Synthesis of α,ω-Dicarboxylic Acid Dimethyl Esters from Cycloalkanones

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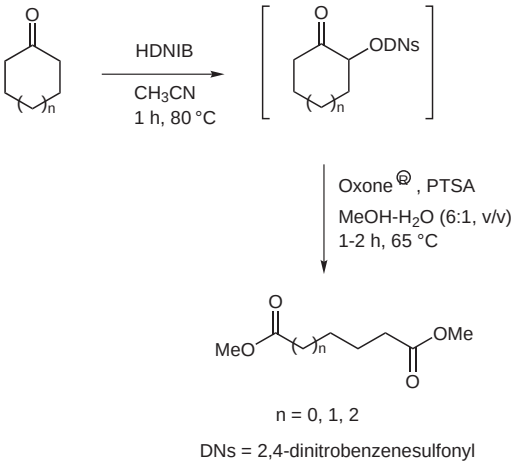
Abstract: Reaction of cycloalkanones with [hydroxy(2,4-dinitrobenzenesulfonyloxy)iodo]benzene and subsequent treatment of α-[(2,4-dinitrobenzene)sulfonyl]oxy cycloalkanone intermediates with Oxone® and PTSA in MeOH–H_2O (6:1, v/v) solution provided dicarboxylic acid dimethyl esters in high yields.

Key words: carboxylic acids, esters, ketones, oxidations, ring opening

There have been continuing interests in α,ω-dicarboxylic acid dimethyl esters due to their unique chemical properties and usefulness as synthetic intermediates for the various synthetic transformations.[1] The α,ω-dicarboxylic acid dimethyl esters can be prepared by a variety of methods which include the oxidative ring opening reaction of α-nitrocycloalkanones,[1,2] α-halocycloalkanones,[3] and oxidation of α-hydroxy cycloalkanones.[4] Among these methods, the oxidative cleavage reaction of α-nitrocyloalkanones with potassium persulfate in methanolic sulfuric acid solution has constituted the most valuable method for the synthesis of α,ω-dicarboxylic acid dimethyl esters.[1] However, preparation of the α-nitrocyloalkanone precursors were found not to be straightforward involving several indirect pathways.[5] Moreover, reported methods for the preparation of α-nitrocycloalkanones directly from cycloalkanones have been very scarce and proved to be ineffective for practical applications.[6] There has been little attention made for direct conversion of cycloalkanones to the corresponding α,ω-dicarboxylic acid dimethyl esters. In this context, to our best knowledge, reaction of cycloalkanones with $VO(OEt)Cl_2$ in the presence of molecular oxygen is the only direct method reported for the preparation of α,ω-dicarboxylic acid diethyl esters.[7] Therefore, the development of an improved method for the preparation of α,ω-dicarboxylic acid dimethyl esters that involves oxidative ring cleavage of cycloalkanones using reaction intermediates other than α-nitrocycloalkanones should be a valuable progress.

Recently, we have described efficient methods for the conversion of carbonyl compounds to α-arenesulfonyloxy ketones.[8] In an effort to expand the scope of chemical transformations involving α-arenesulfonyloxy ketone intermediates, we undertook a study for the oxidative ring cleavage reaction of α-[(2,4-dinitrobenzene)sulfonyl]oxy cycloalkanones to α,ω-dicarboxylic acid dimethyl esters. This method is based on the formation of α-[(2,4-dinitrobenzene)sulfonyl]oxy cycloalkanone intermediates, which subsequently react with Oxone® in the presence of *p*-toluenesulfonic acid (PTSA) under aqueous methanol solution (Scheme 1). Initially, we have assumed that α-[(2,4-dinitrobenzene)sulfonyl]oxy group is able to show equivalent or superior reactivity for the oxidative ring cleavage reactions as like the nitro functional group in α-nitrocycloalkanones.



Scheme 1

In this regard, we examined the reactions of various α-[(2,4-dinitrobenzene)sulfonyl]oxy cycloalkanones under present reaction conditions in order to evaluate the utility of α-[(2,4-dinitrobenzene)sulfonyl]oxy group toward oxidative ring cleavage reactions. As shown in the parentheses of Table 1, the reaction of α-[(2,4-dinitrobenzene)sulfonyl]oxy cyclohexanones with Oxone® in the presence of *p*-toluenesulfonic acid under MeOH-H_2O (6:1, v/v) solution for 1–2 h at 65 °C provided corresponding diesters in the excellent yields. The required α-[(2,4-dinitrobenzene)sulfonyl]oxy cycloalkanones were readily obtained and isolated in 65–75% yields by following the procedures in the previously reported method, which utilized the reaction of cycloalkanones with [hydroxy(2,4-dinitrobenzenesulfonyl-oxy)iodo]benzene (HDNIB, 1.2 equiv) in acetonitrile at reflux.[8a] The α-[(2,4-dinitrobenzene)sulfonyl]oxy cycloalkanones were stable upon storage for several days at room temperature. Being established synthetic utility of α-[(2,4-dinitrobenzene)sulfonyl]oxy cycloalkanones for the preparation of diesters, we have conducted one-pot preparation of diesters from cycloalkanones without isolation of α-orga-

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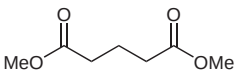
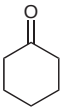
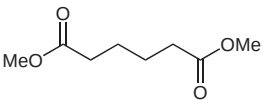
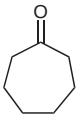
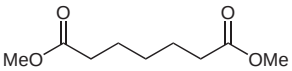
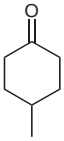
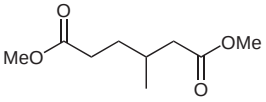
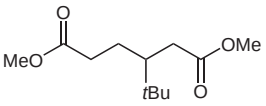
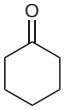
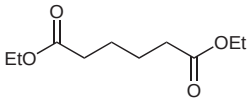
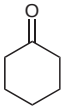
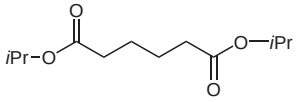
nosulfonyloxy cycloalkanone intermediates. Thus, the ring cleavage reactions of cycloalkanones were conducted in the one-pot reaction conditions by the in situ formation of α-[(2,4-dinitrobenzene)sulfonyl]oxy cycloalkanone intermediates from cycloalkanones and subsequent oxidation of the intermediates under present reaction conditions to provide diesters.[9] As shown in Table 1, the desired diesters were obtained in satisfactory yields in less than 3 h of reaction times. Replacing –ODNs group with –OTs leaving group by use of [hydroxy(tosyloxy)iodo]benzene, and HTIB[10] instead of HDNIB, dramatically reduced the yield of reactions as shown in the entries 1 and 2.

With regards to effects of ring size of cycloalkanones, there was no apparent difference in reactivity at present reaction conditions. In addition, varying alcohol solvents did not significantly alter the reactivity or yield when we performed oxidative cleavage reaction in the presence of ethanol or isopropyl alcohol by replacing methanol (entries 6 and 7). The oxidative ring cleavage reaction of α-[(2,4-dinitrobenzene)sulfonyl]oxy cycloalkanones with Oxone® presumably occurred by initial formation of α-diketones and successive ring opening reactions of α-diketones in analogy with what has been observed with oxidative cleavage of α-hydroxy ketones.[4]

In conclusion, present method clearly offers advantages over the method utilizing α-nitrocycloalkanones, particularly in view of the operational simplicity and use of readily available intermediates.

Table 1 Yields Oxidative Ring Cleavage Reaction of Cycloalkanones

Entry	Substrate	Diester	Yields (%)[a,b]
1			57, 20[c] (80)
2			68, 32[c] (90)
3			60 (92)
4			67 (90)
5			62 (90)
6			66 (95)
7			60 (85)

[a] Isolated yields.
[b] Yields in parantheses are obtained starting from α-[(2,4-dinitrobenzene)sulfonyl]oxy cycloalkanones.
[c] Yield obtained by replacing HDNIB with HTIB.

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(9) General experimental procedure: To a solution of ketone (1.0 mmol) in 20 mL of acetonitrile, [hydroxy(2,4-dinitrobenzenesulfonyloxy)iodo]benzene (HDNIB, 0.70 g, 1.5 mmol) was added and the reaction mixture was stirred for 1 h at reflux. The solvent was removed under reduced pressure. The resulting residue was dissolved in methanol (30 mL) and H_2O (5 mL). To the reaction solution, Oxone® (1.35 g, 2.20 mmol) and PTSA (0.19 g, 1.0 mmol) were added and the mixture was stirred for 2 h at 65 °C. The reaction mixture was filtered through pad of Celite, and organic solvent in filtrate was evaporated and the residue was extracted with ethyl acetate (2 × 30 mL), washed with H_2O (2 × 20 mL), and dried over $MgSO_4$. After evaporation of solvent, the residue was purified by flash column chromatography (SiO_2, ethyl acetate–hexane = 1:3) to give desired diester.
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