Heterocycles

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Synthesis of Bis(heteroaryl) Ketones by Removal of Benzylic CHR and CO Groups**

*Arun Maji, Sujoy Rana, Akanksha, and Debabrata Maiti**

Abstract: *A copper-catalyzed method for synthesis of diaryl ketones (Ar-CO-Ar′) through removal of benzylic -CH_2-, -CO-, and -CHR- groups from Ar-CO-CXR-Ar′ has been discovered. A number of symmetrical and unsymmetrical heterocyclic ketones, which are usually difficult to synthesize, can be prepared in good to excellent yields. This method was applied to the synthesis of the nonsteroidal anti-inflammatory drug suprofen (47% yield over three steps). Based on preliminary mechanistic and kinetic studies, an active Cu/O_2 species is proposed to mediate the rearrangement reaction.*

Carbon–carbon bonds constitute the basic foundation of synthetic chemistry. Protocols for the generation and cleavage of such bonds are indispensable for the synthesis of new organic scaffolds. Although carbon–carbon bond-formation techniques have been studied extensively, the cleavage of carbon–carbon bonds is still a difficult objective. The inert nature of the carbon–carbon bond makes its cleavage problematic, and gaining control of it is even more challenging.[1] Despite reports on carbon–carbon single-,[2] double-,[3] and triple-bond cleavage,[4] the development of a C–C bond-disconnection approach to construct a new C–C bond still remains a formidable task.

Industrially ketones are utilized as pharmaceutical drugs, polymer precursors, and as biologically and chemically important building blocks. Development of a new synthetic approach for their synthesis is therefore of great significance (Figures 1 and 2). Synthetically C(CO)-C(α) bond cleavage has been utilized (Figure 1) to generate acid,[5] ester,[6] amide,[7] aldehyde,[8] acyl transfer,[9] ketonic partner exchange,[10] and rearrangement reactions.[11] However, diaryl ketone and heterocyclic ketone synthesis starting from α-arylated ketones by C(CO)-C(α) bond cleavage is yet to be reported.

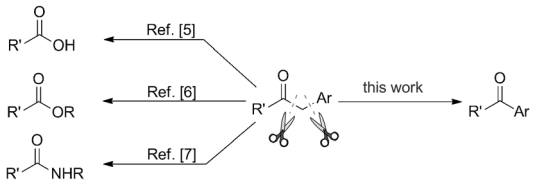


Figure 1. The cleavage of the C(CO)-C(α) bond of a ketone.

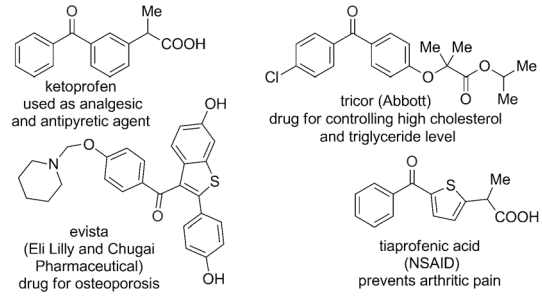
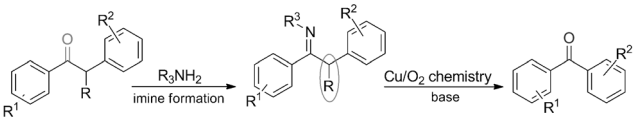


Figure 2. Select examples of diaryl ketones as pharmacueticals.

Herein, we report an effective method of removing a benzylic carbon moiety to synthesize symmetrical/unsymmetrical diaryl ketones and bis(heteroaryl) ketones. This method connects the benzylic aromatic ring directly to the ketone by eliminating the benzylic -CH_2-, -CHR-, and -CO- groups without changing the connectivity with the ring (Scheme 1).



Scheme 1. Diaryl ketone synthesis by C(CO)-C(α) cleavage.

We envisioned removal of the α-carbon centers of 2-phenylacetophenone through formation of an imine and subsequent Cu/O_2 chemistry/rearrangement reactions. Such a reaction, in essence, also mimics DNA demethylase activity wherein an active methyl group is removed from nucleotide in DNA.[12] Notably, 2-phenylacetophenone derivatives are accessible by various methods, for example, α-arylation of acetophenone,[13] Wacker oxidation of internal olefin,[3b,14] etc.[15]

We started our investigation by reacting an imine, generated in situ from aniline and 2-phenylacetophenone, with a Cu/O_2 active species to induce rearrangement reaction (Table 1). Polar aprotic solvents such as DMF and DMSO proved to be high yielding. DMSO is likely to stabilize the copper catalyst and also assist in the aerobic oxidation process.[16] Subsequently we realized *p*-toluidine was better

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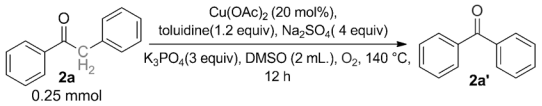
Table 1: Optimization of reaction conditions.[17]



Entry	Cu salt	Solvent	Yield [%]
1	$Cu(OAc)_2$	DMSO	85
2	$Cu(OTf)_2$	DMSO	65
3	$CuCl_2$	DMSO	65
4	$CuCO_3$	DMSO	n.d.
5	CuBr	DMSO	66
6	$Cu(OAc)_2$	DMSO	85[a]
7	$Cu(OAc)_2$	DMSO	85[b]
8	$Cu(OAc)_2$	DMSO	30[a,b]
9	$Cu(OAc)_2$	TFT[c]	4
10	$Cu(OAc)_2$	anisole[c]	2
11	$Cu(OAc)_2$	cyclohexane[c]	2

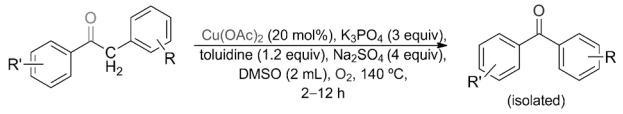
[a] 2 h. [b] 20 mol% toluidine. [c] K_2CO_3. DMSO = dimethylsufoxide, Tf = trifluoromethansulfonyl, TFT = trifluorotoluene.

for this reaction compared to aniline, and use of base was found to be beneficial. Under the optimized reaction conditions, the demethylenated product benzophenone (**2a′**) was obtained from 2-phenylacetophenone (**2a**) in 85% yield (GC). The reaction was equally successful with both isolated and in situ generated imines.[17] Without $ArNH_2$, **2a′** was formed in only 20% yield. In the absence of O_2, the formation of an imine was observed without a trace of the desired diaryl ketone compound.[17]

At first 2-phenylacetophenone derivatives were tested (Table 2) under the standard reaction conditions. A chloro (**2b**) and a bromo (**2c**) phenylacetophenone gave the desired demethylenated product in 70% (**2b′**) and 68% (**2c′**) yield, respectively. Notably, unsymmetrical a hetero-carbocylic ketone can also be synthesized by this method (**2e′**).

Next, we tested a variety of intervening groups other than $-CH_2-$ (Table 3). Diaryl ketones can also be obtained from benzoin derivatives (**3a** and **3f**). Benzophenone was also

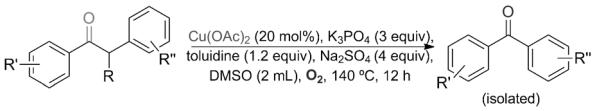
Table 2: Removal of benzylic $-CH_2-$ groups.



Substrate	Product
2a: R'=H **2b**: R'=Cl **2c**: R'=Br	**2a'**, 80%[a] **2b'**, 70%[b] **2c'**, 68%[b]
2d	**2d'**, 67%[c]
2e	**2e'**, 63%[c]

All the reactions were performed in 0.25 mmol scale. [a] 2 h, [b] 12 h, [c] 6 h.

Table 3: Generation of diaryl ketone through removal of benzylic -CHR- groups.



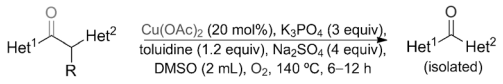
Substrate	Product
3a: R=OH **3b**: R=Br **3c**: R=Ph **3d**: R=*i*Pr **3e**: R=OEt	**2a'**, 66% (from **3a**) **2a'**, 75% (from **3b**) **2a'**, 70% (from **3c**) **2a'**, 50% (from **3d**) **2a'**, 30% (from **3e**)[a]
3f	**2b'**, 65% (6 h)

[a] Ethylbenzoate was isolated in 65% yield.

obtained by removal of -CHBr- (**3b**), -CHPh- (**3c**), -CH*i*Pr- (**3d**), and -CH(OEt)- (**3e**) groups.

Efforts were made to apply this methodology for the synthesis of symmetrical and unsymmetrical heterocyclic ketones (Table 4). The classical method of diaryl ketone synthesis involving arylmetal species[18] and Friedel–Crafts acylations are often incompatible for heteroaromatic moiety.[19] Although carbonylative methods[20] are known for heterocylic ketone synthesis, formation of homocoupled products without insertion of CO restricts its applicability.[20d,21] Alternative pathways of aldehyde arylation have

Table 4: Bis(heteroaryl) ketone synthesis.

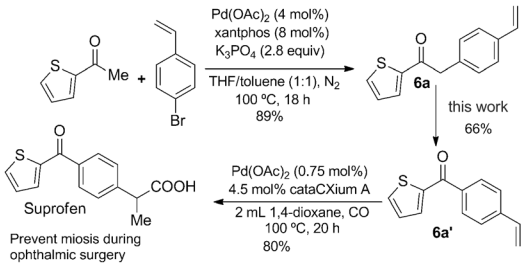


Substrate	Product
4a	**4a'**, 69%[a]
4b	**4b'**, 85%[b]
4c	**4c'**, 88%[b]
4d	**4a'**, 45%[a]
4e	**4e'**, 73%[c]
4f	**4f'**, 81%[c]

All the reactions were done in 0.25 mmol scale. [a] 12 h. [b] 6 h. [c] 8 h.

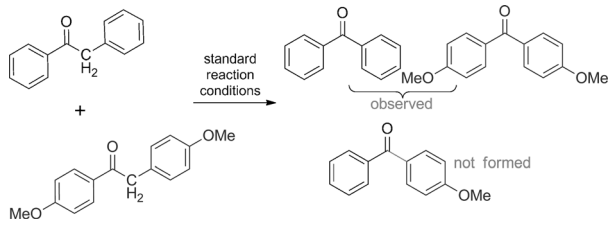
been developed for the synthesis of bis(heteroaryl) ketones.[22] Still new methods for the synthesis of such ketones are of great importance.

A dipyridyl ketone was obtained from two distinct substrates, **4a** and **4d**. Unsymmetrical heterocylic ketones such as **4b′**, **4c′**, **4e′**, and **4f′** were obtained in good to excellent yields. Pyridin-3-yl(thiophen-2-yl)methanone (**4c′**), the precursor of an insulin release stimulator,[23] was also synthesized under the optimized reaction conditions in 88% yield. Suprofen (profenal), a nonsteroidal anti-inflammatory drug from Janssen Pharmaceutica, can be synthesized following present method in 47% overall yield (3 steps; Scheme 2).[24]



Scheme 2. Synthesis of suprofen. THF = tetrahydrofuran, xantphos = 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene.

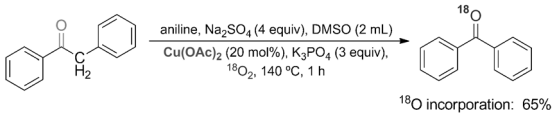
A series of experiments were carried out to gain insights into the reaction mechanism. Under standard reaction conditions, a mixture of two α-phenylacetophenone derivatives gave the corresponding diaryl ketones only, without a trace of crossover product (Scheme 3). Such an observation indicates that a concerted rearrangement reaction is likely to be operative. Further, 2-ethoxy-2-phenylacetophenone (**3e**) produced ethyl benzoate as the major product, thus indicating close correlation between migratory apptitude of the α substituents and that of the product composition (see Scheme S3 in the Supporting Information).[17]



Scheme 3. Crossover experiment.

In the presence of a radical scavenger, the desired product yield was significantly reduced (see Scheme S1).[17,25] With $^{18}O_2$, incorporation of ^{18}O into the benzophenone product was been observed (Scheme 4).

The progress of the reaction was monitored using a number of different excess experiments with respect to 2-phenylacetophenone.[17] A second-order rate dependance was



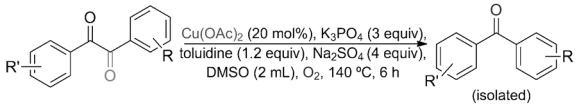
Scheme 4. Isotope-labeling experiment.

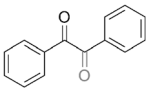
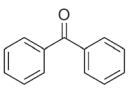
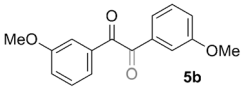
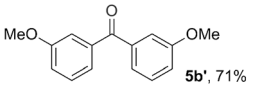
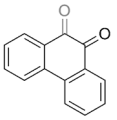
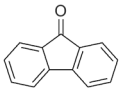
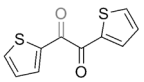
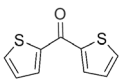
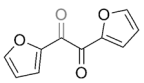
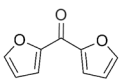
established under an initial-slope method (see Figure S2),[17] which indicates the involvement of two molecules of **1**.[26] The reaction was complete within 2 hours (**2a**) using 1.2 equivalents toluidine. Upon further progress the amine oxidizes to the diazo compound, 1,2-di-*p*-tolyldiazene (see Figures S3 and S).[17]

Since PhCOCOPh was obtained from $PhCH_2COPh$ and PhCH(OH)COPh in 61% and 98%, respectively, at room temperature,[17] diketo compounds were subsequently explored as the starting material for synthesizing diaryl ketones.

Benzil (**5a**) produced benzophenone in 80% yield (Table 5). In the presence of a methoxy group on both phenyl rings of benzil, the desired product was obtained in 71% yield (**5b′**). Notably, in this case the 3-substituted benzylic group was converted into the corresponding 3-substituted aryl group without any internal scrambling (**5b**). This outcome indicates that a concerted rearrangement pathway is likely to be operative. In case of a cyclic system like phenanthraquinone the desired fluorenone **5c′** was obtained in 75% yield. The symmetrical diheterocyclic ketones **5d′** and **5e′** were also generated from corresponding diketo precursors **5d** and **5e**. In all these cases, a benzylic -CO- moiety was removed successfully to produce the diaryl

Table 5: Ketone synthesis by removal of benzylic -CO- groups.

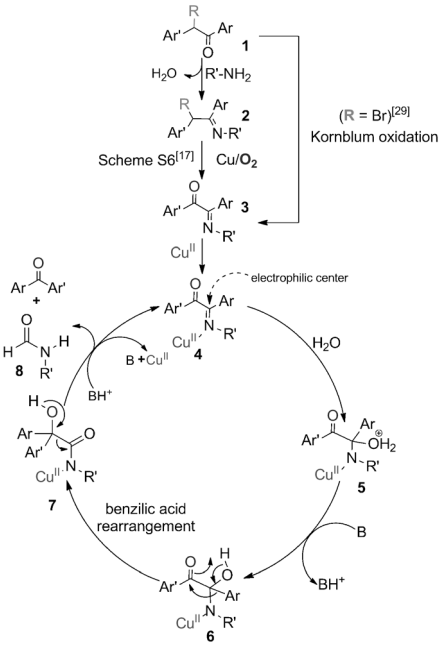


Substrate		Product	
	**5a**		**2a'**, 80%[a]
	**5b**		**5b'**, 71%
	**5c**		**5c'**, 5%
	**5d**		**5d'**, 87%
	**5e**		**5e'**, 61%[b]

All the reactions were done in 0.25 mmol scale. [a] 2 h. [b] 8 h.

ketone product. Notably, the yield obtained from benzil (**5a**) is comparable to that of **2a** (Table 2).

Based on preliminary mechanistic studies, we proposed imine formation (**2**) and subsequent Cu/O_2-mediated oxidation of the benzylic position to the corresponding ketone (**3**; Scheme 5).[17,27,28] The pathway for the generation of **3** depends on the nature of the starting materials. For example,



Scheme 5. Plausible catalytic pathway.

the transformation of $-CH_2-$ to -CO- involves formation of an α-hydroxy ketone intermediate, which upon oxidation generates the diketo derivative **3**.[17] In the case of -CHBr- the reaction proceeds through a Kornblum oxidation.[29] Once formed, **3** undergoes a benzylic acid rearrangement leading to **7**,[30] which decomposes to the desired ketone product.

In summary, we have developed a copper-catalyzed method for the synthesis of diaryl ketones and bis(heteroaryl) ketones by removal of benzylic $-CH_2-$, -CO-, and -CHR- groups under aerobic conditions. This transformation introduces direct bonding between the carbonyl carbon atom and the β-carbon atom by eliminating the α-carbon atom and keeping the bond connectivity intact for rest of the molecule.

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