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Efficient Synthesis of Substituted Benzenes From 1,3-Dienes or 1,4-Cyclohexadienes With $KMnO_4$ Under Mild Conditions

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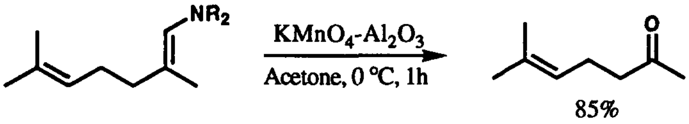
Abstract: Potassium permanganate absorbed on alumina is used to oxidize 1,4-cyclohexadienes to the corresponding aromatic compounds. Intermolecular Diels-Alder reactions followed by dehydrogenation of the products with potassium permanganate supported on alumina gives an efficient two step synthesis of highly substituted aromatic compounds from acyclic precursors.

In the last twenty years the use of potassium permanganate adsorbed onto solid supports has provided a mild heterogeneous oxidizing reagent. The initial studies indicated that impregnation of $KMn0_4$ onto molecular sieves, silica gel, or certain clays, allowed the oxidation of a number of alcohols to the corresponding ketones.[1] The solid oxidant $KMn0_4$-$CuS0_4(H_20)_5$, facilitates the conversion of secondary alcohols into ketones while primary alcohols and alkenes are unaffected.[2] Consequently, unsaturated alcohols can be converted into the corresponding carbonyl compounds readily.[3] An array of hydrated metal salts have also been used as solid supports each having a slightly different selectivity.[4] All of these methods have the advantage of isolating the product by a simple filtration. One study showed that solid supported potassium permanganate on silica gel could be used as a reagent to perform oxidations consistent with traditional permanganate chemistry but without using phase transfer catalysis or cyclic polyethers.[5] The selectivity and reactivity of the solid supported reagent is dependent on the support and the amount of water present. It is now possible to synthesize aldehydes from alkenes and diketones from alkynes using supported permanganate oxidations.[6,7]

We have recently shown that an alumina supported potassium permanganate reagent oxidativly cleaved β,β-disubstituted enamines to give ketones containing one less carbon atom.[8] Alkynes, nitriles and secondary alcohols were unaffected by this reagent and it selectively cleaved electron rich enamine alkenes without touching other alkenes of difunctional substrates as illustrated in (eq. 1).



(1)

We speculated that, since the alumina supported potassium permanganate readily cleaved the electron rich enamine carbon double bond, enol ethers might also be oxidatively cleaved. Therefore we investigated the reactivity of 1-methoxy-1,4-cylohexadiene with alumina supported potassium permanganate at 0 °C in acetone. Expecting oxidative cleavage of the enol carbon double bond to give aliphatic methyl Z-hex-3-ene-6-al-carboxylate, we were surprised to find that the only product was the methoxy substituted benzene, anisole.[9]

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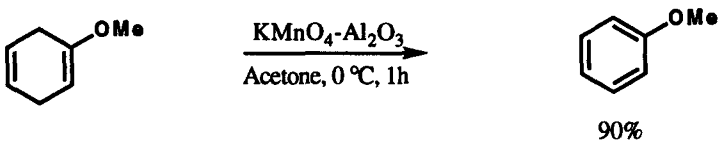
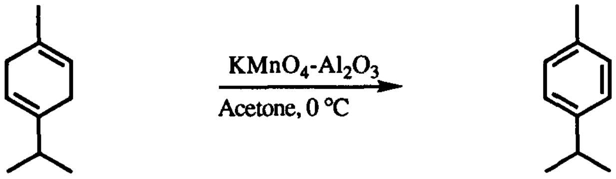
Furthermore, the product anisole could be isolated in 90% yield by a simple filtration and evaporation of the solvent acatone (eq. 2).



(2)

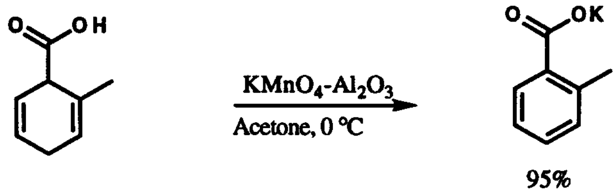
The most well known method for the dehydrogenation of 1,4-cyclohexadienes is catalytic dehydrogenation in liquid or gas phase over a Pd catalyst which requires temperatures typically exceeding 300° C.[10] 1-Methoxy-1,4-cylohexadiene can be converted into anisole through the reaction of its anion with benzaldehyde.[11] Some highly substituted 1,3- or 1,4-cyclohexadienes are effectively dehydrogenated by manganese dioxide in refluxing benzene.[12] Nonconjugated cyclohexadienes have been aromatized by $KMnO_4$ in benzene with an equimolar amount of dicyclohexyl-18-crown-6.[13] When Hantzsch 1,4-dihydropyridines are treated with $KMnO_4$-Al_2O_3 in refluxing water and benzene (1:2) solvent system, aromatization takes place in 6 hours.[14] Our method of aromatizing 1-methoxy-1,4-cylohexadiene with $KMnO_4$-Al_2O_3 is extremely mild procedure and nicely compliments the existing methods of aromatization of cyclohexadienes.

In order to test the generality and versatility of our reagent for making aromatic compounds, various 1,3- and 1,4-cyclohexadienes containing several functional groups, such as enol ether, acids and esters, were selected so that the sensitivity of this aromatization procedure to these functional groups could be tested. Both 1,4-cyclohexadiene as well as 1-methyl-1,4-cyclohexadiene underwent rapid aromatization with alumina supported potassium permanganate and afforded benzene and toluene respectively in practically quantitative yields. Similarly, γ-Terpinene reacted readily with $KMnO_4$-Al_2O_3 and gave *p*-cymene at ambient reaction conditions (eq. 3).



(3)

It is important to note that since permanganate oxidations generate hydroxide, any carboxylic acid products are present in the solution as carboxylate ions. Thus, oxidation of 1,4-dihydro-2-methylbenzoic acid produced potassium *o*-toluate in essentially quantitative yield. The product was isolated by filtering the reaction mixture and washing the filter cake with ether to remove any non-acidic products. The filter cake was washed with water and the aqueous filtrate was acidified to isolate *o*-toluic acid (eq. 4). A summary of the oxidations performed is given in Table I.



(4)

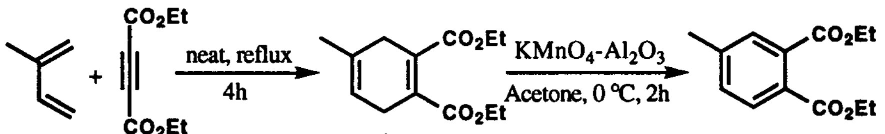
Table I: Oxidations of 1,4-Cyclohexadienes to Form the Corresponding Aromatics

Diene Substrate		%Yield^a of aromatics	mmol KMnO4 : Substrate
1,4-Dihydroanisole		80^b	1.5
γ-Terpinene		95^b	1.0
1,4-Dihydrobenzene		90^b	2.0
1-Methyl-1,4-cyclohexadiene		95^b	2.0
1,4-Dihydrobenzoic acid		85	1.5
1,4-Dihydro-2-methylbenzoic acid		90	1.5
Diethyl 4-methyl-1,4-cyclohexadiene-1,2-dicarboxylate	(1)	80	2.0
Diethyl 3-methoxymethyl-1,4-cyclohexadiene-1,2-dicarboxylate	(2)	70	2.0
Diethyl 4,5-dimethyl-1,4-cyclohexadiene-1,2-dicarboxylate	(3)	75	2.0

^{a}Yields are isolated unless otherwise noted. ^{b}Yield determined using internal standard (mesitylene)

Attempts to perform the same aromatization reactions on 1,3-cyclohexadienes were not as fruitful. For example, the oxidation of α-terpinene gave a mixture of products, including a great deal of unreacted substrate and the corresponding aromatic *p*-cymene.

A promising application of our mild aromatization reaction is the synthesis of aromatic compounds with novel substitution patterns unavailable by either electrophilic or nucleophilic substitution reactions. The preparation of 1,4-cyclohexadienes via Diels-Alder reactions and their oxidation to substituted aromatic compounds should provide a route to aromatic compounds with substitution patterns that are difficult to achieve by traditional methods. This tandem route to substituted metacyclophanes has been carried out using DDQ for the dehydrogenation step.[15] To demonstrate the application of our mild dehydrogenation procedure, diethyl 4-methyl-*o*-phthalate was prepared in two steps starting from acyclic substrates. Thus, when isoprene was allowed to react with diethyl acetylenedicarboxylate, a Diels-Alder reaction provided diethyl 4-methyl-1,4-cyclohexadiene-1,2-dicarboxylate. Oxidation of this diene using alumina supported potassium permanganate, under very mild reaction conditions, afforded diethyl 4-methyl-*o*-phthalate in 70% isolated yield (eq. 5).



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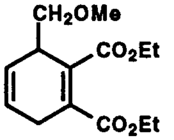
70% isolated yield

(5)

Similarly, substituted 1,4-cyclohexadienes 2 and 3 were prepared from diethyl acetylenedicarboxylate and 1-methoxy-2,4-pentadiene and 2,3-dimethyl-1,3-butadiene respectively. Dehydrogenation of these cyclohexadienes using potassium permanganate supported on alumina provided a convenient two-step pathway to the benzenes with substitution patterns which are difficult to obtain by conventional methods.



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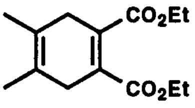

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In conclusion, potassium permanganate, when supported on alumina and used in acetone, reacts very differently than potassium permanganate in aqueous solution. Intermolecular Diels-Alder reactions followed by dehydrogenation of the products with potassium permanganate supported on alumina gives an efficient two step synthesis of highly substituted aromatic compounds from acyclic precursors. These heterogeneous reactions are run at 0 °C, in air, and allow the simple and convenient workup procedures associated with supporte reagents.

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9. **General procedure for the oxidation of 1,4-cyclohexadienes:** Alumina is dehydrated by heating to 400° C while stirring over a Bunsen burner for 15 minutes. Following cooling in a dessicator, the alumina is ground together with potassium permanganate (3 mmol $KMn0_4$ / g reagent) in a mortar and pestle. The diene was dissolved in technical grade acetone and cooled to 0° C in a 50-mL roundbottom flask previously dried in an oven. The $KMn0_4$ • Al_20_3 reagent was added in small portions over 15 minutes using a spatula. After two hours the cooling bath was removed and the mixture was allowed to warm to room temperature, then filtered through 3 mm of Celite and the filter plug was washed with ether. Upon drying over magnesium sulfate and evaporating the solvent, the corresponding aromatic compound was obtained.
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