Cerium (IV) Ammonium Nitrate Promoted Oxidative Cyclization of Dimethyl 4-Pentenylmalonate

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Abstract: *CAN promoted oxidative cyclization of dimethyl 4-pentenylmalonate has been investigated in MeOH and in AcOH. The product distribution and the regioselectivity of the reaction (5-exo/6-endo ratio) appear to be very sensitive to the reaction conditions as well as to the presence and the nature of copper salts, which can also be exploited from the synthetic point of view.*

Cyclization reactions of 5-hexenyl radicals have attracted considerable interest since long from both the theoretical and practical point of view.[1] Out of the two possible cyclization modes, 5-*exo* and 6-*endo*, the former is the one largely favored when the process is kinetically controlled, whereas the second is the major pathway when the cyclization is reversible.[2] The latter situation is generally met when the radical centre is electrophilic and trapping of the cyclized radical is not sufficiently fast.

Recently, Curran and Snider and their associates have reported that the 5-*exo* cyclization of dimethyl 4-pentenylmalonate radical (an electrophilic carbon centered radical) is about 9 times faster than the 6-*endo* cyclization either when the radical is generated by dimethyl 4-pentenyliodomalonate and hexabutylditin (the atom transfer method)[3] or when it is generated by reaction of dimethyl 4-pentenylmalonate with $Mn(OAc)_3$ in the presence of $Cu(OAc)_2$.[4] It has been suggested that, under both conditions, the ring closure should be irreversible, due to the very fast reaction of the cyclized radical with the starting iodomalonate, in the atom transfer process, and with $Cu(OAc)_2$ in the Mn(III)-induced oxidation reaction.

Our long interest in the mechanistic and synthetic aspects of the cerium(IV)-promoted formation of ketoalkyl radicals[5] has led us to investigate the properties of these systems also from the point of view of the cyclization reactions. Thus, in this paper we wish to report results concerning our own study of the cyclization

of dimethyl 4-pentenylmalonate (**1**) induced by cerium(IV) ammonium nitrate (CAN) in MeOH and in AcOH, in the absence and in the presence of copper salts.

RESULTS AND DISCUSSION

The reaction of **1** with CAN have been carried out in MeOH and in AcOH, at 20°C, using a 2:1 CAN:substrate molar ratio. Copper salts were included in some experiments in a 1:1 or 2:1 molar ratio with respect to **1**. For the reactions in acetic acid experiments have also been carried out in the presence of acetic anhydride, to check the possible effect of the crystallization water contained in the various copper salts. The structures of the reaction products were established either by comparison with authentic specimens or by spectroscopic methods, whereas the yields have been obtained by NMR analysis of the crude reaction product. No significant interconversion of the products has been noted. The material balances have been excellent, in most cases greater than 85%. All the results are collected in Tables 1 (MeOH) and 2 (AcOH).

The reaction of CAN with **1** in MeOH is a faster process than the corresponding reaction with Mn(OAc)$_3$/Cu(OAc)$_2$ in AcOH. In the former case, a conversion of 78% is reached in 4 h at room temperature, In the second case, a similar conversion requires 43 h at 55°C. As shown in Table 1, entry 1, the products of the CAN-promoted reactions are the bicyclic lactone **2**, the cyclopentylmethyl nitrate **3**, the cyclohexene derivative **6**, the exocyclic alkene **4** and the methylcyclopentane **5**. The formation of these products can easily be rationalized by a Scheme analogous to that proposed for the corresponding Mn(OAc)$_3$-induced reactions.
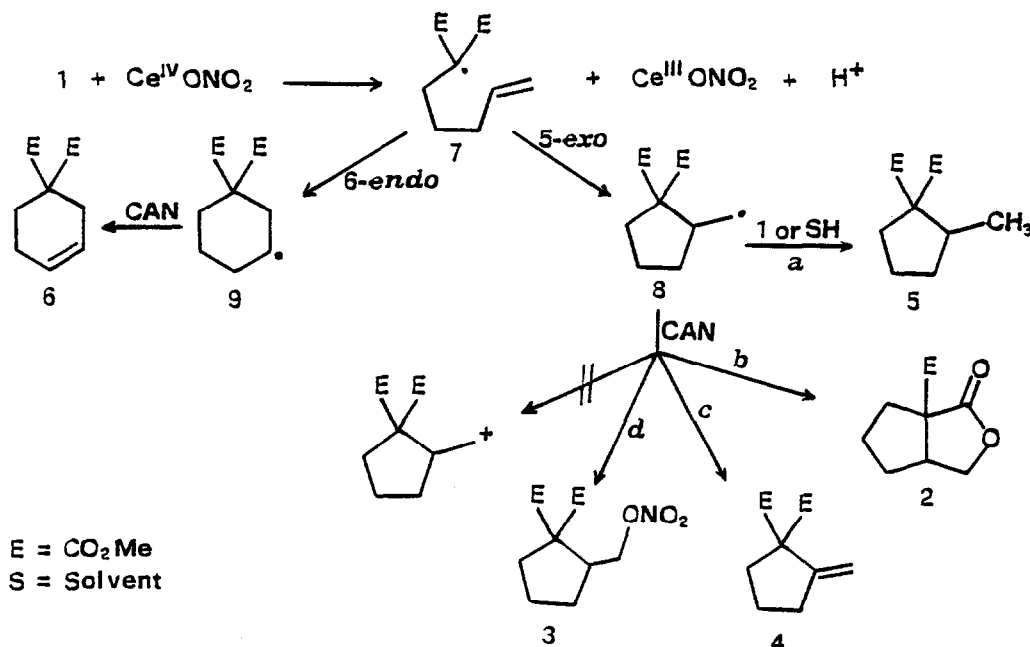
Scheme

First, the electrophilic radical **7**, which is formed by reaction of the dicarbonyl compound with CAN, undergoes either *5-exo* or *6-endo* ring closure to the cyclized radicals **8** and **9**, respectively. For the former radical several reaction paths are then available: (a) abstraction of a hydrogen atom (presumably from **1** or from the solvent) to give the methylcyclopentane **5** (path *a* in the Scheme); b) oxidation by CAN to give the bicyclic lactone **2** or the methylenecyclopentane **4** (paths *b* and *c*, respectively), probably through an alkylcerium intermediate, since the formation of the free carbocation **10** seems excluded by the absence of products deriving from solvent participation. The alkylcerium complex can give oxidative elimination to alkene or form a cationoid species undergoing an intramolecular attack by one of the two carbomethoxy groups leading to the lactone. An additional pathway is a ligand transfer process to form the alkyl nitrate **3** (path d). For the cyclohexyl radical **9**, oxidative elimination is the predominant reaction path since the cyclohexene derivative **6** is the only 6-member ring compound detected in the reaction product.

The products of *5-exo* cyclization are obtained in a 64% combined yield, whereas the yield of cyclohexene **6**, from *6-endo* cyclization, is 6%. Thus, the *5-exo/6-endo* reactivity ratio is *ca* 11, a value quite close to those found in the corresponding reactions of **1** induced by $Mn(OAc)_3/Cu(OAc)_2$ in $AcOH$[4] and in the cyclization reactions of 4-pentenyliodomalonate promoted by hexabutylditin.[3]

Table 1. CAN Promoted Oxidative Cyclization of **1** in Methanol at 20°C.

Cooxidant[a]	Reaction time (h)	Product distribution (%)[b]						Recovered material (%)	*5exo/6endo* ratio
		1	**2**	**3**	**4**	**5**	**6**		
1. -	5	29.8	19.8	22.5	10.2	11.7	6.0	73	11
2. $Cu(OAc)_2$	5	12.8	58.3	-	24.8	-	4.1	96	20
3. $Cu(NO_3)_2$	5	29.0	38.7	-	30.0	-	2.3	91	30
4. $Cu(BF_4)_2$	15	46.5	31.0	-	20.7	-	1.8	87	29

[a] 1:CAN:Cu(II) = 1:2:2. [b] Average of at least three determinatios. Error, ± 5%.

Data in Table 1 also show that when copper salts are added there is a significant change in the product composition, accompanied by a substantial increase in the *5-exo/6-endo* ratio. More precisely, the lactone **2** and the alkene **4** are by far the main reaction products, whereas the alkyl nitrate **3** and the methylcyclopentane **5** are no longer present. Since Cu^{+2} salts are more efficient than CAN in the oxidation of alkyl radicals,[6] an alkylcopper complex is more likely to be formed than the alkylcerium complex, enhancing the rate of paths *b* and *c* so much as to make these paths the exclusive reactions of the cyclized radical **8**. It can also be noted that no ligand transfer is observed when the copper salt is $Cu(NO_3)_2$.

A noteworthy observation is that also the *5-exo/6-endo* reactivity ratios are significantly influenced by the presence and the nature of copper salts. Thus, in MeOH, the ratio is 20 in the presence of $Cu(OAc)_2$, 30 in the presence of $Cu(NO_3)_2$ and 29 in the presence of $Cu(BF_4)_2$, these values comparing with that (11) obtained with CAN alone (Table 1). In general, it appears that the *5-exo/6-endo* ratios increase when in the Cu^{+2} salt the acetate ligand is replaced with a ligand less strongly coordinating (NO_3^- and BF_4^-).

A possible explanation is that the observed changes in the *5-exo/6-endo* ratios reflect changes in the degree of the kinetic control of the cyclization process. Indeed, as the ligand becomes less strongly coordinating, the efficiency of Cu^{+2} in the oxidation of carbon centered radicals is expected to increase.[6] This should reduce the possibility that ring reopening of radical **8** competes with the irreversible trapping by Cu^{+2}, making the system to approach a situation of complete kinetic control.

Another possibility is that the presence of Cu^{+2} may favor the *5-exo* ring closure with respect to the *6-endo* one since Cu^{+2} might stabilize the incipient alkyl radical which develops in the transition state of the cyclization process better when this radical is primary (*5-exo* closure) than when it is secondary (*6-endo* closure). Accordingly, it is known that Cu^{+2} salts interact more effectively with primary than with secondary alkyl radicals, the strength of these interactions also depending on the ligand nature.[6]

Concerning the reactions in AcOH (Table 2), a first important and very surprising observation is that, both in the absence and in the presence of copper salts, the results depend on whether or not acetic anhydride is added to the reaction medium. Thus, with CAN alone in AcOH the main products are the lactone **2** and a compound, which is not formed in MeOH, whose structure has been established to be that of the nitro derivative **11** (entry 1 of Table 2) probably deriving by the reaction of the radical **8** with NO_2 which may form by redox processes, favored by the acid nature of the solvent, involving HNO_3 produced in the course of the reaction. However, when acetic anhydride is added (entry 2) the nitrate **3** becomes the main reaction product, at the expense of the lactone **2**, whereas **11** is still formed in substantial amounts. The *5-exo/6-endo* ratio also changes upon addition of Ac$_2$O, increasing from 23 to 31. It can also be noted that under both the above reaction conditions there is no appreciable formation of the methylcyclopentane **5**. Clearly, CAN is a better oxidant in AcOH than in MeOH and path *a* cannot compete in the former solvent.

Table 2. CAN Promoted Oxidative Cyclization of **1** in Acetic Acid at 20°C

Cooxidant[a]	Reaction time (h)	Product distribution, (%)[b]						Recovered material (%)	*5exo/6endo* ratio
		1	2	3	4	6	11		
1. -	22	16.2	34.7	5.6	1.8	3.5	38.2	88	23
2. -[c]	22	6.6	13.1	45.7	1.0	2.9	30.7	95	31
3. Cu(OAc)$_2$[d]	22	10.0	51.9	31.8	3.1	3.1	-	87	28
4. Cu(NO$_3$)$_2$[d]	22	27.0	21.5	43.9	-	2.0	4.9	92	35
5. Cu(BF$_4$)$_2$[d]	22	-	16.0	81.0	-	3.1	-	93	31
6. Cu(OAc)$_2$·H$_2$O	30	13.5	77.5	-	3.8	5.1	-	72	16
7. Cu(NO$_3$)$_2$·3H$_2$O	23	7.9	85.7	-	1.8	4.5	-	86	19
8. Cu(BF$_4$)$_2$·6H$_2$O	30	12.0	83.0	-	1.3	4.1	-	83	20

[a] 1:CAN:CuX$_2$ = 1:2:1. [b] Average of at least two determinations. Error, ± 7%. [c] In the presence of 0.33 M Ac$_2$O. [d] In the presence of Ac$_2$O in equimolar amount with respect to the crystallization water present in the copper salt.

The addition of copper salts has the main effect of practically suppressing the formation of **11**, formed in very small amounts only in the presence of $Cu(NO_3)_2$ (entry 4). For the rest the same situation holds already noted for the reactions promoted by CAN alone, that is the presence of Ac_2O favors the formation of the nitrate **3**, whereas the absence of Ac_2O favors the formation of the lactone **2** (compare entries 3, 4 and 5 with entries, 6, 7 and 8 respectively). The phenomenon is particularly remarkable with $Cu(BF_4)_2$. With this salt, 81% of the reaction product is the nitrate **3** and only 16% the lactone **2**, in the presence of Ac_2O; in the absence of Ac_2O, 83% of the reaction product is the lactone **2** and the nitrate **3** is not detected.

Likewise, also in the presence of copper salts the *5-exo/6-endo* ratio shows the same solvent dependence observed in the cyclizations induced by CAN alone. Values between 16 and 20 are determined in the absence of Ac_2O and between 28 and 35 in the presence of Ac_2O.

A rationalization of the Ac_2O effect upon the product distribution of the CAN-induced cyclizations in AcOH is very difficult. Certainly, Ac_2O should provide us with a very dry medium and it would appear that, under these conditions, oxidation of the radical **8** by CAN, *via* a ligand transfer process, is highly favored, becoming the most important process, even when copper salts, like $Cu(NO_3)_2$ and $Cu(BF_4)_2$ are present. However, why it should be so is not clear at present and further study is certainly necessary to reach some conclusions in this respect, as well as to explain the changes in the *5-exo/6-endo* ratios.

Apart from the mechanistic problems, the present work has clearly shown that CAN is a very efficient reactant in promoting cyclization reactions of 5-hexenyl derivatives *via* the formation of electrophilic carbon centered radicals. The product distribution as well as the *5-exo/6-endo* ratio are very sensitive to the reaction conditions, which can also be appropriately exploited from the synthetic point of view. Thus, in AcOH, in the presence of copper salts, the lactone **2** is the almost exclusive reaction product whereas in AcOH/Ac_2O the nitrate **3** is the predominant product in the presence of $Cu(BF_4)_2$.

EXPERIMENTAL SECTION

^{1}H-NMR were recorded at 200 MHz on a Bruker AC 200 spectrometer in CDCl$_3$ solution and in the presence of tetramethylsilane as an internal standard. GC-MS analyses were performed at 70 eV on a HP 5890 gas-chromatograph equipped with 30 m x 0.2 mm SPB-5 (Supelchem) capillary column and coupled with an HP 5970 MSD spectrometer. Elemental analyses were performed on a Carlo Erba M 1106 Elemental Analyzer.

Starting Materials. Dimethyl 4-pentenylmalonate (**1**) was prepared by reaction of dimethyl malonate with 5-bromo-1-pentene and sodium methoxide in refluxing methanol according to the general procedure described in the literature.[7] Methanol (Aldrich 99.9%) was used without further purification. Ceric ammonium nitrate (Merk, 99%) was dried by heating at 85°C for 1 h. $Cu(OAc)_2 \cdot H_2O$, $Cu(NO_3)_2 \cdot 3\ H_2O$, $Cu(BF_4)_2 \cdot 6\ H_2O$, acetic anhydride, of the highest grade of purity (Carlo Erba RPE), were used as received.

General Oxidative Cyclization Procedure. To a methanol (10 mL) solution of CAN (3.0 mmol) and the copper salt (3.0 mmol) substrate (1.5 mmol) was added and the mixture was stirred at 20°C until complete reaction of CAN (iodometric titration). The mixture was poured into water (50 mL) and extracted with diethyl ether (3 x 20 mL). The collected extracts were washed with water (2 x 50 mL), with a saturated solution of sodium hydrogen carbonate (50 mL) and dried with sodium sulfate. After addition of hydroquinone dimethyl

ether as an internal standard, the solvent was evaporated at reduced pressure (15 mm Hg, 20°C) and the residue was analyzed by ^{1}H-NMR. The reaction products were isolated by column chromatography on silica gel by eluting with 1:1 petroleum ether diethyl ether mixture. The same procedure was used in the reaction in acetic acid except that acetic anhydride was added, when specified, in equimolar amount with respect to the crystallization water present in the copper salts. The products **2, 4, 5** and **6** were identified by comparison of their spectroscopic characteristics with those described in the literature. Products **3** and **11** were identified on the basis of their analytical and spectral data.

Dimethyl 2-(nitroxymethyl)cyclopentane-1,1-dicarboxylate (3): ^{1}H NMR δ 4.76 (dd, J = 10.8 and 6.1 Hz, 1 H), 4.46 (dd, J = 10.8 and 7.1 Hz, 1 H), 3.76 (s, 3 H), 3.75 (s, 3 H), 2.9 (m, 1 H), 2.21-1.96 (m, 4 H), 1.96-1.50 (m, 2 H); IR (neat) 2960-2835, 1730, 1630, 1435, 1282, 1265, 1170, 1070, 860 cm-1; MS m/z(%) 230 (M$^+$- CH$_3$O, 5), 199 (1), 183 (2), 155 (16), 125 (38), 95 (62), 67 (100), 59 (52), 46 (48). Anal. Calcd for C$_{10}$H$_{15}$NO$_7$: C, 45.98; H, 5.79; N, 5.36. Found: C, 45.81; H, 5.83; N, 5.42. **Dimethyl 2-nitromethylcyclo-pentane-1,1-dicarboxylate (11):** ^{1}H-NMR δ 4.83 (dd, J=13.1, 4.3 Hz, 1 H), 4.40 (dd, J=13.1, 9.8 Hz, 1H), 3.76 (s, 3 H), 3.74 (s, 3 H), 3.2 (m, 1 H), 2.46-1.55 (m, 6 H); IR (neat) 2960-2850, 1760, 1555, 1383, 1270, 1162 cm-1; MS m/z (%) 214 (M$^+$-OCH$_3$, 10), 199 (9), 154 (12), 139 (55), 107 (25), 79 (100), 59 (46). Anal. Calcd for C$_{10}$H$_{15}$NO$_6$: C, 48.98; H, 6.16; N, 5.71. Found: C, 49.11; H, 6.27; N, 5.78.

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