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A QUICK ONE-POT SYNTHESIS OF LACTONES FROM CYCLIC ETHERS USING SILICA MEDIATED POTASSIUM DICHROMATE

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ABSTRACT

A novel method for synthesis of lactones from cyclic ethers using $K_2Cr_2O_7$, and H_2SO_4 as catalyst in presence of silica is reported. The $K_2Cr_2O_7$, H_2SO_4, and silica are stirred at room temperature in dichloromethane, followed by addition of ether compounds provide lactones in 60-70% yield. The reaction takes place under mild condition, and easy to operate.

KEYWORDS: Heterocycles, Multi-component reactions, Spiroindoline, One-pot synthesis.

INTRODUCTION

Lactones are a class of important heterocyclic compounds which have been well documented throughout the literature for its use as flavours and fragrances,[I] and occur in many of pharmacologically important molecules.[II] Many compounds with lactone moiety are responsible for the characteristic flavor of many type of food products, the most common include coumarine with the scent of fresh hay and jasmine lactone with a sweet floral scent.1 During the process of maturation of wines and other alcoholic beverages while stored in oak casks, it releases 4-n-butyl-5-methyl-γ-lactone, known as whiskey lactone.1 Extensive effort has been expended in the search for efficient processes to synthesis these compounds.

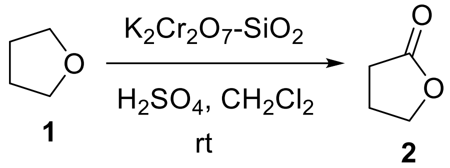
The most common methodologies adopted for the synthesis of lactones are C-H oxidation of cyclic ethers using DIB/TBHB,[III] cobalt with molecular O2,[IV] KMnO4,[V] RuO4,[VI]siloxide complexes of chromium(II) and chromium(IV),[VII] Iron catalyst,[VIII] H_2O_2 with Br_2,[IX] Cu(II) complexes with H_2O_2,[X] Cu along with tert-butyl hydroperoxide,[XI] using catalysts like, H_3PO_5,[XII] Iridium complexes,[XIII] Mn_2O_7,[XIV] or dehydration of corresponding hydroxy acids. In most of these cases, H_2O_2 is used in stoichiometric quantity or O_2 along with different metal catalysts are used for oxidation. The handling of H_2O_2 needs precautions, its storage may lead to the decomposition, and a commercial scale has several disadvantages owing to its inherent instability. Crabtree et. al has reported oxidation of tetrahydrofuran to corresponding lactone by using Iridium complex.[XIII] Tetrahydrofurans can be oxidised to lactones by using

CrO_3/trimethylsilylylnitrate,[XV] as reported by Vankar and co-workers.

Limberg and co-workers has reported conversion of tetrahydrofuran to lactone by using siloxide Complexes of Chromium(II) and Chromium(IV).[VII]

H_2SO_4-SiO_2 is an efficient and recyclable solid catalyst. This solid catalyst is used for many organic transformations and its simple to operate.[XVI] Herein we report a new method for synthesis of lactones in a single step from cyclic ethers by using $K_2Cr_2O_7$, and H_2SO_4 as catalyst in presence of silica. silica-promoted $K_2Cr_2O_7$oxidation, leading to C-H oxidation adjacent to the oxygen in the ether ring.

We envisioned that silica promoted $K_2Cr_2O_7$ can be the preferred reagent for many commercially manufactured lactones, thus making their handling and storage more suitable. Our main effort was directed towards exploring the possibility of using silica along with modified Jones reagent (CrO_3/H_2SO_4).[XVII] We started our feasibility study for the silica mediated oxidation reactions of cyclic ethers feasible in the presence of $K_2Cr_2O_7$ (in place of CrO_3), H_2SO_4, and silica.



Scheme 1. Synthesis gamma Butyrolactone from THF using silica media.

A model oxidation reaction of THF to form gama butyrolactone was selected for this investigation (Scheme 1). As a first step, without using silica and various amounts of silica were screened to find suitable conditions for the reaction (Table 1). Based on prior experience, all screening experiments were performed using dichloromethane as the solvent at room temperature with 1.0 equivalents of silica (Table 1). The reaction

did not work out without silica. The conversion of starting material and formation of product were determined by GC-MS. The products identified by comparing GC-MS with authentic samples.$K_2Cr_2O_7$ is a well-known good oxidizing agent. Using 1-2 moles of silica firstly adsorbing sulphuric acid on silica, the adsorbed sulfuric acid and $K_2Cr_2O_7$complex will react with the substrate. As evident from Table 1, silica played major role in the reaction conversion THF to gama butyrolactone.

EXPERIMENTAL SECTION

Chemicals and apparatus

All solvents were of commercial grade, Reagents were purchased from major commercial sources and without further purification. GC-MS Agilent(EI), NMR analysis was done on 300-600MHz and the chemical shift was referenced to residual solvent peak. Products of oxidation of THF,methylTHF,tetrahedropyran,1,4-dioxane,3-phenyltetrahydrofuran,2-(3-methoxyphenyl) tetrahydrofuran, 3-butyltetrahydrofuran, 2-oxabicyclo[3.2.1]octane,oxepane, 4-ethyloxepane,4-phenyloxepane, and N-methyl morpholine were confirmed by comparing the GC-MS with reported literature. The THF oxidation product gamma butyrolactone was confirmed by 1NMR, 13NMR which matches with literature.

General experimental procedure

A In 250 ml RBF charged silica(10.0 g, 0.166 mol), dichloromethane(50 mL), sulfuric acid (0.012 g, 0.001 mol), stirred for 10 min, then added THF(10 ml, 0.123 mol) into the RBF, stirred for 10 min. Then potassium dichromate (54.27g, 0.184 mol) was added, stirred at RT for overnight. The reaction mass was filtered, and the organic layer was quenched with sodium bicarbonate (2 g, 0.023 mol), stirr for 1-2 hrs at RT. Finally, the reaction mass was filtered, and dichloromethane layer was distilled under vaccum. The crude mass was purified by using flash chromatography. The desired product 2a was eluted by using ethylacetate:petether (20:80). 1H NMR (500MHz, CDCl3) δ 4.3 (t, J =7.1Hz, 2H), 2.5 (t, J = 8.2Hz, 2H), 2.2 (m, 2H). 13C NMR (125MHz,CDCl3) δ 177.5, 68.2, 27.3, 21.7; GC-MS Calculated C4H6O2: 86.09, Found:86.
All products were characterized by GC-MSand ^{1}H NMR spectra(**5a-n**).

Synthesis of gamma valerolactone(2b)[2]

GC-MS Calculated $C_5H_8O_2$: 100.05, Found:100.0.1H-NMR(500MHz,DMSOd6)4.56-4.63(m,1H),2.47–2.52(m,2H),2.26–2.28(m,1H),1.72-1.76(m,1H),1.29-1.30(d,3H).13CNMR(500MHz,DMSOd6)20.58,28.50,29.04,76.65,176.95.

Synthesis of delta valerolactone(2c)[3]

GC-MS Calculated $C_5H_8O_2$:100.05 , Found:100.2.
1H-NMR(500MHz,dMSOd6)4.24-4.26(t,2H),2.43–2.46 (t,2H),1.72-1.80(m,4H).13CNMR(500MHz,DMSOd6)18.34,21.69,29.34,68.69,171.00.

Synthesis of 1,4-dioxane-2-one(2d)[4]

GC-MS Calculated $C_5H_8O_2$:102.03, Found:102.0.
1H-NMR(500MHz,DMSOd6)4.41-4.43(m,2H),4.32 (s,2H),3.82-3.84(m,2H).13CNMR(500MHz,DMSOd6)166.99,68.52,65.58,61.91.

Synthesis of 5-cyano phthalide(2e)[5]

1H- NMR(500MHz,DMSO-d6)8.2(s,1H),8.02(s,2H),5.47(s,2H)
13C NMR (500 MHz,DMSO-d6)
169.20,147.63,132.72,128.86,127.43,125.90,117.95,116.05,69.88.

Synthesis of 5-bromo phthalide(2f)[6]

GC-MS Calculated $C_8H_5BrO_2$:211.95 , Found:211.9.
1H-NMR(400MHz,CDCl3)7.67(m,2H),7.78 (m,1H),5.31(s,2H).13CNMR(400MHz,CDCl3)124.68,125.55,126.98,129.24,132.66, 148.19, 169.97.

Synthesis of 2-coumaranone(2g)[7]

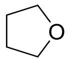
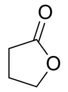
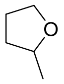
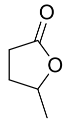
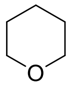
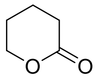
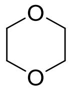
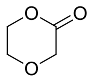
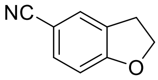
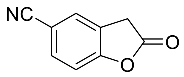
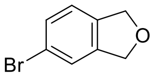
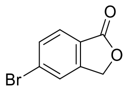
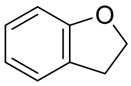
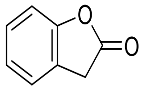
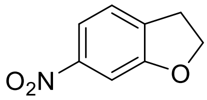
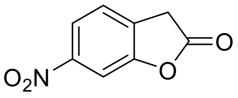
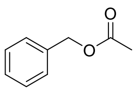
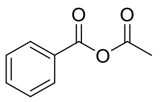
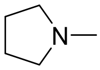
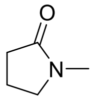
1H- NMR(500MHz,DMSO-d6)8.6(dd,1H),8.52(d,1H),7.97(d,1H),5.57(s,2H).
13C NMR (500 MHz,DMSO-d6)
174.42,154.12,128.28124.82,124.34,123.77,110.11,32.60.

Synthesis of 6-Nitro phthalide(2h)[8]

GC-MS Calculated $C_8H_5NO_4$:211.95 , Found:211.9.
1H-NMR(400MHz,CDCl3)7.67(m,2H),7.78 (m,1H),5.31(s,2H).13CNMR(400MHz,CDCl3)124.68,125.55,126.98,129.24,132.66, 148.19, 169.97

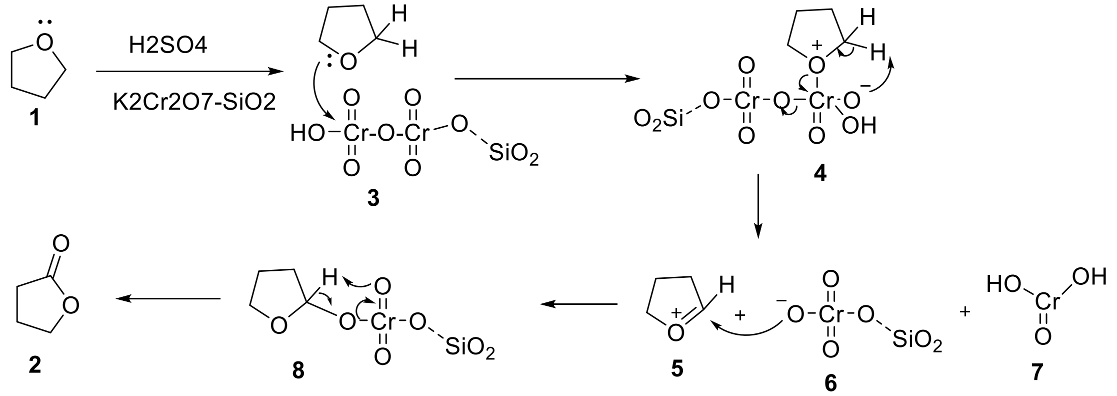
RESULTS AND DISCUSSION

Table1: Substrates study of the $K_2Cr_2O_7$, SiO_2-mediated oxidation.

S.No	Reactant	Product	SiO_2[1]	T[2] h	$K_2Cr_2O_7$ (moles)[3]	Conversion (%)
1	 **1a**	 **2a**	0.0	24	1.5	0
			1.0	24		60
2	 **1b**	 **2b**	0.0	24	1.5	0
			1.0	24		60
3	 **1c**	 **2c**	0.0	24	1.5	0
			1.0	24		50
4	 **1d**	 **2d**	0.0	24	1.5	0
			1.0	24		60
5	 **1e**	 **2e**	0.0	24	1.5	0
			1.0	24		50
6	 **1f**	 **2f**	0.0	24	1.5	0
			1.0	24		60
7	 **1g**	 **2g**	0.0	24	1.5	0
			1.0	24		60
8	 **1h**	 **2h**	0.0	24	1.5	0
			1.0	24		60
9	 **1i**	 **2i**	0.0	24	1.5	0
			1.0 to 2.0	48		0
10	 **1j**	 **2j**	0.0	24	1.5	0
			1.0	24		0

[1] These reactions all carried out using 1 equivalent of silica in dichloromethane.
[2] Reaction conversion time for all the above reactions taking nearly same as above mentioned for complete conversion.
[3] $K_2Cr_2O_7$ ratio for all the reactions nearly equal and conversion is ~100% with this.

Scheme-2. Plausible mechanism for oxidation of cyclic ethers to lactones.



The first step involves addition of ether **1** to chromium atom of **3**. The formed oxyanion will abstract the proton attached to the ortho carbon atom of cyclic ether to get the intermediate **4**, which is similar to Etard reaction.[XV] Then the chromate intermediate **6** will attack the electrophillic carbonyl carbon of intermediate **5**,[XIX] and followed by elimination to provide the desired lactone **2**.

This reaction describes a new method for synthesis of lactones. It is easy to handle, mild reaction condition, and can be applied for industrial process too. This work shows that silica played major role in the oxidation of cyclic ethers with $K_2Cr_2O_7$ to lactones.

Table 2 : Validation of $K_2Cr_2O_7$, SiO_2-mediated oxidation

Entry	Silica (eq.)	$K_2Cr_2O_7$ (eq.)	Reaction time(h)	Temp (°C)	conversion (%)[1]
1	0.5	1.0	24	rt	20
2	1.0	1.0	24	rt	40
3	1.0	1.0	48	rt	40
4	1.0	1.5	24	rt	60
5	1.0	1.5	12	rt	40
6	0.0	1.5	24	rt	0

[1] Determined by GC-MS analysis

CONCLUSION

This reaction describes a new method for synthesis of lactones. It is easy to handle, mild reaction condition, and can be applied for industrial process too. This work shows that silica played major role in the oxidation of cyclic ethers with $K_2Cr_2O_7$ to lactones.

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