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3-ACYL-2-OXAZOLONE-ZIRCONIUM COMPLEXES AS EXCELLENT REAGENTS FOR HIGHLY REGIOSELECTIVE ACYLATION OF POLYALCOHOLS

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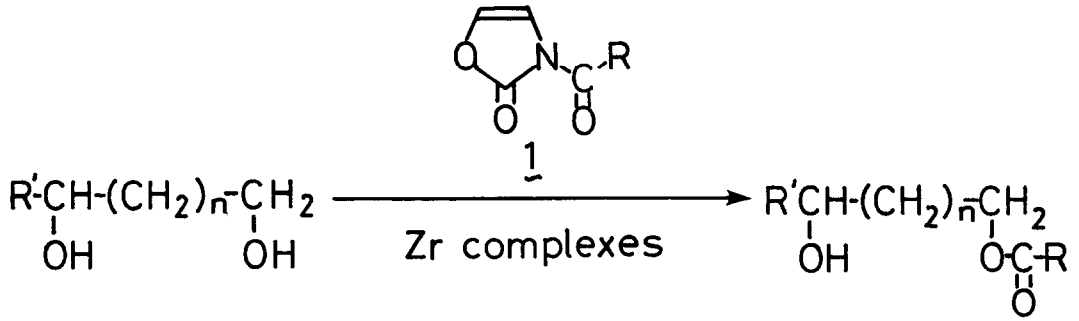
Summary: In combination with 3-acyl-2-oxazolones, zirconium complexes such as zirconium acetylacetonate and zirconocene chloride hydride-Mg serve well as effective catalysts for regioselective acylation of polyalcohols including 1,2-diols to permit highly preferential protection of primary hydroxyl groups.

Regioselective acylation of di- and polyhydroxyl compounds including nucleosides and carbohydrates is of great value as a fundamental process in a wide scope of chemical conversions. Several methods for this purpose have been developed[2-5], and only few are satisfactory to perform high selectivity in acylation of 1,2- and 1,3-diol systems, which might cause facile intramolecular migration of acyl groups.

In previous papers[6,7], we introduced 3-acyl-2-oxazolones (1), readily available from carboxylic acids and DPPOx[7], as a versatile acylating reagent of amines and thiols to give peptides and thioesters. This type of compounds was, however, nearly unreactive toward hydroxyl groups to permit selective N-acylation of aminoalcohols[7]. We have now found that certain zirconium complexes serve well as an effective catalyst for highly preferential acylation of primary hydroxyl groups of polyalcohols by 3-acyl-2-oxazolones (1) under quite mild conditions.



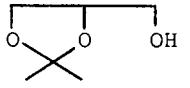
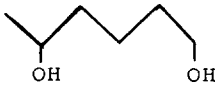
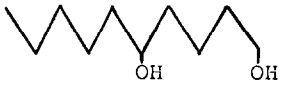
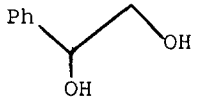
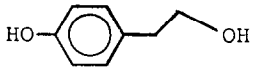
Thus, 1,5-hexanediol was treated with excess 3-acetyl-2-oxazolone (1) ($R=CH_3$) in the presence of catalytic amounts of zirconium acetylacetonate [$Zr(acac)_4$] at room temperature to give 88% yield of 1-monoacetate in addition to 8% of 1,5-diacetate. The 5-monoacetate was not detectable. The selectivity was enhanced to the mono to dibenzoate ratio of 49:1 by the use of benzoyl derivative (1) ($R=C_6H_5$). Among metallic salts examined so far, $Zr(acac)_4$ or zirconocene chloride hydride(Cp_2ZrHCl)-Mg couple was a catalyst of choice for regioselective acylation of primary alcohols by acyl-oxazolides(1). In competitive acylation of phenethyl alcohol and 1-phenyl-2-propanol, the latter catalytic system gave the phenethyl acetate in nearly 100% selectivity, while the selectivity by $Zr(acac)_4$ was 96%. Acid labile tert-Boc and acetal groups were completely unaffected under these conditions (Table). Coupled metal salts such as $PdCl_2$-Mg[8] or -Zn, $SnCl_2$-Mg[8] , $FeCl_3$-Mg and $CuCl_2$-Mg were also effective for protection of primary hydroxyl groups under an inert atmosphere in less regioselectivity, while Lewis acids such as $AlCl_3$ and $ZrCl_4$ or CsF may be counted as non-regioselective catalysts. In the acylation of vicinal diol systems, Cp_2ZrHCl-Mg was much superior to $Zr(acac)_4$, which deposited insoluble complexes within a few hours. Even in the 1,2-diols such as phenylglycol, of which regioselective acylation was difficult by the conventional ways due to facile migration of acyl groups, the use of such Zirconium catalysts gave primary alkyl ester in over 92% selectivity, suggesting a versatile utility in carbohydrate chemistry.

Reactivity toward oxazolone reagents was in an order of primary >> phenolic > secondary hydroxyl groups, when $Zr(acac)_4$ was used as a catalyst, while the combination of (1) ($R=CH_3$) and $PdCl_2$-Mg gave the order of primary = phenolic >> secondary hydroxyl groups. Thus, β-estradiol gave the 3-acetate (83%) predominantly in the acetylation catalyzed by $PdCl_2$-Mg.

The present reagent system may be advantageous over the reagents previously developed in the terms of high regioselectivity, mildness of the conditions and simple handling procedure, though mechanistic details should await further investigation.

The preparation of 5-hydroxyhexyl benzoate provides a typical procedure: A solution of $Zr(acac)_4$(0.1g, 0.20mmol), 3-benzoyl-2-oxazolone(0.38g, 2.0mmol) and 1,5-hexanediol(0.12g, 1.0mmol) in dichloromethane(2ml) was stirred at 25° for 68h. The reaction mixture was chromatographed on silica gel to afford 5-hydroxyhexyl benzoate(0.20g, 90%). Nmr spectrum showed the formation of dibenzoate in less than 2% yield.

Table. Acylation of Alcohols by 3-Acyl-2-oxazolones(1) in the Presence of Zirconium Complexes[a]

Alcohol	Catalyst	Solvent	Time	Total Yield[b]	Product Ratio monoAc[c] : diAc
$PhCH_2CH_2$-OH	None	CH_3CN	24h	0%	
	$Zr(acac)_4$	CH_3CN	17	94	
	Cp_2ZrHCl	CH_3CN	17	14	
	Cp_2ZrHCl-Mg[d]	CH_3CN	17	87	
t-BocNH-$(CH_2)_5$-OH	$Zr(acac)_4$	CH_2Cl_2	40	85	
	$Zr(acac)_4$	CH_2Cl_2	22	86	
	$Zr(acac)_4$	CH_2Cl_2	23	96	92 : 8
	e)	pyridine	23	99	58 : 42
	$Zr(acac\text{-}F_3)_4$	CH_3CN	39	70	96 : 4
	$Zr(acac)_4$	CH_2Cl_2	68	91[f]	98 : 2
	$Zr(acac)_4$	CH_3CN	22	87	94 : 6
	$Zr(acac)_4$	CH_2Cl_2	16	84	94 : 6
	Cp_2ZrHCl-Mg[d]	CH_3CN	19	84	92(6)[g] : 2
	$Zr(acac)_4$	Et_2O	39[h]	77	92 : 8

a) These reactions were carried out with 1.5 equiv. of 3-acetyl-2-oxazolone(1)(R=CH_3) in the presence of the Zr complexes(0.2 equiv.) at r.t. b) Yield of acetates. c) Primary alkyl ester. d) Cp_2ZrHCl(0.2 equiv.) and Mg(2 equiv.) were used under Ar. e) Ac_2O(1.5 equiv.)-pyridine were used as an acylating reagent. f) Benzoyl esters : This reaction was carried out with 3-benzoyl-2-oxazolone(2 equiv.). g) Secondary alkyl ester. h) At 0°.

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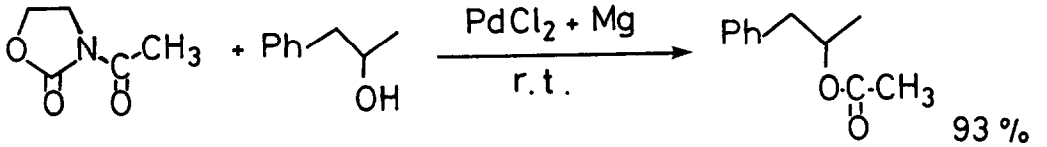
8. These couples also catalyzed acylation of alcohols by 3-acyl-2-oxazolidones to afford esters in good yields.



The catalyst systems may be applied to alcoholysis of chiral 3-acyl-2-oxazolidones derived from the method of Evans[9].

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