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Copper-Catalyzed Synthesis of Indoly Diketones via C–H Oxidation/Diacylation of Indoles with Arylglyoxal Hydrates

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1. General Experimental Method

1.1 General Considerations

All reactions were performed in dried two-neck round bottom flask. Cu catalysts, indoles, SeO₂, methyl ketones and solvents were purchased from commercial sources and used without further purification. Arylglyoxal hydrates were prepared from oxidation of corresponding methyl ketones with SeO₂ according to the reported procedure.¹ 2-(1*H*-indol-3-yl)-2-oxoacetaldehyde was obtained as a gift from AmberMolTech LLC or prepared as described by Rinehart.²

Thin layer chromatography (TLC) employed glass 0.25 mm silica gel plates. Flash chromatography columns were packed with 300-400 mesh silica gel in petroleum ether. All melting points were determined on a WRS-2A microprocessor melting-point apparatus and uncorrected. ¹H NMR and ¹³C NMR data were recorded on Bruker Advance NMR spectrometer (500 MHz) in C₂D₆SO or C₃D₆O as solvent. Chemical shifts (δ) were reported in parts per million (ppm) using tetramethylsilane (TMS) as the internal standard. The peak patterns were indicated as follows: s, singlet; d, doublet; t, triplet; m, multiplet. The coupling constants, *J*, were reported in Hertz (Hz). HRMS (ESI) analysis of the product was obtained from Micromass UPLC/Q-TOF Micro Mass Spectrometer. HRMS (APCI) analysis of the reaction mechanism was obtained from Agilent 6530 Accurate-Mass Q-TOF LC/MS. XRD powder diffraction was carried out on Bruker's D8 ADVANCE X-Ray Diffractometer with Guinier imaging plate detector (Cu-K_{a1} radiation, λ = 154.056 pm).

1.2 General procedure for the copper-catalyzed C–H oxidation/diacylation of indoles with arylglyoxal hydrates

A dried 25 mL two-neck round bottom flask was charged with indole (0.5 mmol, 1.0 equiv), 2oxoacetaldehyde hydrate (0.6 mmol, 1.2 equiv), $Cu(OAc)_2 H_2O$ (20.0 mg, 20 mol%) and dioxane/HOAc (4.0/0.5, v/v, 4.5 mL) under air atmosphere. The reaction mixture was stirred at 100 °C until the complete consumption of starting material as monitored by TLC or HPLC. After completion of the reaction, the reaction mixture was cooled to room temperature and diluted with ethyl acetate and water. The aqueous phase was extracted with ethyl acetate. The combined organic extracts were washed with saturated brine, dried with anhydrous Na₂SO₄ and evaporated under reduced pressure. The crude products were purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate, 10/1, v/v) to afford the desired products.

2. Powder X-Ray Diffraction Analysis (XRD Analysis)

XRD powder diffraction was performed on Bruker's D8 ADVANCE X-Ray Diffractometer with Guinier imaging plate detector (Cu-K_{α 1} radiation, λ = 154.056 pm).

A dried 25 mL two-neck round bottom flask was charged with indole (468.6 mg, 4.0 mmol), 2-(4bromophenyl)-2-oxoacetaldehyde hydrate (1.1 g, 4.8 mmol), $Cu(OAc)_2 H_2O$ (159.7 mg, 0.8 mmol, 20 mmol%) and dioxane/HOAc (4.0/0.5, v/v, 4.5 mL) under air atmosphere. The reaction mixture was stirred at 100 °C. After completion of the reaction, the reaction mixture was cooled to room temperature and diluted with ethyl acetate and water, then the precipitate was collected by centrifugation and filtration, washed with ethyl acetate and water, dried in the vacuum and was analyzed by XRD. Significant peaks labeled were assigned to Cu₂O, implying that Cu(OAc)₂ H₂O can be considered as the oxidant as well as the catalyst in the reaction and reduced to Cu₂O after the reaction.



Figure S1. XRD of the precipitate after the reaction

3. Chromatographic conditions and LC-APCI-MS/MS analysis

LC-MS analysis was performed on an Agilent 6530 Accurate-Mass Q-TOF LC/MS equipped with atmospheric-pressure chemical ionization (APCI) interface and high performance liquid chromatography (HPLC) analyses were carried out using an Agilent 1260 Infinity two pump equipped with an online degasser, an auto sampler, column heater and a diode-array detector (DAD, wavelength: 254 nm). Analytical chromatographic separations of samples were carried out on a chromolith performance SB-C18 column (150×4.6 mm, Agilent, America) protected by a chromolith guard column of the same company. The flow rate was 0.8 mL/min. The mobile phase consisted of methanol (80%) and water (20%). The injection volume was 2μ L and the column temperature was maintained at 30 °C.

A 6530B LC/MS system from Agilent was used for the detection, which is a hybrid quadrupole timeof-flight (Q-TOF) mass spectrometer. The analyses were performed using an atmospheric-pressure chemical ionization (APCI) source in negative modes. The operation conditions were as follows: scan range of 90–1500 amu, ion source temperature 350 °C, nebulizer 60 psi, gas flow 4 L/min, capillary voltage 3500. Nitrogen was used in all cases. Agilent Mass Hunter software (version B.07.00) was used for data acquisition and processing.

4. Detailed LC-MS analysis for the intermediates 4a, 5a, 10, 11 and the product 3a in the different reaction systems

4.1 Detailed LC-MS analysis for the reaction of 1a and 2a in dioxane/HOAc without copper catalyst

Detailed LC-MS result on the reaction of **1a** and **2a** in dioxane/HOAc (4.0/0.5, v/v, 4.5 mL) without copper catalyst at 100 °C for 6 h under air atmosphere was presented. The result showed that the two isomeric intermediates **4a** and **5a** were detected besides the product **3a** (Figure S2).





Figure S2. Detailed LC-MS result of the reaction without copper catalyst

4.2 Detailed LC-MS analysis for the reaction of 1a and 2a in dioxane/HOAc with copper catalyst

Detailed LC-MS result on the reaction of **1a** and **2a** in dioxane/HOAc (4.0/0.5, v/v, 4.5 mL) in the presence of $Cu(OAc)_2 H_2O$ at 100 °C for 6 h under air atmosphere was presented. The result was identical with that of the reaction without copper catalyst. The two isomeric intermediates **4a** and **5a** were also detected besides the product **3a** (Figure S3).





Figure S3. Detailed LC-MS result of the reaction with copper catalyst

4.3 Detailed LC-MS analysis for the reaction of 1a and 2a with pyrrolidine in DMSO

Detailed LC-MS result on the reaction of **1a** and **2a** in the presence of pyrrolidine in DMSO at 80 $^{\circ}$ C under air atmosphere was presented. The result showed that the intermediate **10** was detected besides the product **3a** and the two isomeric intermediates **4a** and **5a** were not detected in this reaction system. It is worth noting that another intermediate was detected. This structure was suspected to be (2-(4-bromophenyl)-1-(1*H*-indol-3-yl)-2-oxoethylidene)oxonium **12** according to the mass ([M-H]⁼=326.9892 and 328.9892). The oxonium may be stable in polar solvent DMSO in LC-MS and was converted to the product slowly (Figure S4).









Figure S4. Detailed LC-MS result of the reaction with pyrrolidine in DMSO

4.4 Detailed LC-MS analysis for the reaction of 1a and 2a with morpholine in DMSO

Detailed LC-MS result on the reaction of **1a** and **2a** in the presence of morpholine in DMSO at 80 $^{\circ}$ C under air atmosphere was presented. The result showed that the intermediate **11** was detected besides the product **3a** and the two isomeric intermediates **4a** and **5a** were not detected in this reaction system. It is worth noting that another possible intermediate (2-(4-bromophenyl)-1-(1*H*-indol-3-yl)-2-oxoethylidene)oxonium **12** was also detected in this system (Figure S5).





Figure S5. Detailed LC-MS result of the reaction with morpholine in DMSO

4.5 Detailed LC-MS analysis for the reaction of 1a and 2a with pyrrolidine in toluene

Detailed LC-MS result on the reaction of 1a and 2a in the presence of pyrrolidine in toluene at 40 °C under air atmosphere was presented. The result was identical with that of the reaction in dioxane/HOAc with or without copper catalyst. The two isomeric intermediates 4a and 5a were also detected besides the product 3a (Figure S6).





4.6 Detailed LC-MS analysis for the reaction of 1a and 2a with morpholine in toluene

Detailed LC-MS result on the reaction of **1a** and **2a** in the presence of morpholine in toluene at 40 °C under air atmosphere was presented. The result was identical with that of the reaction in Dioxane/HOAc with or without copper catalyst. The two isomeric intermediates **4a** and **5a** were also detected besides the product **3a** (Figure S7).







4.7 Detailed LC-MS analysis for the reaction of 1a and 2a in dioxane with copper catalyst

Detailed LC-MS result on the reaction of **1a** and **2a** in dioxane with copper catalyst at 100 °C for 6 h under air atmosphere was presented. The result showed that the two isomeric intermediates **4a** and **5a** were also detected besides the product **3a** (Figure S8).





Figure S8. Detailed LC-MS result of the reaction in dioxane with copper catalyst

5. References

- [1] H. A. Riley and A. R. Gray, Organic Syntheses, Wiley & Sons: New York, 1943; Vol. 2, pp. 509.
- [2] S. Tsujii and K. L. Rinehart, J. Org. Chem., 1988, 53, 5446–5453.

























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