

Facile α -Ketonization of Carbonyl Compounds Utilizing CuBr₂ on Alumina

Bong Ser Park,* Hye Mi Lee, and Sungsu Cho

Department of Chemistry, Dongguk University, Seoul 100-715, Korea. *E-mail: parkbs@dongguk.edu

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Many interests have been drawn for α -diketones due to their utility as an important precursor of biological and organic synthesis.¹ Several methodologies are known for the preparation of the diketones² and new methods are being continuously updated.³ The best known procedures are oxidation of α -methylene ketones to α -diketones using various oxidants such as selenium dioxide, pyridinium chlorochromate (PCC), or potassium permanganate. Multi step approaches are also known like α -halogenation of ketones followed by the Kornblum oxidation of the haloketones using DMSO.⁴ Recently a few other methods such as a microwave promoted oxidation⁵ or a nitrosation method⁶ have been added to the list of diketone synthesis. Even though various methodologies toward synthesis of α -diketones have been developed as described above, most of these methods still require harsh reaction conditions or rather exotic environment.

In the course of our research on photochemistry of carbonyl compounds,⁷ we needed to synthesize a few α -diketones and decided to use a relatively simple two-step reaction sequence of a bromination followed by the Kornblum oxidation. Stimulated by recent advances in organic synthesis using inorganic solid supported reagents⁸ as an environment friendly method,⁹ we tried to use CuBr₂ adsorbed onto Al₂O₃

as a brominating reagent instead of using a classical method using Br₂ or CuBr₂ in organic solvents. To our pleasant surprise, the reaction gave α -diketones directly in good yields. Here we wish to report a convenient process for conversion of α -methylene ketones to α -diketones and to describe a few experiments leading into a mechanistic reasoning.

Initially we ran an experiment which used a mixture of α -phenylacetophenone (deoxybenzoin) and CuBr₂ adsorbed onto Al₂O₃ for the purpose of brominating the alpha position to the carbonyl. When the crude mixture was analyzed after 8 hrs' refluxing in CCl₄, benzil was detected in addition to the expected brominated ketone. The stimulating result led us to investigate the reaction more closely. The reaction was repeated at several different reaction conditions to obtain the best yield of the desired diketone. At the same time, a few other ketones were also tested to get an idea of the scope and limitation of this reaction. Our results are summarized in Table 1.

As the Table 1 shows, the ketonization proceeds smoothly when there is an aryl group at the alpha position to the carbonyl. (entry 1-5) If there is no aryl group, only the brominated products are formed even at elongated reaction time. (entry 6-7) In order to test the selectivity more closely, 1-phenyl-2-butanone was treated with CuBr₂/Al₂O₃. The reaction gave a complex mixture of three sets of products shown below, whose ratios were time dependent. The reaction was monitored by ¹H NMR spectrum of each aliquot taken at regular intervals. The result is summarized in Table 2.

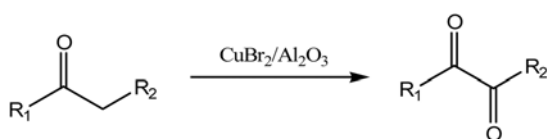
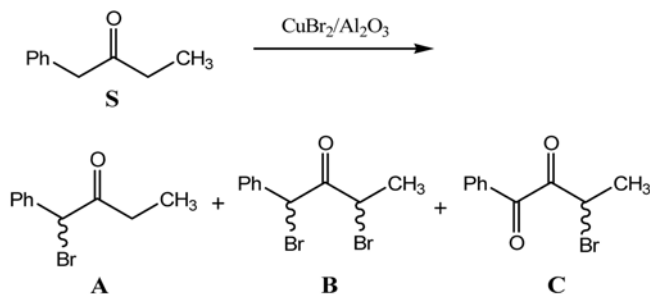


Table 1. Reaction Data of α -Methylene Ketones with CuBr₂ Adsorbed on Alumina

Entry	R1	R2	Isolated Yield of Diketones, %	Isolated Yield of α -Brominated Products ^a , %
1	Ph	Ph	93	
2	Ph	<i>o</i> -Tolyl	91	
3	Ph	<i>o</i> -Ethylphenyl	89	
4	Ph	2,4,6-trimethylphenyl	74	
5	2,4,6-trimethylphenyl	Ph	82	
6	Ph	<i>n</i> -Propyl		95
7	Indanone			90

^aSum of mono- and di-brominated products. The ratios varied depending on time and concentration.



The ketonization occurred selectively at the methylene activated by an aromatic group and the possible triketone or its derivative was not detected. The amount of the diketones increased at longer reaction time at the expense of the brominated products, which implied that the ketonization occurred *via* the brominated products.

The intermediacy of the bromo ketone in the formation of

Table 2. Relative Ratios of Starting Ketone and Products in Reaction Times

Time (hrs)	S (%)	A (%)	B (%)	C (%)
3	19.1	60.5	10.3	10.1
9	0	14.2	62.1	23.7
15	0	0	66.8	33.2

diketone was further evidenced by the following experiment. When the isolated bromo ketone was treated with Al_2O_3 , the diketone was formed cleanly in nearly quantitative yields. In the absence of alumina, the reaction gives only the brominated products even after prolonged reaction time. With alumina alone, all the ketones tested were recovered unreacted at the above reaction condition. Therefore, the alumina had to play an important role at the stage of the ketonization of the bromo ketones. It is not certain at the moment where the oxygen of the newly formed carbonyl came from. Interestingly the addition of a few drops of water to the reaction mixture seemed to accelerate the ketonization. (The addition of water had to be careful because excess water caused dissolution of the CuBr_2 out of alumina.) Even though all the reagents used were carefully dried before the reaction, a small amount of water left behind adventitiously might have caused the oxidization. Oxygen in the air would be a strong candidate of the oxygen source of the newly formed carbonyl group. However, a controlled experiment under argon atmosphere still produced the diketones. More importantly, the oxidation of the bromo ketones did not occur in the absence of alumina. We have previously reported that the diketone is formed from α -(ortho-ethylphenyl)-acetophenone in the interior of RbX or CsX zeolite.¹⁰ Considering that alumina and zeolites have similar composition, it is speculated that both of the oxidation reactions may follow similar pathways. We are currently investigating such a possibility with more model compounds.

In summary, we have found a convenient method converting methylene ketones to 1,2-diketones using CuBr_2 adsorbed onto alumina. The ketonization turned out to go through bromo ketones and alumina seemed to play an important role in the oxidation step. We believe our method will be a nice addition to other classical methods of such conversion due to the simplicity of the whole reaction procedure.

Experimental

A typical synthetic procedure is as follows.

A 100 mL round bottomed flask was charged with an α -methylene ketone (2.5 mmols), CCl_4 (50 mL), and CuBr_2 adsorbed onto alumina¹¹ (15 mmols based on CuBr_2). The mixture was refluxed for up to 72 hours until all the starting ketone disappeared. After cooled to room temperature, the reaction mixture was filtered and washed with CCl_4 . Evaporation of the solvent from the combined filtrate under reduced pressure yielded the desired diketone.

Each product was isolated by column chromatography using hexane and ethyl acetate in 6 to 1 ratio as eluents and characterized by routine spectroscopic methods. The structure of each product was further confirmed by comparing them with authentic samples.¹²

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