Catalytic radical acetylation of adamantanes with biacetyl by a cobalt salt under atmospheric dioxygen

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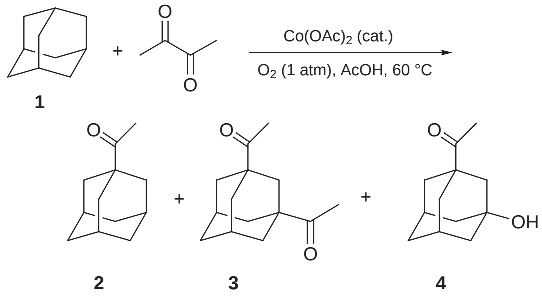
Exposure of a mixture of adamantane and biacetyl under O_2 in the presence of $Co(OAc)_2$ (0.1 mol%) in AcOH led to 1-acetyladamantane (47%) and 1,3-diacetyladamantane (20%) as major products along with small amounts of adamantan-1-ol (4%) and adamantan-2-one (3%).

The introduction of an acyl group to alkanes is one of the most difficult transformations in organic synthesis. Until recently, there have been a few reports on the acetylation of cycloalkanes under irradiation of light or by using a radical initiator such as benzoyl peroxide.[1–4] Although the catalytic acetylation of alkanes is of interest and would be more useful in organic synthesis, such a method has not yet been developed. Here, we report the first successful catalytic radical acetylation of adamantanes using biacetyl as an acetylating agent by a cobalt salt under O_2 atmosphere [eqn. (1)].



(1)

Table 1 shows the results for the acetylation of adamantane **1** with biacetyl under various conditions.† The acetylation of **1** with biacetyl in the presence of $Co(OAc)_2$ (0.1 mol%) and O_2 (1 atm) in AcOH at 60 °C for 2 h gave 1-acetyladamantane **2** (47%), 1,3-diacetyladamantane **3** (20%) and 3-acetyladamantan-1-ol **4** (6%) along with several oxygenated products such as adamantan-1-ol **5** (4%) and adamantan-2-one **6** (3%) (run 1). Photoacetylation of **1** with biacetyl is reported to form **2** in 13.8% under N_2 and 40% under O_2, but no diacetyl compound **3** is formed.[1] Therefore, our reaction provides an efficient catalytic method for the synthesis of acetyl derivatives of **1** which are technically interest compounds. When the acetylation was carried out for 4 h, **3** was obtained in preference to **2** (run 2). Among the solvents examined, AcOH was found to be the best solvent (runs 3 to 5). From the mechanistic point of view, it is important to note that no reaction takes place when a Co^{III} ion was employed in place of the Co^{II} ion (run 6). The reaction proceeded smoothly even in the presence of a very small amount (0.01 mol%) of $Co(OAc)_2$ or $Co(acac)_2$ at 80 °C to give **2** and **3** in satisfactory yields (runs 7 to 9). When the amount of biacetyl was reduced to half (3 equiv.) so that the concentration of biacetyl was halved with respect to O_2, the selectivity to **2** decreased and the amount of partly oxygenated **4** increased (run 10). In the absence of biacetyl, however, no reaction took place and the starting **1** was recovered unchanged (run 11). This fact shows that the aerobic oxidation of **1** is also induced by the presence of biacetyl. The reaction did not take place either in the presence of hydroquinone (0.1 mol%) or in the absence of O_2 (runs 12 and 13). These observations strongly suggest that a radical chain process is involved in the present acetylation, and that molecular oxygen is an essential component to promote the acetylation. Indeed, adamantyl radical, generated *in situ* from 1-bromoadamantane (3 mmol) by the action of Bu_3SnH (3.6 mmol) and AIBN (0.3 mmol) in AcOH (3 ml) reacted with biacetyl (18 mmol) and O_2 (1 atm) at 80 °C for 4 h to form **2** and **5** in 5 and 4% yields, respectively, although it abstracted more easily the hydrogen atom from the Bu_3SnH to give **1** (39%) as the major product. The reaction using benzil in place of biacetyl resulted in the recovery of the starting materials (run 14).‡

Table 1 Acetylation of **1** with biacetyl catalyzed by metal salts[a]

Run	Metal salt (mol%)	Solvent	*t*/h	Conversion (%)	Yield (%) 2	3	4	5	6
1	$Co(OAc)_2$ (0.1)	AcOH	2	94	47	20	6	4	3
2[b]	$Co(OAc)_2$ (0.1)	AcOH	4	99	22	37	10	2	4
3	$Co(OAc)_2$ (0.5)	AcOH	2	> 99	10	30	11	1	4
4	$Co(OAc)_2$ (0.5)	$ClCH_2CH_2Cl$	2	65	51	4	trace	2	3
5	$Co(OAc)_2$ (0.5)	MeCN	2	2	trace	—	—	1	trace
6	$Co(acac)_3$ (0.1)	AcOH	2	no reaction					
7[c]	$Co(OAc)_2$ (0.01)	AcOH	4	98	21	35	9	2	5
8[c]	$Co(acac)_2$ (0.01)	AcOH	4	92	49	28	4	2	5
9[c]	$Co(OAc)_2$ (0.0025)	AcOH	4	77	51	14	1	2	3
10[d]	$Co(OAc)_2$ (0.5)	AcOH	4	98	20	25	16	4	4
11[e]	$Co(OAc)_2$ (0.5)	AcOH	2	no reaction					
12[f]	$Co(OAc)_2$ (0.5)	AcOH	2	no reaction					
13[g]	$Co(OAc)_2$ (0.5)	AcOH	2	no reaction					
14[h]	$Co(OAc)_2$ (0.5)	AcOH	4	no reaction					

[a] **1** (3 mmol) was allowed to react with biacetyl (6 equiv., 18 mmol) in the presence of a metal salt under O_2 (1 atm) in AcOH (3 ml) at 60 °C. [b] Polyfunctionalyzed products and adamantane-1,3-diol were also formed. [c] 80 °C [d] Biacetyl (3 equiv., 9 mmol) was used. [e] In the absence of biacetyl. [f] Hydroquinone (0.1 mol%) was added. [g] Under argon. [h] Benzil was used in place of biacetyl.

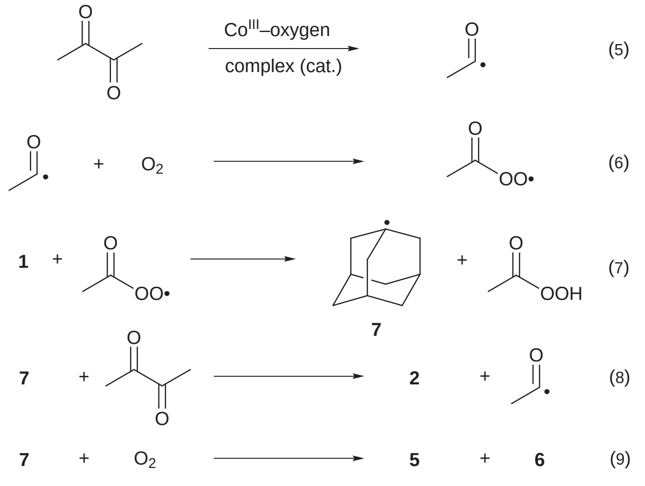
In order to gain insight into the role of cobalt salts in the present reaction, acetylations of **1** with biacetyl by Co^{II} and Co^{III} ions under O_2 (1 atm) at 75 and 80 °C were monitored by GC at appropriate time intervals (Fig. 1). The acetylation of **1** was efficiently catalyzed by Co^{II} at 75 °C, while the reaction with Co^{III} did not take place at all at this temperature. However, when the reaction temperature was raised to 80 °C, the acetylation of **1** by Co^{III} was prompted after an induction period of about 1 h. It is well-known that Co^{III} ions are reduced to Co^{II} ions by organic substrates such as toluene and cyclohexane *via* a one-electron transfer process.§ Therefore, the induction period of about 1 h observed at 80 °C would correspond to the time needed for the formation of Co^{II} by the one-electron transfer to Co^{III} from biacetyl and/or **1**. At 75 °C, however, owing to the difficulty of the electron transfer to Co^{III} from these substrates, no acetylation is induced. Therefore, if the reduction of Co^{III} to Co^{II} is performed by adding an additive like aldehyde, **1** was acetylated by Co^{III} even at 75 °C [eqn. (2)]. These findings indicate that the Co^{II} ion, which reacts easily with O_2 to generate labile dioxygen complexes such as a superoxocobalt(III) or μ-peroxocobalt(III) complex, plays an important role in the present acetylation [eqns. (3) and (4)].[7,8]

$$\mathrm{PhCHO} + \mathrm{Co^{III}} \longrightarrow \mathrm{PhCO}\bullet + \mathrm{Co^{II}} + \mathrm{H^+} \tag{2}$$

$$\mathrm{L}_n\mathrm{Co^{II}} + \mathrm{O_2} \rightleftharpoons \underset{\text{superoxocobalt(III)}}{\mathrm{L}_n\mathrm{Co^{III}\text{-}O\text{-}O}\bullet} \tag{3}$$

$$\mathrm{L}_n\mathrm{Co^{III}\text{-}O\text{-}O}\bullet + \mathrm{L}_n\mathrm{Co^{III}} \rightleftharpoons \underset{\text{μ-peroxocobalt(III)}}{\mathrm{L}_n\mathrm{Co^{III}\text{-}O\text{-}O\text{-}Co^{III}L}_n} \tag{4}$$

Although the mechanistic details are still obscure, the fact that the acetylation did not take place with Co^{II} in the absence of O_2 or with Co^{III} even in the presence of O_2 suggests that a cobalt(III)–oxygen complex is the key species in the present acetylation of **1** with biacetyl. The resulting cobalt(III)-oxygen complex reacts with biacetyl to generate an acetyl radical which is readily trapped by O_2 under the present conditions to form an acetyl peroxyl radical [eqns. (5) and (6)]. The formed acetyl peroxyl radical undergoes hydrogen abstraction from **1** to form an adamantyl radical **7** and peracetic acid [eqn. (7)]. The formed radical **7** would react with biacetyl to give **2** and an acetyl radical which serves as a chain carrier in the reaction [eqn. (8)]. In addition, **7** reacts with O_2 to produce oxygenated products **5** and **6** [eqn. (9)]. Under the present reaction conditions in which O_2 exists in the reaction system, the direct abstraction of the hydrogen from **1** by the acetyl radical may be disregarded, since the rate of hydrogen abstraction from an alkane by acetyl radical is much slower than that of the addition of O_2 to acetyl radical.¶ The acetyl peroxyl radical can also abstract the hydrogen from **1** to form **7** and peracetic acid. It is probable that peracetic acid formed in the reaction is easily subjected to redox decomposition by Co ions to generate a radical species which acts as a radical carrier. In fact, the reaction of **1** (3 mmol) with biacetyl (18 mmol) under the influence of MCPBA (3.6 mmol) and Co^{III} (0.015 mmol) in acetic acid (3 ml) in an inert atmosphere at 60 °C for 1 h afforded **2** with 60% selectivity, although the conversion of **1** was low (5%) probably because of the rapid decomposition of MCPBA by Co ion.



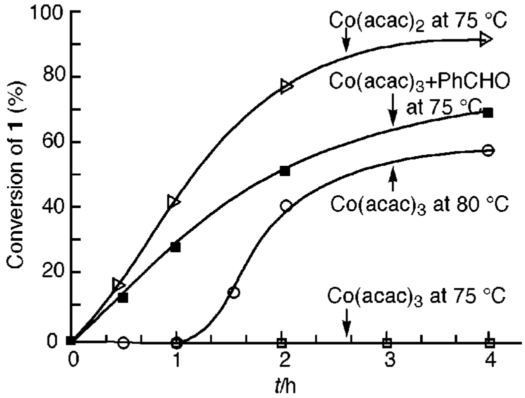


Fig. 1 Time-dependence curves for the conversion of **1** with biacetyl catalyzed by $Co(acac)_2$, $Co(acac)_3$ and $Co(acac)_3$ combined with benzaldehyde in AcOH at 75 or 80 °C. Conditions: **1** (3 mmol), biacetyl (18 mmol), AcOH (3 ml), cobalt salt (3.0×10^{-4} mmol), benzaldehyde (1.5×10^{-2} mmol).

In order to extend the present acetylation to substituted adamantanes, 1,3-dimethyladamantane **8** and **5** were allowed to react with biacetyl under the same reaction conditions as employed for **1** in Table 1, run 3. As expected, **8** was satisfactorily acetylated to the corresponding mono- and diacetyladamantanes in 54 and 21% yields, respectively. Similarly, **5** afforded **4** in 54% yield along with 3,5-diacetyladamantan-1-ol (7%). It is interesting to note that the reaction of **5** with biacetyl did not take place on the hydroxy function, which is different from the usual acetylation procedure using Ac_2O or AcCl, in which the hydroxy group is preferentially acetylated.

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Notes and references

† *Typical reaction*: To a solution of adamantane **1** (3 mmol) and $Co(OAc)_2$ (0.1 mol%) in AcOH (3 ml) was added biacetyl (18 mmol), and the mixture was stirred under O_2 (1 atm) at 60 °C for 2 h. Products were isolated by column chromatography on silica gel with hexane–EtOAc.

‡ Treatment of biacetyl with O_2 in the presence of Co^{II} under these conditions afforded AcOH in 192% (based on Co^{II}), however, benzil was recovered unchanged by the same treatment.

§ The reaction of a Co^{III} ion with cyclohexane (ref. 5) or alkylbenzenes (ref. 6) is known to involve one-electron transfer from the substrate to Co^{III}, yielding a Co^{II} ion and radical cation which readily liberates H^+ to give an alkyl radical.

¶ The reaction of acetyl radical with O_2 is reported to occur very fast [$k = (1.8 \pm 0.5) \times 10^9\ M^{-1}\ s^{-1}$] compared with the hydrogen abstraction from *n*-hexane by acetyl radical ($k \leqslant 5 \times 10^3\ M^{-1}\ s^{-1}$) (ref. 9).

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