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Oxidative Rearrangement *via* Oxycerication with Ce(IV) Salt

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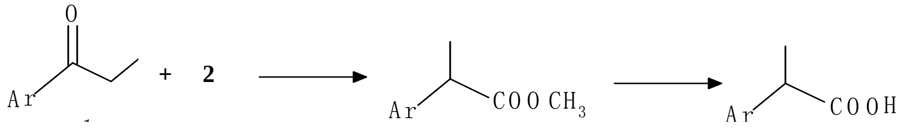
Abstract: A mild and reliable procedure for the preparation of α-arylpropanoic acids from arylpropanone by Ce(IV) salt oxidative rearrangement is discribed.

Keywords: Oxidative rearrangement, α-arylpropanoic acids, Ce(IV) salt.

α-Arylpropanoic acids are pharmaceutically interesting compounds, some of them exhibit anti-flammatory and analgestic activities[1]. Even the enormous progress made in the synthesis of α-arylpropanoic acids by 1,2-aryl rearrangement of arylpropanone using thalium (III) nitrate[1,2], silver (I) compounds,[3,4] lead (IV) acetate[5,6] and iodinate[7] during the last decades. The route is, however, unsuitable for the preparation of pharmaceutical products (Naproxen, Ibuprofen and so on) because of the high toxicity of the oxidants, and the development of oxidative-catalyzed rearrangement remains a challenging area of research.

We now report that the facile synthesis of methyl α–arylpropanoates from aryl ethylketones using Ce(IV) salt oxidative reagents. The reaction is performed by treatment of ketones **1** with reagent **2** in trimethyl orthoformate as shown in **scheme**. After the mixture was stirred for 2 h **3** was formed, yield 70-98% according to GLC analysis of the crude reaction product, cerium (IV) being almost completely reduced to cerium (III) by titration of **KI-$Na_2S_2O_3$**. Remarkably, the process can be performed more smoothly under higher temperature and with a higher yield of **3**, and **$(NH_4)Ce(NO_3)_4$** is more effective than that of **$(NH_4)Ce(SO_4)_2 \cdot 6H_2O$**. Furthermore when the two salts adsorbed on K-10 montmorillonite clay, the reaction proceeded more rapid, selective and the yield is higher than at room temperature. The **Ce(IV)**/K-10 reagent is readily prepared by stirring K-10 with a solution of **Ce(IV)** salt in a mixture of ethanol and trimethyl orthoformate followed by evaporation to dryness. The resulting pale-yellow, free-flowing powder was stored in wellcapped bottles for months.

Scheme



1 **3** **4**

Experimental

*Synthesis of methyl α-arylpropanoate **3b***

A suspension mixture of **1b** (1.35g, 0.01mol), **$(NH_4)Ce(NO_3)_4$** (0.05mol), 70% perchloric acid (4.3ml, 0.01mol) and trimethyl orthoformate (30ml) was stirred at 25℃ until a starch iodide test for **Ce (IV)** salt was negative. The products were isolated by removing of the spent reagent system by filtration, the filtrate was washed with aqueous sodium bicarbonate, then water, dried over silica, evaporation of the solvent, the residue was recrystallized with $CHCl_3$ or distilled.

*Synthesis of α-arylpropanoic acids **4b***

A mixture of **3b** (2.2g, 0.01mol) and ethanol (30ml), 30% NaOH solution (30ml) was heated under reflux for 3 h until the reaction mixture becomes clear and cooled solution was acidified with concentrated hydrochloric acid to precipitate a white solid which was recrystallized from hexane to give the pure acid **4b**. m.p.75-76℃. (Ref.[4], 75-76℃）.

Table The yield of α-arylpropanoate **3**

compound	Regent **2**	Reac. time/ min	Yield of **3** (%)	IR($CHCL_3$) $V_{C=0}$ M.S.(*m/z*)M+	1HNMR(80MHz,$CDCl_3$ /TMS_{INT}) σ（*ppm*),J(*Hz*)
3a Ar= σ-methoxy-naphthyl	$(NH_4)Ce(NO_3)_4$	15	52	1720cm^{-1}	1.49(d,J=7.5,3H)
	$(NH_4)Ce(SO_4)_2 \cdot 6H_2O$	15	44		3.62(s,3H);3.70(s,3H)
	$(NH_4)Ce(NO_3)_4$/K-10	12	70	244	3.65(q,J=7.6,1H)
	$(NH_4)Ce(SO_4)_2 \cdot 6H_2O$/K-10	10	58		7.01-7.35(m,12H)
3b Ar=4-isobutylphenyl	$(NH_4)Ce(NO_3)_4$	20	46	1725 cm^{-1}	0.90(d,J=6.5,6H)
	$(NH_4)Ce(SO_4)_2 \cdot 6H_2O$	25	38		1.50(d,J=7.5,3H)
	$(NH_4)Ce(NO_3)_4$/K-10	16	64		1.8(m,1H);3.43(d,J=7,2H)
	$(NH_4)Ce(SO_4)_2 \cdot 6H_2O$/K-10	18	50	220	3.62(s,3H)
					3.65(q,J=7.5,1H)
					6.96-7.28(m,4H)
3c Ar=4-Biphenyl	$(NH_4)Ce(NO_3)_4$	30	49	1722cm^{-1}	1.50(d,J=7.5,3H)
	$(NH_4)Ce(SO_4)_2 \cdot 6H_2O$	30	40		3.62(s,3H)
	$(NH_4)Ce(NO_3)_4$/K-10	20	60		3.66(q,J=7.6,1H)
	$(NH_4)Ce(SO_4)_2 \cdot 6H_2O$/K-10	18	42	240	6.89-7.15(m,4H)
					7.19-7.40(m,5H)
3d Ar=naphthyl	$(NH_4)Ce(NO_3)_4$	16	53	1723cm^{-1}	1.48(d,J=7.5,3H)
	$(NH_4)Ce(SO_4)_2 \cdot 6H_2O$	17	49		3.62(s,3H);3.70(s,3H)
	$(NH_4)Ce(NO_3)_4$/K-10	10	62		3.66(q,J=7.6,1H)
	$(NH_4)Ce(SO_4)_2 \cdot 6H_2O$/K-10	10	51	214	6.95-7.45(m,7H)

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