/Aza-Michael Addition/Annulation Cascade Reactions in One-Pot

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An efficient method to access functionalized quinolines from the readily available saturated ketones and anthranils have been explored. This one-pot reaction cascade involves the in situ generation of α,β-unsaturated ketones by the copper catalysed dehydrogenation of saturated ketones followed by the aza-Michael addition of anthranils and subsequent annulations.