equipped with a data station. Substrate concentrations were approximately 10^{-5} mol dm^{-3}, and the substrate was added as a concentrated solution in 10^{-5} dm^3 of acetonitrile to a volume of 2.5 10^{-3} dm^3 of the aqueous solution. Rate constants were obtained by recording the change in absorbance at 273 nm at pH 3 for about 10 half-lives. The end value method was used to calculate the rate constants. All measurements were done in triplicate, and the rate constants were found to be reproducible to within 2% for the aqueous solutions of monosaccharides and to within 3% for the aqueous solutions of disaccharides.

Product Analysis. The reaction mixtures were analyzed for the presence of carbohydrate-derived esters. Aqueous solutions of D-glucose, D-galactose, and methyl β-D-glucopyranoside were employed. In a typical experiment 10^{-3} M of the substrate was hydrolyzed in the presence of 0.01 mol kg^{-1} of carbohydrate. The small concentration of carbohydrate is necessitated by experimental limitations. After the hydrolysis had gone to completion, the mixture was freeze-dried. The samples were silylated with hexamethyldisilazane–chlorotrimethylsilane–pyridine (1:1:5) for 30 min at room temperature. Combined GLC and GLC/MS experiments showed that no carbohydrate-derived esters had been formed.

Gas–Liquid Chromatography. GLC was performed on a Varian 3700 gas chromatograph equipped with a capillary SE-30 fused silica column (25 m, 0.32 mm, Pierce) and FID. The oven temperature was programmed from 130 to 220 °C at 4 °C per min. The injector temperature was 210 °C. The detector temperature was 230 °C.

Gas–Liquid Chromatography/Mass Spectrometry. Combined GLC–MS was performed on a Carlo-Erba GC/Kratos MS 80/Kratos DS 55 system; electron energy, 70 eV; accelerating voltage, 2.7 kV; ionizing current, 100 μA; ion source temperature, 225 °C; capillary CP sil 5 column (25 m, 0.32 mm); oven temperature program, 140 °C during 2 min, 140–260 °C at 4 °C per min.

Through-Space Oxygen Distances. The through-space oxygen distances (Table IV) were obtained by introducing the crystallographic data from the Cambridge Crystallographic Database into a CHEMX program.[42]

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Supplementary Material Available: Pseudo-first-order rate constants for the hydrolysis of 1 in aqueous solutions of carbohydrates at 298 K (3 pages). Ordering information is given on any current masthead page.

(42) CHEMX, developed and distributed by Chemical Design Ltd. Oxford, England.

Cobalt(II) Chloride Catalyzed Acylation of Alcohols with Acetic Anhydride: Scope and Mechanism

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Cobalt(II) chloride catalyzes the acetylation of a variety of alcohols with acetic anhydride in excellent yield. Primary hydroxyl groups can be selectively acylated in the presence of secondary and tertiary ones while the secondary hydroxyl groups can be preferentially acetylated in the presence of tertiary ones. Tertiary alcohols have been found to give ketones, acetoacetates, olefins, and diketene in addition to the acetate. The β-hydroxy esters and ketones can be acylated under these conditions without any elimination, and this reaction has been compared with 4-(dimethylamino)pyridine (DMAP)-mediated acylations where elimination of the resulting β-acetoxy carbonyl compound is observed. A detailed investigation of the acylation of tertiary alcohols has revealed that these reactions proceed via a tertiary alkoxy radical and ketene. A mechanism for these acylations is proposed by invoking an electron-transfer process.

Introduction

The acylation of alcohols by acetic anhydride or acetyl chloride is very routinely carried out[1,2] with amine bases such as triethylamine, pyridine, or 4-(dimethylamino)-pyridine (DMAP). In these reactions the base is considered to provide activation[2b,3] to the acylating reagent (nucleophilic activation) whereas in some cases the base, e.g., triethylamine, is mainly used to trap the generated acid. Primary and secondary alcohols can be very easily acylated with acetic anhydride by using pyridine or triethylamine whereas the tertiary alcohols show very little tendency to undergo acylations in presence of these bases. However, the acylation of tertiary alcohols can be efficiently carried out in the presence of DMAP.[2] When we attempted to acylate a β-hydroxy carbonyl compound using the protocol followed in the DMAP method, a mixture of the acetate and α,β-unsaturated carbonyl compound was obtained (Table II). This may be attributed to the basic medium which causes elimination of the resulting acetate. To circumvent this problem, the acylation under nonbasic conditions seemed an attractive alternative although this has received little attention[4] in the past. This consideration for selectivity prompted us to search for a Lewis acid-based acylation catalyst, and in a preliminary communication we have shown[5] that cobalt(II) chloride is

(1) (a) Verley, A.; Bosling, F. *Ber.* **1901**, *34*, 3354. (b) Einhorn, A.; Hollandt, F. *Liebigs Ann. Chem.* **1898**, *301*, 95. (c) Fitton, A. O.; Hill, J. *Selected Derivatives of Organic Compounds*; Chapman Hall: London, 1970.

(2) (a) Hofle, G.; Steglich, W.; Vorbruggen, H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 569. (b) Scriven, E. F. V. *Chem. Soc. Rev.* **1983**, *12*, 129.

(3) Butler, A. R.; Gold, V. *J. Chem. Soc.* **1961**, 4362.

(4) (a) Mukaiyama, T.; Pai, F.; Onaka, M.; Narasaka, K. *Chem. Lett.* **1980**, 563. (b) Posner, G. H.; Oda, M. *Tetrahedron Lett.* **1981**, *22*, 5003.

(5) Ahmad, S.; Iqbal, J. *J. Chem. Soc., Chem. Commun.* **1987**, *114*.

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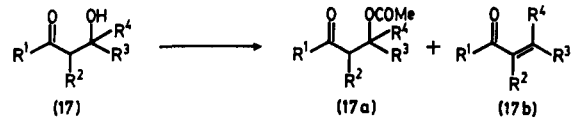
Table I. Cobalt(II) Chloride Catalyzed Acylation of Primary and Secondary Alcohols

entry	alcohols	reaction conditions			acetate (% yield)[a,b]
		Ac_2O (equiv)	temp (°C)	time (h)	
1	1-butanol (1)	2.	25.	2	**1a** (92)
2	benzyl alcohol (2)	2.	25.	4	**2a** (98)
3	cyclohexanemethanol (3)	2.	25.	2	**3a** (78)
4	(*E*)-3-buten-1-ol (4)	2.	25.	3	**4a** (90)
4	(*E*)-cinnamyl alcohol	2.	25.	4	**5a** (82)
6	2-phenyl-4-penten-1-ol	2.	25.	8	**6a** (100)
7	cyclohexanol (7)	2.	80.	3	**7a** (88)
8	(−)-menthol (8)	2.	80.	2	**8a** (89)[c]
9	cholesterol (9)	2.5	80	3	**9a** (69)
10	D-glucose (10	10.	80.	6	**10a** (75)[d]
11	1-phenylethanol (11)	2.5	80.	2	**11a** (95)
12	1-phenylpropanol (12)	2.	80.	2	**12a** (92)
13	1-phenyl-3-buten-1-ol (13)	2.	80.	3	**13a** (90)
14	6-hepten-3-ol (14)	2.	80.	4	**14a** (72)[e]
15	1-(phenylthio)-2-butanol (15)	2.	80.	4	**15a** (96)
16	methyl 2-allyl-3-hydroxybutanoate (16)	2.	80.	6	**16a** (72)[f]

[a] Yield of isolated product. [b] Biacetyl (5–10%) was formed in most of the reactions. [c] Some loss in the optical activity was observed. [d] Only pentaacetate was formed under these conditions. [e] Tetrahydrofuran **14b** was also obtained in minor amounts. [f] Tetrahydrofuran **16b** was obtained in minor amounts.

Table II. Cobalt(II) Chloride Catalyzed Acetylation of β-Hydroxy Carbonyl Compounds Compared with DMAP Method



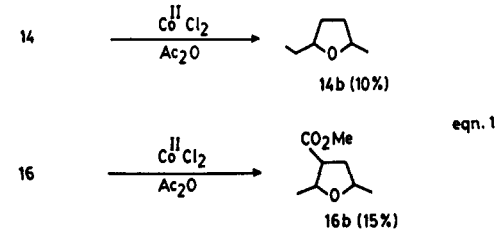
entry	R^1	R^2	R^3	R^4	reaction conditions[b]	product(s) (% yield)
1	Ph	H	H	Me	A	**17a** (78)
2	Ph	H	H	Me	B	**17a** (63) + **17b** (27)
3	Ph	Me	H	Me	A	**17a** (83)
4	Ph	Me	H	Me	B	**17a** (59) + **17b** (25)
5	Me	H	H	H	A	**17a** (89)
6	Me	H	H	H	B	**17a** (67) + **17b** (21)
7	Me	H	H	Me	A	**17a** (87)
8	Me	H	H	Me	B	**17a** (53) + **17b** (28)
9	Me	H	Me	Me	A	**17a** (89)
10	Me	H	Me	Me	B	**17a** (45) + **17b** (33)
11	EtO	H	H	Ph	A	**17a** (72)
12	EtO	H	H	Ph	B	**17a** (52) + **17b** (18)
13	MeO	C_3H_5	H	Me	A	**16a** (95)
14	MeO	C_3H_5	H	Me	B	**17b** (83)

[a] Isolated yield of the acetylated products. [b] Condition A: $CoCl_2$, 80 °C, Ac_2O (2 equiv), 3–4 h. Condition B: DMAP–Et_3N, room temperature, 3–4 h.

an efficient catalyst for the acylation of alcohols, amines and thiols. A systematic study of cobalt(II) chloride catalyzed acylation has revealed that these reactions, in some cases, may be proceeding via a nonionic pathway involving free radicals. This paper describes a detailed account of these acylations along with a proposed mechanism.

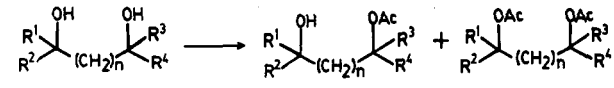
Results

It has been shown earlier[5] that primary, secondary, and tertiary alcohols are efficiently acylated with acetic anhydride in the presence of catalytic quantity of cobalt(II) chloride in acetonitrile at ambient temperature or at 80 °C. The quantity of acetic anhydride is quite crucial to the success of acylation; when the molar amounts of alcohol and acetic anhydride are equal the yield of acetate is low and it is accompanied by unchanged alcohol and some byproducts. However, the yield of the acetate can be increased by using 2 equiv of acetic anhydride. The results for the acylation of primary and secondary alcohols are compiled in Table I. A small amount (5–10%) of biacetyl is also obtained in all the acylations. Primary alcohols do not require any heating, while secondary alcohols require heating to 80 °C. The optically active alcohols like (−)-menthol and D-glucose are acylated with ease although some loss in their optical activity is observed in the recovered alcohols and acetate. The olefinic alcohols 14 and 16 (Table I) on acylation with 1 equiv of acetic anhydride gave tetrahydrofurans **14b** and **16b**, respectively, in minor amounts (eq 1) although no such cyclization was observed with alcohol 6.



Cobalt(II) chloride catalysed acylations are particularly useful for acylating β-hydroxy carbonyl compounds. A comparative study of these acylations with DMAP-mediated acylation[2] has shown that the later method yields a mixture of α,β-unsaturated carbonyl compound and the acetate on acylation of β-hydroxy carbonyl compounds. On the other hand the acylations conducted under the catalysis of cobalt(II) chloride did not show the presence of any eliminated product (Table II, entries 1, 3, 5, 7, 9, 11).

Table III. Cobalt(II) Chloride Catalyzed Selective Acylation of Hydroxy Compounds

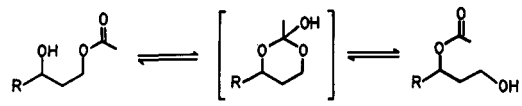


(18) (18a) (18b)

entry	R^1	R^2	R^3	R^4	reaction conditions: Ac_2O (equiv)	temp (°C)	time (h)	products[a] (% yield)
1, n = 1	Me	H	H	H	1	80.	2	**18a** (21) + **18b** (23)
2, n = 1	Me	H	H	H	2.5	80.	3	**18b** (72)
3, n = 2	Me	H	H	H	1	80.	2	**18a** (45)
4, n = 2	Me	H	H	H	2.5	80.	4	**18b** (81)
5, n = 1	Ph	H	H	H	1	80.	3	**18a** (31) + **18b** (27)
6, n = 1	Ph	H	H	H	2.5	80.	3	**18b** (87)
7, n = 2	Ph	H	H	H	1	80.	4	**18a** (53)
8, n = 2	Ph	H	H	H	3	80.	3	**18b** (79)
9, n = 1	Me	Me	Me	H	1	80.	4	**18a** (72)
10, n = 1	Me	Me	Me	H	3	80.	5	**18b** (79)
11, n = 2	Me	Me	H	H	1	80.	4	**18a** (62)
12, n = 2	Me	Me	H	H	2.5	80.	5	**18b** (77)

[a] Yield of the isolated products.

Scheme I



This method is also suitable for the selective acylation of a primary or secondary hydroxy group in the presence of a tertiary one as evidenced by the formation of monoacetate by employing 1 equiv of acetic anhydride (Table III). In the same manner a primary alcohol can be completely acylated in the presence of a secondary one (Table III, entries 3 and 7). In contrast, no selectivity was observed between a primary and secondary hydroxy group of a 1,3-diol (e.g. butane-1,3-diol) when the reaction was carried out at 80 °C (Table III, entries 1 and 5). The 1,3-diols do not undergo selective monoacylation as they yield a mixture of mono- and diacylated product by treatment with 1 equiv of acetic anhydride. The indiscriminate acylation in these diols can be explained if the acylation of secondary hydroxyl group is taking place by an intramolecular migration of the acetyl group from the primary acetate via a six-membered cyclic intermediate (Scheme I). The later assumption was proved by isolating a mixture of **18a** and **18b** on reacting monoacetate **18a** (n = 1) with cobalt(II) chloride in acetonitrile at 60 °C. However, in case of 1,4-diols the primary hydroxy group can be selectively acetylated in preference to the secondary one (Table III, entries 3 and 7). Similarly, D-glucose underwent smooth pentaacetylation (Table I, entry 10) but was not subject to the selective monoacylation of the primary hydroxy group instead a mixture of di- and triacetates was obtained.

The acylation of tertiary alcohols give rise to some minor byproducts along with the expected acetate in low yield. Thus, tertiary alcohols derived from acetophenone (Table IV, entries 1–6) show a strong tendency to eliminate and yield the corresponding olefin (Table IV, entries 1, 3, 4, 5, and 6). Surprisingly, diketene and the acetoacetates derived from corresponding alcohol were obtained as minor byproducts in some reactions (Table IV, entries 1, 2, 7, 11, and 19). Biacetyl is formed in varying amounts (5–10%) in the acylation of all the tertiary alcohols mentioned in Table IV, and its yield increased with the increase in the quantity of acetic anhydride used for acylation. Acetophenone is obtained as a byproduct in the acylation of alcohols **19**, **23**, and **27**. Similarly, cyclic tertiary alcohols gave the corresponding ketone as a minor product along with the expected acetate (Table IV, entries 7–20). The cyclic alcohols also underwent ring cleavage to give acyclic ketones in small amounts (Table IV, entries 8, 10, 12, 18, and 20). However, no such cleavage was observed in case of alcohol **42**, and it was smoothly converted to the corresponding acetate in excellent yield. It is also interesting to note that the formation of byproducts can be increased by decreasing the quantity of acetic anhydride as shown in Table IV.

The formation of rather unusual products clearly show that these reactions may be proceeding via a nonionic pathway, and the following section deals with the mechanistic interpretation based on these results.

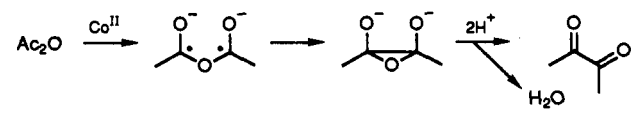
Discussion

The role of cobalt(II) chloride in these reactions seems to be quite unusual as a careful analysis of the reaction mixture has revealed the presence of byproducts that cannot be derived by a typical ionic process. The presence of biacetyl, ketene, olefin, and acetoacetates clearly suggests that these reactions may be proceeding partially, if not completely, via a nonionic pathway. In the light of this assumption a plausible explanation for the formation of these byproducts can be offered as given below.

(a) Formation of Biacetyl. It has already been shown[6] that cobalt(II) chloride in acetonitrile reacts with acetic anhydride to give biacetyl. The formation of biacetyl can be explained[7a] by electron transfer[7b] from cobalt(II) complex to acetic anhydride leading to the formation of a radical anion **51** (Scheme II). The anion **51** may yield the acetyl radical **52** which will eventually give biacetyl **53**. There is no precedent in the literature for the formation of acetyl radical from acetic anhydride-metal interaction although it is clear that an ionic process will not convert the acetic anhydride into biacetyl.

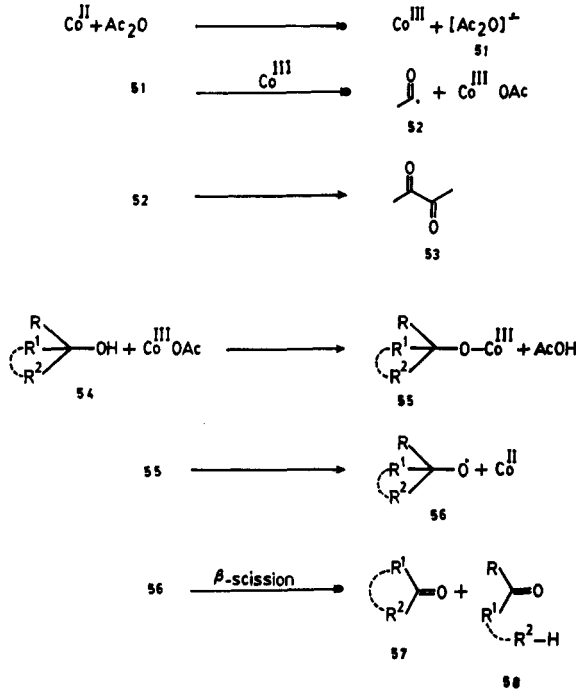
(b) Formation of Ketones. The formation of ketones from secondary and tertiary alcohols have been observed

(6) Ahmad, S.; Iqbal, J. *J. Chem. Soc., Chem. Commun.* **1987**, 692.
(7) (a) The editor has suggested an acyloin type mechanism for the formation of biacetyl from acetic anhydride as shown below:

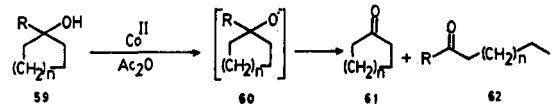


(b) The formation of biacetyl is also observed when these acylations are carried out with acetyl chloride.

Scheme II



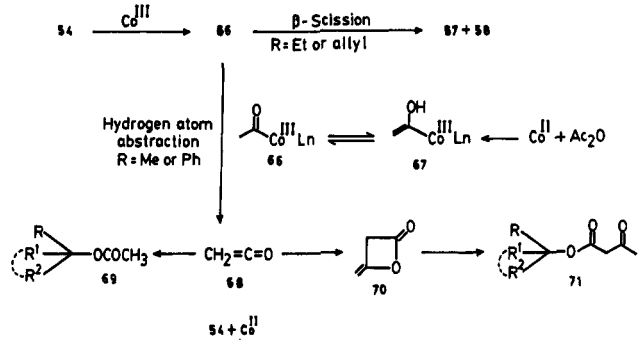
Scheme III



during a metal-mediated oxidation[8] of alcohols. Cobalt(III) complexes are known to oxidize alcohols to the corresponding ketones via an alkoxy radical, and based on this precedent, the formation of ketones can be explained in the following manner.

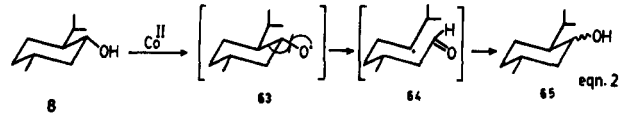
The oxidation of alcohols by metal oxidants commonly proceeds[8a,b] through an innersphere complex, followed by a rate-limiting homolytic cleavage of oxygen–metal bond. Thus, the cobalt(III) complex, obtained as shown in Scheme II, can cleave the oxygen–hydrogen bond in alcohols **54** to give a oxygen–cobalt(III) complex **55** and acetic acid. The complex **55** can undergo a homolytic cleavage to give an alkoxy radical **56** and cobalt(II) complex (Scheme II). It is known from the previous studies that alkoxy radicals generated from alkyl hydroperoxide or alcohols with cobalt(II) complex are sufficiently long-lived to allow β-scission to compete[9] with hydrogen transfer and reduction. Therefore, the alkoxide **56** may lead to the formation of ketone **57** and **58** via β-scission followed by hydrogen atom abstraction. The selectivity in the carbon–carbon bond cleavage of alkoxy radicals follows the stability of the liberated alkyl radical R$^{\bullet}$. The cyclic tertiary alcohols **59** undergo ring opening via a β-scission process to give cyclic and acyclic ketones (Scheme III).

Scheme IV



The nature of R group controls[9b,c] the mode of cleavage, as for R = Et or allyl, more of cyclic ketone **61** is obtained in these reactions (Table IV, entries 10, 14, 16, and 18), whereas for R = Me and Ph, acyclic ketones **62** are formed in preference to the cyclic ones (Table IV, entries 12 and 20). The pattern in carbon–carbon bond cleavage of the alkoxy radical is in agreement with the earlier findings.

If these reactions are proceeding via alkoxy radical, then the loss in optical activity of (−)-menthol (Table I, entry 8) during acylation can be explained as shown in eq 2. The



alkoxy radical **63** derived from (−)-menthol **8** may undergo β-scission to yield aldehydic radical **64**, which on ring closure will yield a mixture of alcohol **65**. The racemization[10] of optically active cyclic alcohol via an alkoxy radical is fairly well precedented in the literature. The formation of tetrahydrofurans **14b** and **16b** from olefinic alcohols **14** and **16** can be explained by the intermediacy of an alkoxy radical because such radicals are known[11] to undergo intramolecular cyclization with an olefin. However, their formation via an electrophilic cyclization[12] cannot be ruled out.

(c) Formation of Diketene, Acetoacetates, and Olefins. The presence of diketene **70** and acetoacetates (Table IV, entries 1, 2, 7, 11, and 19) clearly suggests that these reactions are proceeding via ketene formation. The presence of diketene in this reaction is quite intriguing although Chandrasekaran and co-workers[13] have shown earlier that ketene is formed from acetic anhydride 4-(dimethylamino)pyridine (DMAP)-mediated acylation of alcohols. In their case the presence of a base was responsible for the formation of ketene, whereas in this reaction its formation cannot be accounted for by a similar ionic process. It also seems quite unlikely that the mildly acidic medium of this reaction may cause the formation of ketene. The observation that the ketene **68** and the acetoacetates **71** (Scheme IV) are formed only during the acylation of tertiary alcohols suggests that the tertiary alcohols may be playing a role toward its formation. Also, since tertiary alcohols are oxidized to alkoxy radical during this reaction, it is conceivable that the alkoxy radicals may

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(9) (a) Kochi, J. K. *J. Am. Chem. Soc.* **1962**, *84*, 1193. (b) Walling, C.; Padwa, A. *J. Am. Chem. Soc.* **1963**, *85*, 1593. (c) Bacha, J. D.; Kochi, J. K. *J. Org. Chem.* **1965**, *30*, 3272. (d) Kochi, J. K. *Free Radicals*; Wiley: New York, 1973; Vol. II, p 686.

(10) (a) Nickon, A.; Iwadare, T.; McGuire, F. J.; Mahajan, J. R.; Narang, S. A.; Umezawa, B. *J. Am. Chem. Soc.* **1970**, *92*, 1688. (b) Spero, G. B.; Thompson, J. L.; Schneider, W. P.; Kagan, F. *J. Org. Chem.* **1963**, *28*, 755. (c) Tsang, R.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1986**, *108*, 8102.

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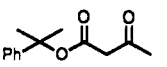
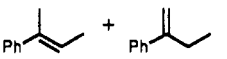
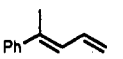
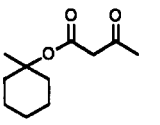
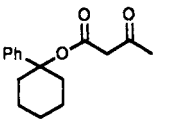
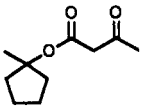
(12) (a) Corriu, R. J. P.; Lanneau, G. F.; Massee, J. P.; Samate, D. *J. Organomet. Chem.* **1977**, *127*, 281. (b) MacPhail, A. T.; Oran, K. D.; Lee, K. H.; Furokawa, H.; Piantadosi, C. *Tetrahedron Lett.* **1973**, 4641. (c) Irwin, M. A.; Geissman, T. A. *Phytochemistry* **1969**, *8*, 305.

(13) Bhushan, V.; Chakraborty, T. K.; Chandrasekaran, S. *J. Org. Chem.* **1984**, *49*, 3974.

Table IV. Cobalt(II) Chloride Catalyzed Acylation of Tertiary Alcohols

				reaction conditions			acetate	alkene	
entry	alcohols	R	no.	Ac_2O (eq)	temp (°C)	time (h)	(% yield)	(% yield)	other (% yield)
1		Me	**19**	2.0	25	8	**20** (35)	 **21** (40)	 **22** (10)
2				0.8			(20)	–	(10)[c] diketene (15)[g]
3		Et	**23**	2.0	50	8	**24** (31)	 **25** **26** (56)[f]	–
4				0.8		7	(20)	– (25)	(17)[c]
5		allyl	**27**	2.0	45	7	**28** (31)	 **29** (49)	–
6				0.8		8	(15)	–	(23)[c]
7		Me	**30**	2.0	80	12	**31** (65)	 **32** (10)	 **33** (19)
8				1.0			(21)	–	(12)[d]
9		Et	**34**	2.0	70	8	**35** (33)	–	(19)[d]
10				0.8			(10)	–	(25)[d]
11		C_6H_5	**36**	2.0	80	10	**37** (61)	 **38** (18)	 **39** (12)
12				1.0		12	(15)	–	phenyl pentyl ketone (13)
13		allyl	**40**	2.0	80	6	**41** (51)	–	(15)[d]
14				0.8		8	(23)	–	(19)[d]
15		alkynyl	**42**	2.0	70	2	**43** (91)	–	 **46** (17)
16		Me	**44**			10	**45** (73)	–	
17				0.8	70	12	(21)	–	(8)[e] 2-hexanone (11)
18		Et	**47**	2.0	70	8	**48** (52)	–	(19)[e]
19				0.8			(17)	–	(22)[e] 3-heptanone (8)
20		allyl	**49**	2.0	80		**50** (37)	–	(13)[e]
21				0.8		10	(17)	–	(21)[e]

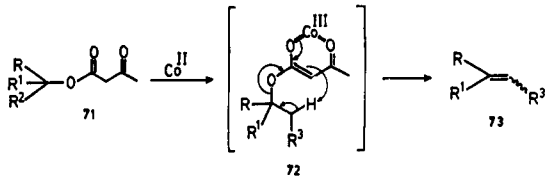
[a] Yield of the isolated products. [b] Biacetyl (5–10%) was formed in all the reactions. [c] Yield of acetophenone. [d] Yield of cyclohexanone. [e] Yield of cyclopentanone. [f] Combined yield of the olefins **25** and **26**(g) diketene is obtained by distillation on Kugherlhor.

be responsible for the formation of ketene. In view of this assumption, the formation of ketene may take place via a hydrogen atom abstraction from the acetyl–cobalt complex[14] **66** or its enol **67** by tertiary alkoxy radical **56** (Scheme IV). The complex **66** may result from acetic anhydride and cobalt(II) chloride according to Scheme II. The ketene thus generated can either acylate the alcohol to give esters or on dimerization will yield diketene **70** which will react with alcohol to give acetoacetates **71**. It is clearly evident from the results in Table IV that the ketene and the acetoacetate formation depends upon the structure of tertiary alcohol as the two competing[8d,e] pathways, β-scission and hydrogen atom transfer, are available to the resulting tertiary alkoxy radical. If the tertiary alkoxy radical has an ethyl and allyl group, then β-scission is a favored pathway and the acetate is obtained in low yield and the ketones **57** and **58** (Table IV, entries 3, 5, 6, 9, and 15) are obtained in comparatively higher amounts. On the other hand, if the alkoxy radical contains a methyl or phenyl group, then hydrogen atom transfer from the methyl group of the acetyl–cobalt complex **66** to the alkoxy radical becomes the predominant pathway. This leads to the formation of ketene which also dimerizes to diketene, and the alcohols react with them to give acetate **69** and acetoacetate **71**, respectively. The formation of olefins **73** during the acylation of alcohols (Table IV, entries 1, 3, 4, 5, 6, 7, and 11) may take place via the elimination of acetoacetates **71**. The acetoacetates are known to undergo[15] such elimination at higher temperature (100–150 °C); however, the presence of cobalt(II) may

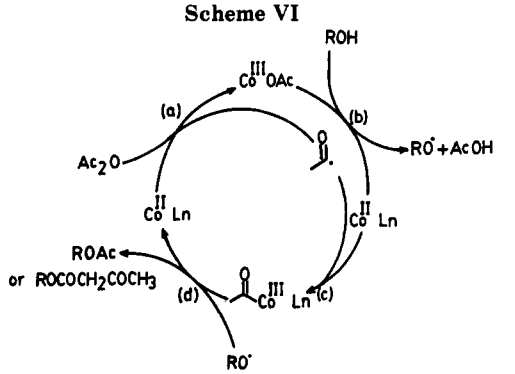
(14) For keto–enol form of acylcobalt complex, see: Francalanci, F.; Gardauo, A.; Abis, L.; Fiorani, T.; Foa, M. *J. Organomet. Chem.* **1983**, *243*, 87.

(15) Frisell, C.; Lawesson, S. O. *Ark. Kemi.* **1961**, *17*, 401.

Scheme V



Scheme VI



facilitate the process of elimination even at 60–80 °C via a cobalt–acetoacetate complex **72** (Scheme V).

The byproducts formed during the acylation of tertiary alcohols clearly suggests that these products cannot be obtained by an ionic process. In view of these observations the catalytic role of cobalt(II) chloride during the acylation of tertiary alcohols can be explained as shown in Scheme VI. Thus, cobalt(II) complex may transfer an electron to acetic anhydride (path a) leading to the formation of cobalt(III) complex and an acetyl radical. The cobalt(III) complex can oxidize the alcohol (path b) to give an alkoxy radical and regenerate a cobalt(II) complex which may react with the acetyl radical (produced in path a) to yield acetyl–cobalt(III) complex (path c). The acetyl–cobalt(III) complex may be attacked by the alkoxy radical (path d) to yield ester and acetoacetate as described in Scheme IV.

In conclusion, the acylation of primary and secondary alcohols with acetic anhydride can be efficiently catalyzed by cobalt(II) chloride in acetonitrile. However, tertiary alcohols can be acylated in moderate yield only because these reactions are complicated by the formation of artifacts derived from tertiary alcohols and acetic anhydride. A detailed investigation of the products in the reaction mixture has revealed that the acylation of tertiary alcohols may be proceeding via an alkoxy radical and ketene.

Experimental Section

Materials and Methods. ^{1}H NMR spectra were recorded at 60, 80, or 90 MHz in $CDCl_3$ or CCl_4. The identity of the minor products was confirmed by comparing them with the retention times of authentic samples on HPLC. Acetonitrile and acetic anhydride were purified by the standard procedure.[16] $CoCl_2$ was purchased from LOBA India Ltd., Bombay, and dried at 120 °C for 2–3 h before the reaction. Flash chromatography was performed by using Acme TLC silica gel. The secondary and tertiary alcohols were prepared by the reaction of carbonyl compounds with Grignard reagents.

General Procedure for the Acylation of Alcohols. Alcohol (10 mmol) and acetic anhydride (20 mmol) were added to a stirred solution of anhydrous $CoCl_2$ (5 mol %) in anhydrous acetonitrile (50 mL). The mixture was stirred at rt under N_2 (for primary alcohols) or heated to 60–80 °C (for secondary and tertiary alcohols) for 2–12 h. The solvent was evaporated in vacuo, and the residue was dissolved in ether. The ether layer was washed successively with saturated aqueous NH_4Cl (3 × 20 mL), $NaHCO_3$ (3 × 25 mL), and water (3 × 20 mL). Drying ($MgSO_4$) and evaporation of solvent gave the crude product, which was purified by flash chromatography on silica gel or by Kugelrohr distillation.

Methyl 2,5-Dimethyltetrahydrofuran-3-carboxylate (16b). This compound was prepared from **16** (2.2 g, 14 mmol), acetic anhydride (2.85 g, 28 mmol), and $CoCl_2$ (30 mg). The crude product was chromatographed over silica gel and yielded **16b** (0.33 g, 15%): IR (CH_2Cl_2) 1732 cm^{-1}; ^{1}H NMR (CCl_4) 4.09 (m, 1 H), 3.81 (m, 1 H), 3.71 (s, 3 H), 1.51 (m, 1 H), 1.37 (m, 2 H), 1.23 (d, 3 H, J = 7 Hz), 1.18 (d, 3 H, J = 7 Hz). Anal. Calcd for $C_8H_{14}O_3$: C, 60.75; H, 8.86. Found: C, 60.83; H, 8.92.

3-Acetoxybutyrophenone (17a; R^1 = Ph, R^2 = R^3 = H, R^4 = Me). Reaction of **17** (R^1 = Ph, R^2 = R^3 = H, R^4 = Me) (1.64 g, 10 mmol) with $CoCl_2$ (30 mg) and acetic anhydride (2 g, 20 mmol) by the above described procedure followed by column chromatography on silica gel gave 1.6 g (78%) of **17a**: IR (thin film) 1730, 1700 cm^{-1}; ^{1}H NMR ($CDCl_3$) 6.89–7.45 (m, 5 H), 4.59 (m, 1 H), 2.78 (d, 2 H, J = 6.9 Hz), 2.17 (s, 3 H), 1.19 (d, 3 H, J = 7 Hz). Anal. Calcd for $C_{12}H_{14}O_3$: C, 60.29; H, 6.79. Found: C, 60.35; H, 6.82.

3-Acetoxy-2-methylbutyrophenone (17a; R^1 = Ph, R^2 = R^3 = Me, R^4 = H). Reaction was performed as described above with **17** (R^1 = Ph, R^2 = R^3 = Me, R^4 = H) (0.89 g, 5 mmol), acetic anhydride (1 g, 10 mmol), and $CoCl_2$ (30 mg) at 80 °C for 4 h. Flash chromatography of the crude product yielded 0.90 g (83%) of **17a** (R^1 = Ph, R^2 = R^3 = Me, R^4 = H): IR (CH_2Cl_2) 1732, 1698 cm^{-1}; ^{1}H NMR ($CDCl_3$) 7.05–7.56 (m, 5 H), 4.65 (m, 1 H), 2.81 (m, 1 H), 2.12 (s, 3 H), 1.21 (m, 6 H). Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.9; H, 7.27. Found: 71.12; H, 7.36.

4-Acetoxy-4-methylpent-2-one (17a; R^1 = R^3 = R^4 = Me, R^2 = H). This compound was prepared as described above from **17** (R^1 = R^4 = Me, R^2 = R^3 = H) (1.22 g, 12 mmol), acetic anhydride (2.5 g, 25 mmol), and $CoCl_2$ (30 mg) at 80 °C for 2 h, in 87% (1.5 g) yield: IR (CCl_4) 1735, 1730 cm^{-1}; ^{1}H NMR ($CDCl_3$) 2.96 (s, 2 H), 2.11 (s, 3 H), 1.93 (s, 3 H), 1.30 (s, 6 H). Anal. Calcd for $C_8H_{14}O_3$: C, 61.53; H, 8.86. Found: C, 60.75; H, 8.66.

Ethyl 3-Acetoxy-3-phenylpropionate (17a; R^1 = OEt, R^2 = R^3 = H, R^4 = C_6H_5). Reaction was performed as described above with **17** (R^1 = OEt, R^2 = R^3 = H, R^4 = C_6H_5) (0.98 g, 5 mmol), acetic anhydride (1 g, 10 mmol), and $CoCl_2$ (40 mg) at 70 °C for 3 h. Chromatography of the crude product yielded 0.85 g (72%) of **17a**: IR (thin film) 1735, 1730 cm^{-1}; ^{1}H NMR ($CDCl_3$) 7.19–7.51 (m, 5 H), 5.97 (t, 1 H, J = 7 Hz), 4.19 (q, 2 H, J = 6.9 Hz), 2.81 (d, 2 H, J = 7.5 Hz), 1.98 (s, 3 H), 1.19 (t, 3 H, J = 5.9 Hz). Anal. Calcd for C H O: C, 66.10; H, 6.78. Found: C, 66.22; H, 6.87.

Methyl 2-(1′-Acetoxyethyl)pent-4-enoate (16a; R^1 = OMe, R^2 = C_3H_5, R^3 = H, R^4 = Me). This compound was prepared as described above by the reaction of **17** (R^1 = OMe, R^2 = C_3H_5, R^3 = H, R^4 = Me) (0.7 g, 4.4 mmol), acetic anhydride (1 g, 10 mmol), and $CoCl_2$ (30 mg) at 80 °C for 5 h in 95% (0.95 g) yield: IR (thin film) 1733, 1730 cm^{-1}; ^{1}H NMR (CCl_4) 5.59 (m, 1 H), 4.59 (m, 1 H), 4.97 (m, 2 H), 4.36 (m, 1 H), 3.62 (s, 3 H), 1.96–2.77 (m, 3 H), 1.89 (s, 3 H), 1.05 (d, 3 H, J = 7 Hz). Anal. Calcd for $C_{10}H_{16}O_4$: C, 60.00; H, 8.00. Found: C, 59.89; H, 7.94.

4-Acetoxy-2-methylpentan-2-ol (18a; R^1 = R^2 = R^3 = Me, R^4 = H, n = 1). This compound was prepared as described above by reacting **18** (R^1 = R^2 = R^3 = Me, R^4 = H, n = 1) (0.68 g, 5.8 mmol), acetic anhydride (0.6 g, 5.8 mmol), and $CoCl_2$ (35 mg) at 80 °C for 4 h in 72% (0.67 g) yield; IR (thin film) 3436, 1730 cm^{-1}; ^{1}H NMR (CCl_4) 4.35 (m, 1 H), 1.96 (s, 3 H), 1.89 (d, 2 H, J = 6.8 Hz), 1.21 (d, 3 H, J = 7 Hz), 1.19 (s, 3 H), 1.16 (s, 3 H). Anal. Calcd for $C_8H_{16}O_3$: C, 60.00; H, 10.00. Found: C, 59.78; H, 9.87.

4-Acetoxy-1-phenylbutan-1-ol (18a; R^1 = Ph, R^2 = R^3 = R^4 = H, n = 2). This compound was prepared as described above by reacting **18** (R^1 = Ph, R^2 = R^3 = R^4 = H, n = 2) (0.84 g, 5 mmol), acetic anhydride (0.5 g, 5 mmol), and $CoCl_2$ (35 mg) at 80 °C for 4 h followed by column chromatography (SiO_2) in 53% (0.53 g) yield: IR (CH_2Cl_2) 3467, 1732 cm^{-1}; ^{1}H NMR (CCl_4) 7.05–7.51 (m, 5 H), 4.93 (t, 1 H, J = 6.9 Hz), 4.48 (t, 2 H, J = 7 Hz), 1.89 (s, 3 H), 1.37–1.76 (m, 4 H). Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.23; H, 7.69. Found: C, 69.37; H, 7.72.

1,4-Diacetoxy-1-phenylbutane (18b; R^1 = Ph, R^2 = R^3 = R^4 = H, n = 2). The reaction was carried out as described above

(16) *Vogel's textbook of Practical Organic Chemistry*, 4th ed.; ELBS: England, 1984.

by reacting **18** (R^1 = PH, R^2 = R^3 = R^4 = H, n = 2) (1.67 g, 10 mmol), acetic anhydride (3 g, 30 mmol), and $CoCl_2$ (~20 mg) at 80 °C for 3 h. The crude product upon column chromatography yielded **18b** (1.9 g, 79%): IR (thin film) 1733, 1729 cm^{-1}; ^1H NMR ($CDCl_3$) 6.95–7.59 (m, 5 H), 5.41 (t, 1 H, J = 6.9 Hz), 4.52 (t, 2 H, J = 7 Hz), 1.89 (s, 3 H), 1.97 (s, 3 H), 1.43–1.83 (m, 4 H). Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.20; H, 7.20. Found: C, 67.29; H, 7.31.

1′,1′-Dimethylbenzyl 3-Oxobutanoate (22). The reaction was carried out as described above with **19** (2.72 g, 20 mmol), acetic anhydride (4 g, 40 mmol), and $CoCl_2$ (30 mg) at 25 °C for 8 h. The crude product upon column chromatography yielded **22** (0.44 g, 10%). The ^1H NMR of this product was compared with an authentic sample prepared according to ref 13.

1′-Methylcyclohexyl 3-Oxobutanoate (33). The reaction was carried out as described above with **30** (1.70 g, 15 mmol), acetic anhydride (3 g, 30 mmol), and $CoCl_2$ (35 mg). The crude product upon flash column chromatography yielded **33** (0.55 g, 19%). This product was compared with an authentic sample[13] as described above.

1′-Phenylcyclohexyl 3-Oxobutanoate (39). The reaction was carried out as described above with **36** (2.1 g, 12 mmol), acetic anhydride (2.5 g, 25 mmol), and $CoCl_2$ (40 mg). The crude product upon flash column chromatography yielded **39** (0.37 g, 12%) as a semisolid: IR (CH_2Cl_2) 1733, 1727 cm^{-1}; ^1H NMR ($CDCl_3$) 6.97–7.52 (m, 5 H), 3.48 (s, 2 H), 2.08 (s, 3 H), 1.27–1.89 (m, 10 H). Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.84; H, 7.69. Found: C, 73.71; H, 7.55.

1′-Methylcyclopentyl 3-Oxobutanoate (46). The reaction was carried out as described above with **44** (1.5 g, 15 mmol), acetic anhydride (3 g, 30 mmol), and $CoCl_2$ (30 mg). The crude product upon flash chromatography yielded **46** (0.46 g, 17%): IR (CH_2Cl_2) 1735, 1727 cm^{-1}; ^1H NMR (CCl_4) 3.37 (s, 2 H), 2.09 (s, 3 H), 1.39–1.92 (m, 8 H), 1.21 (s, 3 H). Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.22; H, 8.69. Found: C, 65.30; H, 8.73.

Two New Approaches to the 25-Hydroxy-vitamin D_2 Side Chain

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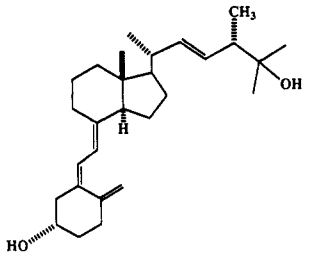
Two approaches to the 25-hydroxy-vitamin D_2 side chain have been developed based on the solvolysis of cyclopropylcarbinyl precursors. The first involves addition of trimethylcyclopropyllithium reagent **4** to a suitably protected C/D system **9**. This reaction leads directly to cyclopropylcarbinols **10a,b** which can be solvolyzed to the vitamin D_2 side chain directly. The second approach uses an intermediate C/D system with a side chain allylic alcohol. Cyclopropanation of the allylic alcohol using Et_2Zn/CH_3CHI_2 produces the same type of cyclopropylcarbinols **10a,b** but in differing isomer ratios. Model studies and stereochemical differences in the two approaches are discussed.

The biological significance and possible uses of 25-hydroxy-vitamin D_2 (**1**) and its metabolites continues to expand.[1] Recent discoveries of the role of vitamin D metabolites in cell differentiation, cell proliferation, and the immune system have prompted renewed interest in synthetic routes.[2] While a classic[3] synthesis of the vitamin D_2 side chain appeared some years ago, several new approaches have recently been reported[4] for the synthesis of 25-OH-D_2 or 1,25-$(OH)_2$-D_2. Nonetheless, good methods for the production of 25-hydroxy side chain isomers are still needed.



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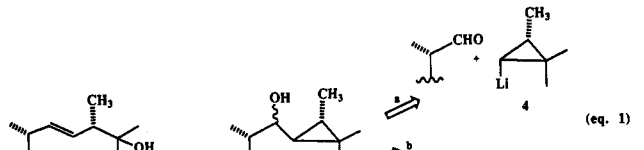
Our own examination of the 25-hydroxy-vitamin D_2 side chain revealed the following retrosynthetic transformations (eq 1). The solvolysis of a cyclopropane such as **3** would produce in one step the vitamin D_2 side chain. The stereocenter at C-24 is created during the cyclopropanation



(eq. 1)

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