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Cesium carbonate promoted aerobic oxidation of arylacetamides: an efficient access to N-substituted α-keto amides

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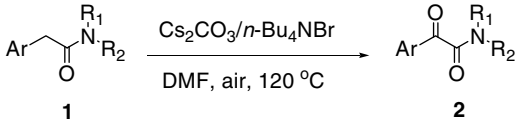
Abstract—A novel cesium carbonate promoted aerobic oxidation reaction to prepare N-substituted α-keto amides in the presence of catalytic amount of tetra-*n*-butylammonium bromide was described. This reaction provides a very simple and convenient route from easily available arylacetamides in good to high yields.

α-Keto amides are valuable intermediates in organic synthesis,[1] have intriguing biological properties,[2] and are present in several natural products as main skeleton.[3] A wide range of chemistry has been exploited for the preparation of α-keto amides, including: (1) traditional amidation of α-keto acids;[4] (2) oxidation of hydroxyamides,[5] cyanoketones,[6] olefins[7] or direct α-oxidation of amides mainly using SeO_2,[8] $(NH_4)_2Ce(NO_3)_2$[9] or RuO_2[10] as metal oxidants; (3) photooxygenation of corresponding amides sensitized by Rose Bengal (RB) or tetraphenyl-porphin (TPP);[11] (4) double-carbonylation reaction of aryl halides catalyzed by palladium complexes in the presence of carbon monoxide;[12] and (5) coupling reaction of acyl chloride with isonitrile developed by Ugi in the 1960s.[13] All these methods, however, are either lack of effective procedure to prepare starting materials, or incompatible with sensitive functionalities due to the harsh conditions during these transformations, or impractical because of the required toxic or expensive reagents. It becomes a synthetic challenge to find an efficient and convenient way to access α-keto amides without using any toxic or expensive reagents, or to avoid harsh conditions.

For our continuous research interest to pursue selective high affinity P2Y receptor antagonists,[14] a series of α-keto amides were designed to be assembled into chemical ligands. Herein, we wish to report a convenient preparation of α-keto amides from readily available arylacetamides in good yields (Scheme 1). The reactions are effective in DMF at 120 °C in the presence of Cs_2CO_3 and *n*-Bu_4NBr under the atmosphere of air.

Pal and co-workers[15] found 1,8-diazabicyclo-[5.4.0]-undec-7-ene (DBU) could facilitate the oxidative cyclization of phenacylamides in acetonitrile under an oxygen atmosphere at room temperature in good to excellent yields. When we applied this reaction condition to 2-phenyl-1-(piperidin-1-yl)ethanone **1a**,[16a] however, no desired α-oxidative product **2a** was observed even at 80 °C (Table 1, entry 1). Using Et_3N or pyridine as base in DMF, only a trace amount of **2a** was detected (Table 1, entries 2–3). Other inorganic bases such as $NaHCO_3$, K_2CO_3, K_3PO_4, or NaOH[17] in DMF gave slightly improved results (Table 1, entries 4–7). To our delight, Cs_2CO_3 (2.0 equiv) turned out to be the base of choice and **2a** could be generated in 81% yield in DMF, albeit with long reaction time to reach completion (Table 1, entry 8). DMSO was found to be equally effective as DMF (Table 1, entry 9), while 1,4-dioxane and toluene resulted in diminished yields with very low



1 2

Scheme 1. Synthesis of α-keto arylacetamides.

Keywords: Oxidation; Atmospheric oxygen; Cesium carbonate; Arylacetamides; α-Keto amides.
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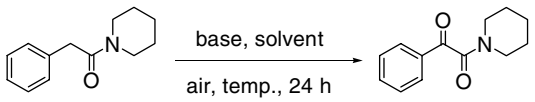
Table 1. Optimization of bases, solvents, and temperature



1a **2a**

Entry	Base (equiv)	Solvent	Temp (°C)	Conv.[a] (%)	Yield[b] (%)
1	DBU (2.0)	CH_3CN	80	0	0
2	Et_3N (2.0)	DMF	80	0	0
3	C_5H_5N (2.0)	DMF	100	28	5
4	$NaHCO_3$ (2.0)	DMF	120	38	10
5	K_2CO_3 (2.0)	DMF	120	44	22
6	K_3PO_4 (2.0)	DMF	120	61	42
7	NaOH (2.0)	DMF	120	74	20
8	**Cs_2CO_3 (2.0)**	**DMF**	**120**	**95**	**81**
9	Cs_2CO_3 (2.0)	DMSO	120	95	76
10	Cs_2CO_3 (2.0)	Dioxane	100	31	11
11	Cs_2CO_3 (2.0)	Toluene	100	29	9
12	Cs_2CO_3 (1.2)	DMF	120	89	60
13	Cs_2CO_3 (0.1)	DMF	120	66	46

[a] Conversion was determined on the basis of **1a** recovered.
[b] Isolated yields.

conversion rates (Table 1, entries 10 and 11). The reason might be the poor solubility of Cs_2CO_3 in less polar solvents. We were surprised to find, when the amount of Cs_2CO_3 was decreased to 1.2 equiv and 0.1 equiv, the reactions still gave **2a** in 60% and 46% yield, respectively (Table 1, entries 12 and 13), the latter clearly indicated that the reaction proceeded in a catalytic manner.

Our further study demonstrated that introduction of *n*-Bu_4NBr[18] as additive could significantly accelerate the reaction (compare Table 2, entry 1 and Table 1, entry 8). Reducing both *n*-Bu_4NBr and Cs_2CO_3 loadings to 1.0 equiv produced similar result (Table 2, entry 2), and catalytic amounts of *n*-Bu_4NBr (0.1 equiv) afforded **2a** in 89% yield within 16 h (Table 2, entry 3). Other quaternary ammonium salts such as *n*-Bu_4NHSO_4 and *n*-Bu_4NF gave satisfactory yields with longer reaction time (entries 4 and 5), while *n*-Bu_4NI and *n*-Me_4NCl were less effective to give lower yields (entries 6 and 7). Furthermore, catalytic amounts of Cs_2CO_3 and *n*-Bu_4NBr still produced **2a** in slightly lower yields (85–86%) after longer reaction time (entries 8 and 9). Considering the reaction time and yield, the best condition was optimized as: Cs_2CO_3 (1.1 equiv) and *n*-Bu_4NBr (0.5 equiv) in DMF at 120 °C under the atmosphere of air, and **2a** was obtained in 93% yield in only 6 h (Table 2, entry 10). It should be noted that when 1,4-hydroquinone (0.1 equiv) was used in the reaction, **2a** was obtained in 52% yield, which ruled out the free radical mechanism.[19] When the reaction was conducted under nitrogen, no desired product was obtained (entry 11).

To explore the scope of this method, a variety of arylacetamides **1a**–**n**[16] were applied under the optimized conditions (Table 2, entry 10). The results are summarized in Table 3.

As shown in Table 3, the α-oxidation reaction proceeded readily to give the corresponding α-keto amides in good

Table 2. Screening of additives and amount of Cs_2CO_3[a]

Entry	Base (equiv)	Additive (equiv)	Time (h)	Yield[b] (%)
1	Cs_2CO_3 (2.0)	*n*-Bu_4NBr (2.0)	5	90
2	Cs_2CO_3 (1.0)	*n*-Bu_4NBr (1.0)	5	90
3	Cs_2CO_3 (1.0)	*n*-Bu_4NBr (0.1)	16	89
4	Cs_2CO_3 (1.0)	*n*-Bu_4NHSO_4 (0.1)	24	88
5	Cs_2CO_3 (1.0)	*n*-Bu_4NF (0.1)	24	83
6	Cs_2CO_3 (1.0)	*n*-Bu_4NI (0.1)	24	70
7	Cs_2CO_3 (1.0)	*n*-Me_4NCl (0.1)	24	52[c]
8	Cs_2CO_3 (0.5)	*n*-Bu_4NBr (0.1)	17	86
9	Cs_2CO_3 (0.1)	*n*-Bu_4NBr (0.1)	24	85
10	**Cs_2CO_3 (1.1)**	***n*-Bu_4NBr (0.5)**	**6**	**93**
11	Cs_2CO_3 (1.1)	*n*-Bu_4NBr (0.5)/N_2	24	0

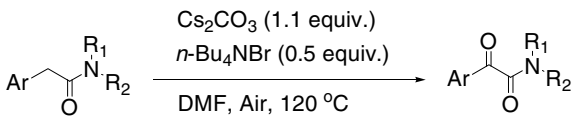
[a] Reaction conditions: **1a** (1.0 mmol) was reacted with Cs_2CO_3 and additives in DMF (4 mL) at 120 °C under atmospheric air.
[b] Isolated yields.
[c] With conversion of 80% based on **1a**.

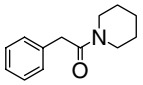
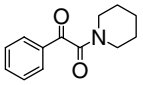
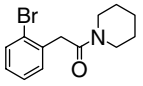
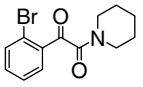
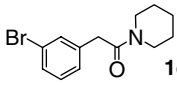
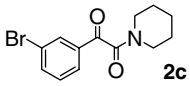
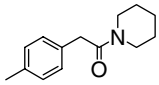
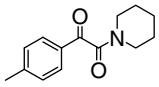
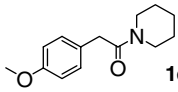
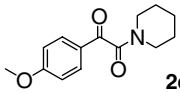
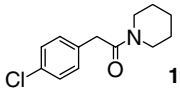
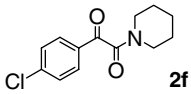
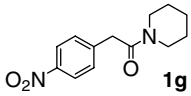
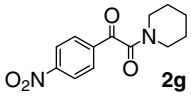
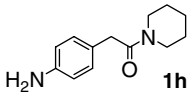
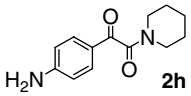
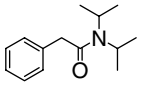
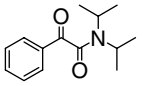
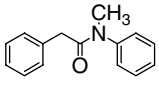
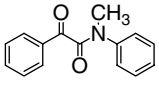
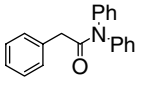
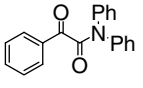
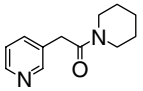
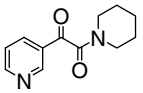
yields. Remarkably clean reactions were observed with functionalized molecules bearing *ortho*, *meta*, and *para* substitutions on aryl ring (entries 2–6 and 8), whereas the substrate with nitro group gave a slightly complicated reaction (entry 7). It should be noted that the easily oxidizable amino group remained intact under the reaction condition (entry 8). The steric and electronic effects of the substitution on the nitrogen atom have also been examined. Compound **2i** bearing two bulky isopropyl groups was obtained in 82% yield (entry 9), while **2k** with two bulky and electron-withdrawing phenyl groups was obtained in only 28% yield (entry 11). For substrate **1j** bearing one methyl and one phenyl group at nitrogen atom, **2j** was isolated as a mixture of s-cis and s-trans isomers in a ratio of 9:1 which was in agreement with the literature result reported by Takahashi et al. (entry 10).[6a] This reaction was not limited to simple benzene-containing aromatics, the pyridine-containing substrate **1l** also afforded **2l** in good yield (entry 12).

When attempted to oxidize one carbon homologated derivative of **1a**, 3-phenyl-1-(piperidin-1-yl)propan-1-one **1m**, no expected product was observed, and the starting material was recovered quantitively. 2-Cycno substituted reactant **1n**[16b] failed to give corresponding oxidation product **2n** using our standard conditions after 8.5 h. Instead, the isoindoline-1,3-dione **3** was isolated in 50% yield (Scheme 2). The formation of **3** may be attributed to a nitrile oxidation–hydrolysis–cyclization–elimination sequence.

The detailed mechanism is not clear at this stage. A possible reaction mechanism to account for the formation of substituted α-keto amides using catalytic amount of base is proposed in Scheme 3.[15a,20] The mechanism may involve deprotonation at the benzylic position of amides **1** and to furnish the carbanions **A**, which then could react with molecular oxygen to provide peroxy anions **B**. After intramolecular abstraction of a proton from the benzylic site[20] by the peroxy anions **B**, products **2** could be formed through ionic pathway, and carbanions **A** could be regenerated from amide **1** and the hydroxide ion released.

Table 3. Synthesis of N-substituted α-keto amides by oxidation of corresponding amides



Entry	Reactant	Product	Time (h)	Yield[a] (%)
1	 **1a**	 **2a**	6	93
2	 **1b**	 **2b**	6.5	78
3	 **1c**	 **2c**	3	80
4	 **1d**	 **2d**	6	75
5	 **1e**	 **2e**	6	91
6	 **1f**	 **2f**	6	78
7	 **1g**	 **2g**	24	40
8	 **1h**	 **2h**	9	75[b]
9	 **1i**	 **2i**	10	82
10	 **1j**	 **2j**	6.5	62[c,d]
11	 **1k**	 **2k**	3.5	28[e]
12	 **1l**	 **2l**	5	81

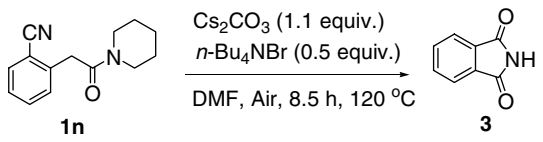
[a] Isolated yields. Products were characterized by ^{1}H and ^{13}C NMR, MS, FT-IR data, and HRMS or elemental analysis was used for all new compounds.

[b] Cs_2CO_3 (2.0 equiv) was used.

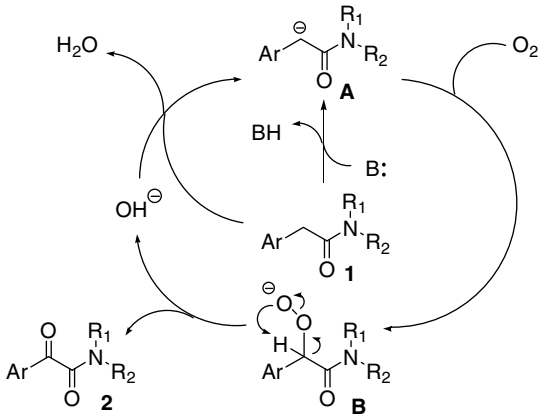
[c] Isolated as a mixture of s-cis and s-trans isomers in a ratio of 9:1.

[d] 13% of **1j** was converted to the corresponding *N*-methylaniline.

[e] 29% of **1k** was converted to the corresponding diphenylamine.



Scheme 2. Reaction of **1n** under optimized conditions.



Scheme 3. Plausible mechanism of α-oxidation reaction.

In summary, we describe here a novel cesium carbonate promoted aerobic oxidation reaction in the presence of tetra-*n*-butylammonium bromide. Compared with other reported methods, the current approach provides a very simple and convenient route to α-keto amides from easily available arylacetamides in good to high yields, and could potentially be carried out in industrial scales. This reaction avoids using toxic reagents and harsh conditions and could proceed catalytically.[21] The scope of this reaction and its applications for bioactive compounds are currently under investigation in our laboratory and will be reported in due course.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.10.099.

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21. *General procedure*: To a solution of 1-(4-aminophenyl)-2-(piperidin-1-yl)ethanone **1h** (175 mg, 0.8 mmol) in DMF (4 mL) was added Cs_2CO_3 (287 mg, 0.88 mmol) and *n*-Bu_4NBr (129 mg, 0.4 mmol). The reaction mixture was stirred for 9 h at 120 °C under the atmosphere of air, which was dried through a calcium chloride tube until **1h** was completely consumed. Ethyl acetate (15 mL) was then added to the mixture after it was cooled to room temperature, and the resulting mixture was filtered. The filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (elution with petroleum ether/ethyl acetate = 2:1) to give **2h** (139 mg, 75%) as a light yellow solid, mp 166–168 °C. IR (KBr): 3428, 3347, 2924, 2853, 1644, 1610, 1593, 1558, 1446 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 7.49 (AA′ of AA′BB′, $J = 8.0$ Hz, 2H), 6.58 (BB′ of AA′BB′, $J = 8.0$ Hz, 2H), 6.43 (s, 2H), 3.60–3.40 (m, 2H), 3.20–3.10 (m, 2H), 1.65–1.45 (m, 4H), 1.40–1.30 (m, 2H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 189.52, 165.93, 155.33, 131.79, 120.24, 112.96, 46.27, 41.00, 25.82, 25.11, 23.84. MS (EI): m/z (%) = 232 (2) [M^+], 120 (100), 112 (3), 92 (17). Anal. Calcd for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.01; H, 6.945; N, 11.96.