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Rapid microwave-promoted solvent-free oxidation of α-methylene ketones to α-diketones

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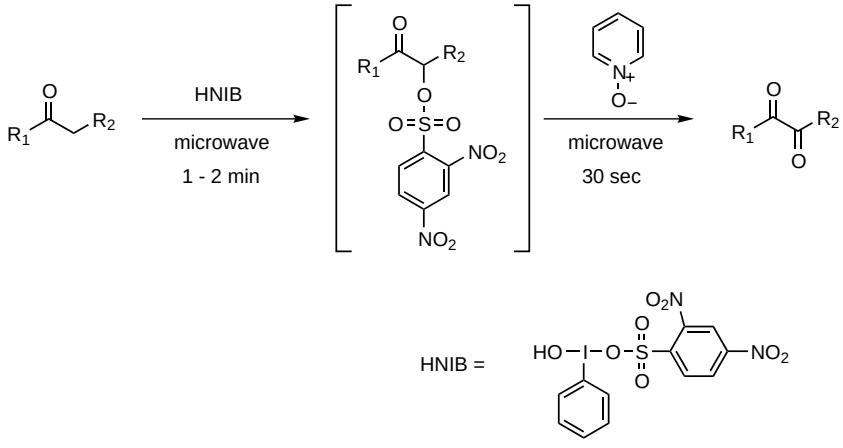
Abstract—A convenient and rapid method for the oxidation of α-methylene ketones to α-diketones has been described involving the reaction of pyridine *N*-oxide with α-nosyloxy ketone intermediates.

Much effort for the efficient preparation of 1,2-diketones has been made due to their biological activity and usefulness as precursors for many useful organic transformations.[1] While a wide variety of methods are described in literature for the preparation of α-diketones,[2] little attention has been paid to the synthesis of α-diketones from α-methylene ketones. Oxidation of a reactive benzylic group to α carbonyl functions can be easily achieved using appropriate oxidants, such as pyridinium chlorochromate[3] and potassium permanganate.[4] By contrast, there has been relatively few reports concerning the conversion of unactivated α-methylene ketones to the corresponding α-diketones. The representative examples include the selenium dioxide oxidation of ketones in acetic acid[5] and the reaction of α-bromo ketones with DMSO in the presence of sodium carbonate.[6] Between these two methods, selenium dioxide has been most successfully applied for the oxidation of α-methylene ketones to α-diketones. However, this method has suffered from inherent vigorous reaction conditions and inconvenient purification steps due to the difficulty in removal of the concomitantly generated selenium. Furthermore, the above two reactions always required either strong acidic or basic reaction conditions, which limits their applications to sensitive ketones. To the best of our knowledge, the only method for the oxidation of α-methylene ketones to α-diketones under neutral reaction conditions was reported by oxidation of enamino ketone intermediates with singlet oxygen.[7] Although this method provided



Scheme 1.

Keywords: α-diketones; *N*-oxides; hypervalent elements; microwave heating; oxidations.

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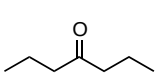
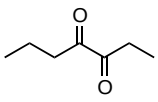
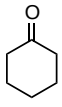
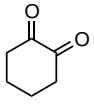
high yields of α-diketones, somewhat exotic reaction conditions limits its practical applications. Therefore, development of a more convenient method for the conversion of α-methylene ketones to α-diketones under neutral reaction conditions is required.

Microwave-assisted organic syntheses attracted much attention because of their fast reaction rates, higher purity of products, and ease of manipulation.[8] In particular, the use of solvent-free microwave-irradiated procedures for organic synthesis have attracted considerable interest in recent years due to their efficient and environmentally benign conditions.[9]

Recently, we have reported the highly efficient microwave-assisted α-organosulfonyloxylation of ketones in solvent-free conditions.[10] Taking advantage of these results, we wish to report here a facile and efficient microwave-assisted oxidation of α-methylene ketones to α-diketones under neutral reaction conditions. Reaction of ketones with [hydroxy(*p*-nitrobenzenesulfonyloxy)iodo]benzene (HNIB)[11] under microwave irradiation for 1–2 min produced α-nosyloxy ketone intermediates, which can then undergo substitution reactions with pyridine *N*-oxide in solvent-free conditions under microwave irradiation to give α-diketones (Scheme 1). A general procedure is as follows: ketone (1.0 mmol) and HNIB (0.507 g, 1.2 mmol) were placed in a 50 mL glass tube. The reaction mixture was immersed in an alumina bath inside domestic microwave oven and irradiated (600 W) three times for a period of 30 s with 10 s intervals. After cooling down the reaction mixture to ambient temperature, pyridine *N*-oxide (0.114 g, 1.2 mmol) was added and irradiated for an additional 30 s. The reaction mixture was extracted with dichloromethane (2×25 mL) and washed with water (2×30 mL). The dichloromethane layer was separated and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by flash column chromatography (SiO_2, ethyl acetate:hexane = 1:3) to give the desired α-diketone. Both symmetrical and unsymmetrical α-diketones were successfully prepared and the results are summarized in Table 1. In general, the reactions were completed within 3 min exposure to microwave irradiation and the yields were fairly high, without any observable by-products. Moreover, the present method proved to work well for an acid sensitive ketone (entry 7), which illustrated the mildness of reaction conditions. The somewhat lower yield (45%) for the 4-heptanone (entry 9) may be due to the slight decomposition of 3-nosyloxy-4-heptanone intermediate under the present reaction conditions. Replacing HNIB with [hydroxy(tosyloxy)iodo]benzene (HTIB)[12] under the same reaction conditions, the yields of oxidations were reduced to 20% on average over prolonged reaction times, which can be explained by the decreased leaving ability of the -OTs group compared to the -ONs group. The oxidation reaction mechanism probably involves nucleophilic substitution of -ONs by pyridine *N*-oxide to form α-oxypyridinium ketone salt followed by removal of the α-proton to carbonyl group. Interestingly, the conversion of deoxybenzoin to benzil occurred spontaneously by microwave irradiation of α-nosyloxy deoxybenzoin intermediate without use of pyridine *N*-oxide (entry 8). By analogy with the formation of diketones from α-mesyloxy ketones,[13] this oxidation process presumably occurred via abstraction of reactive benzylic hydrogen by a sulfonyl oxygen in the α-nosyloxy deoxybenzoin intermediate. Application of this method for oxidation of α-methyl ketones to α-keto aldehyde were unsuccessful to provide complicated side reaction products.

Table 1. Conversion of ketones to α-diketones under microwave irradiation

Entry	Ketones	Product	Yield (%)[a]
1	$C_6H_5COCH_2CH_3$	$C_6H_5COCOCH_3$	83
2	$C_6H_5COCH_2CH_2CH_3$	$C_6H_5COCOCH_2CH_3$	65
3	*p*-$MeC_6H_4COCH_2CH_3$	*p*-$MeC_6H_4COCOCH_3$	78
4	*p*-$MeOC_6H_4COCH_2CH_3$	*p*-$MeOC_6H_4COCOCH_3$	80
5	*p*-$BrC_6H_4COCH_2CH_3$	*p*-$BrC_6H_4COCOCH_3$	90
6	*p*-$ClC_6H_4COCH_2CH_3$	*p*-$ClC_6H_4COCOCH_3$	85
7	*p*-$PhCH_2OC_6H_4COCH_2CH_3$	*p*-$PhCH_2OC_6H_4COCOCH_3$	70
8	$PhCOCH_2Ph$	PhCOCOPh	85[b]
9			45
10			64

[a] Isolated yields after flash column chromatography.
[b] The product was obtained without use of pyridine *N*-oxide.

In summary, we have developed a facile, mild, and remarkably fast reaction method for the oxidation of α-methylene ketones to α-diketones under solvent-free microwave irradiation reaction conditions. The advantages of the present method include rapid reaction rates, ease of manipulation, and mild neutral reaction conditions should provide an added flexibility for the preparation of α-diketones over existing methods. Extensions of this chemistry to other skeletal frameworks are currently underway.

Acknowledgements

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