Lead(IV) acetate: intriguing reactivity profile†

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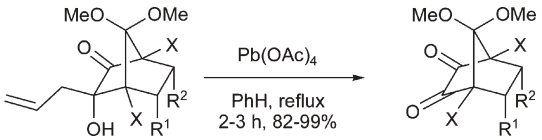
LTA reaction of homoallyl alcohols derived from norbornyl α-diketones exclusively furnished the corresponding α-diketones *via* β-fragmentation of the allyl group in refluxing benzene while changing the solvent to MeOH resulted in the formation of novel methoxy substituted spirocyclic tetrahydrofuran products.

Lead tetraacetate (LTA) is a convenient and widely used lead(IV) precursor employed as a powerful oxidizing agent.[1] Cleavage of glycol[2] and acyloin moieties,[3] oxidative decarboxylation[4] and formation of tetrahydrofurans from alcohols possessing a δ-H[5] are the common examples. Recent years have witnessed the emergence of organolead intermediates in selective organic transformations, particularly for the generation of quaternary carbon centers, C–C bond formation between sterically crowded groups[6] and in natural product syntheses.[7] These developments spurred both theoretical and experimental studies to gain insight into elusive mechanistic aspects.[8]

During the course of our studies directed towards the syntheses of highly functionalized lactones,[9] we became interested in LTA mediated reaction of homoallyl alcohols[10] obtained *via* allylindium addition to the corresponding diketones.[11] Initially we were intrigued to find that the diketone was recovered back upon LTA reaction. However, a literature search revealed that such reaction was recently reported as a 'new reaction',[12] although we found more examples. Kapustina *et al.* reported that LTA reaction of tertiary alkanols, obtained by nucleophilic addition of R group to cycloalkanone, results in β-fragmentation of the intermediate alkoxy radical leading to unsaturated ketone or cycloalkanone, depending on the structural features of the alkanol.[13] When R is allyl group (homoallyl alcohol), dramatic rate acceleration with exclusive formation of cycloalkanone and allyl acetate *via* "a synchronous two-electron transfer mechanism" was observed.

Our substrates are not only prone to LTA reactions similar to the tertiary alkanols but are also amenable to acyloin cleavage due to the presence of an α-carbonyl. When the LTA reactions were performed on substrates **1a–10a** using benzene solvent under reflux conditions, the corresponding α-diketones **1b–10b** were obtained as depicted in Scheme 1.‡ Changing the solvent from benzene to MeOH dramatically altered the outcome of the LTA reaction. Table 1 illustrates the results obtained with substrates **1a–11a** employing MeOH as solvent. Unlike with benzene, the reaction in MeOH proceeded smoothly at room temperature. The substrate **1a** with a five-membered ring appendage to bicyclic framework furnished three products **1b**, **1c** and **1d**. The ^{1}H NMR spectrum of the chromatographically homogeneous fraction turned out to be a mixture of **1c** and **1d** in a ratio of 88 : 12 as calculated from the integrals of the non-overlapping peaks. The initially assigned tentative structures for **1c** and **1d** were subjected to spectroscopic scrutiny after separating them on HPLC.



1a-10a[a] **1b-10b**

[a] For R^1, R^2 and X, see Table 1

Scheme 1 LTA reactions in benzene.

Interestingly, as ring size of the appendage increased to a six-membered in **2a** and seven-membered ring in **3a**, the amount of α-diketone products (**2b** and **3b**) formed gradually decreased to 28 and 14% respectively, while a proportionate increase in spirocyclic product (**c** + **d**) with similar ratio (~9 : 1) as before was recorded. Finally for the eight-membered appendage in **4a**, no diketone product **4b** was observed while **4c** and **4d** were formed in 70% yield. The monosubstituted substrate **5a** also furnished only **5c** and **5d** with further improvement in yield. A similar trend was observed for the chloro compounds **6a–11a**.

The LTA mediated oxidative fragmentation of the allyl group in benzene solvent may be rationalized as follows: at reflux temperature, ligand exchange of one of the acetate groups on LTA with homoallyl alcohol followed by intramolecular coordination of lead with π-bond of allyl group triggers β-fragmentation leading to α-diketone and a π-allyl complex which eventually decomposes to allyl acetate and $Pb(OAc)_2$.[12,13] When the solvent is changed to MeOH, the reaction occurs at room temperature furnishing novel methoxy substituted spirocyclic tetrahydrofuran products. It is known that LTA undergoes ligand exchange with MeOH to produce methoxylead(IV) acetate species (Scheme 2). These species being more electrophilic than LTA,[14] react with the nucleophilic π-bond to give plumbonium cation **12**. An intramolecular opening of the plumbonium cation by hydroxyl group followed by reductive elimination of the intermediate lead species results in tetrahydrofuran products.

In order to explain the formation of diastereomeric products **c** and **d**, a theoretical study to obtain optimized geometry of homoallyl alcohol **6a** was performed using the DFT method at B3LYP/6-31G(d) level.[15] The preferred orientation of the π-bond is such that the terminal carbon is away from the α-carbonyl

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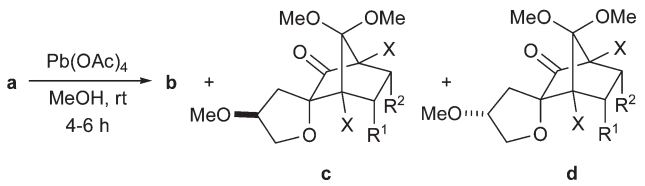
† Electronic supplementary information (ESI) available: Experimental details, spectral data of all new compounds, X-ray analysis of compounds **1d**, **6c**, **10c**, **13c**, **14d** and details of computational methodology. See DOI: 10.1039/b708268a

Table 1 LTA-mediated reaction of **1a–11a**



Entry	Substrate	X	R^1, R^2	Yield[a] (%) b	c + d	(c : d)[b]
1	**1a**	Br	$-(CH_2)_3-$	34	42	88 : 12
2	**2a**	Br	$-(CH_2)_4-$	28	46	90 : 10
3	**3a**	Br	$-(CH_2)_5-$	14	64	88 : 12
4	**4a**	Br	$-(CH_2)_6-$	—	70	87 : 13
5	**5a**	Br	H, Ph	—	84	86 : 14
6	**6a**	Cl	$-(CH_2)_4-$	28	48	90 : 10
7	**7a**	Cl	$-(CH_2)_6-$	—	72	86 : 14
8	**8a**	Cl	$-CH_2-OAc$	—	65	85 : 15
9	**9a**	Cl	H, Ph	—	88	86 : 14
10	**10a**	Cl	$-OCMe_2O-$	14	60	56 : 44
11	**11a**	Cl	H, CO_2Me	—	67	80 : 20

[a] Isolated yields of analytically pure samples. [b] Determined from ^1H NMR integration.

(Scheme 2). Addition of methoxylead(IV) acetate species across the π-bond from the sterically more accessible face leads to **12a** which after ring closure followed by reductive elimination furnishes the major diastereomer **c**. Similarly, **12b** resulting from methoxylead(IV) acetate addition from the hindered face gives the minor diastereomer **d**.

Furthermore, based on the proposed mechanism in Scheme 2 it was anticipated that the homoallyl alcohols with allyl group in sterically encumbered *endo* position should react sluggishly under identical conditions. To verify this, homoallyl alcohols **13a** and **14a** were prepared and subjected to LTA reaction in MeOH. The results are summarized in Scheme 3. Compared to the homoallyl alcohols **1a–11a**, the reactions were indeed slow with incomplete conversion even after 48 h at elevated temperatures (45–50 °C). Interestingly, the diastereomeric ratio of **c** and **d** decreased substantially. This may be explained by considering the fact that the two faces of the π-bond are less distinct due to the presence of *endo*-substitutent R^2 when preferred orientation of the π-bond is such that the terminal carbon is away from the α-carbonyl.[15] The major diastereomer **c** results from the methoxylead(IV) acetate addition from bottom side.

On the other hand, subjecting **13a** to LTA reaction in refluxing benzene furnished the corresponding α-diketone in quantitative yield. This is in accordance with the mechanistic proposals discussed above.

It was difficult to unequivocally establish the configuration of the pure diastereomers **c** and **d** from NMR data alone, and so we relied on single-crystal X-ray analysis.§ As evident from the X-ray crystal structures of **1d**, **6c**, **10c**, **13c** and **14d**, the major isomer in all cases was the one in which the methoxy group on spirocyclic tetrahydrofuran ring is disposed on the beta-face and in case of the minor isomer, the methoxy group is disposed on the alpha-face. The configuration of the remaining compounds was fixed based on the internal consistency in ^1H and ^{13}C NMR data or analogy.

In summary, we have demonstrated that the outcome of LTA reaction with α-keto homoallyl alcohols is highly solvent dependent. In refluxing benzene, oxidative β-fragmentation of the allyl group is the exclusive pathway leading to the corresponding α-diketones. On the other hand, a facile reaction at room temperature leading to diastereomeric methoxy substituted spirocyclic tetrahydrofuran products with high diastereoselectivity was observed in MeOH.

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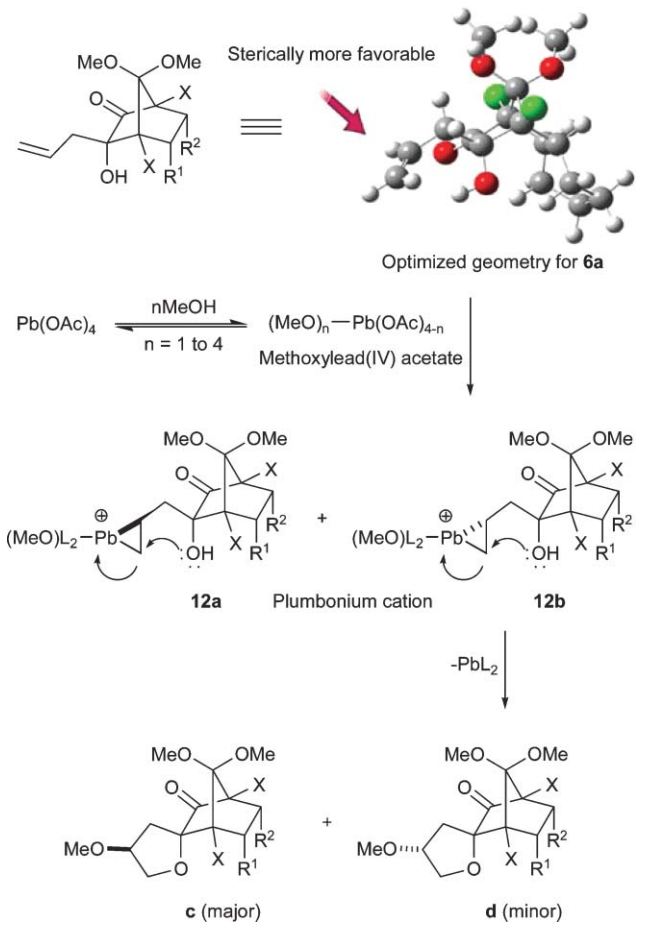
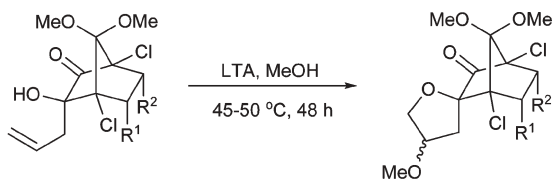


Scheme 2 Possible mechanism for the formation of spirocyclic products.



	R^1, R^2	Yield (%)[a, b] c+d	ratio[c] c:d
13a	H, OEt	84 (85)	63:37
14a	H, CO_2Me	61 (65)	67:33

[a] Based on recovered starting material.
[b] Figures in parenthesis indicate the percentage conversion.
[c] **c**: β-OMe, **d**: α-OMe

Scheme 3 LTA mediated reaction of **13a** and **14a** in MeOH.

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Notes and references

‡ *Typical procedure* for LTA reaction in MeOH: To a stirred solution of acyloin (0.2 mmol) in methanol (3 mL), was added LTA (620 mg, 1.4 mmol) in portions over a period of 10 min at room temperature. After stirring the mixture under specified conditions (Table 1 and Scheme 3), the reaction mixture was diluted with H_2O (6 mL) and extracted with ethyl acetate (3 × 10 mL). The combined ethyl acetate layers were washed with saturated solution of $NaHCO_3$ (5 mL), brine (3 mL) and dried over anhydrous Na_2SO_4. Concentration followed by silica gel column chromatography of the crude mixture afforded analytically pure diketone (**b**) and diastereomeric spirocyclic compounds (**c** and **d**). **c** and **d**, which wherever inseparable were purified by JAI LC-918w preparative recycling HPLC equipped with JAIGEL-OA4100 column.

Typical procedure for LTA reaction in benzene: To a stirred solution of acyloin (0.1 mmol) in benzene (2 mL) was added LTA (133 mg, 0.3 mmol) in one portion at room temperature. After stirring the reaction mixture for 2–3 h at 80–90 °C, the reaction mixture was filtered through a short silica gel pad and the residue was washed with ethyl acetate (10 mL). The combined filtrates were washed with saturated solution of $NaHCO_3$ (3 mL), brine (2 mL) and dried over anhydrous Na_2SO_4. Concentration followed by purification over a short silica gel column afforded analytically pure diketones in excellent yields.

Spectral data for selected compounds: **6c**; white crystals (CH_2Cl_2–hexane); mp 87–88 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.11–4.04 (m, 2H), 3.95–3.91 (m, 1H), 3.62 (s, 3H, OMe), 3.5 (s, 3H, OMe), 3.26 (s, 3H, OMe), 2.93 (td, 1H, J = 11.2, 7.0 Hz), 2.54–2.49 (m, 1H), 2.43–2.29 (m, 2H), 2.23–2.19 (m, 1H), 1.65–1.60 (m, 2H), 1.55–1.46 (m, 2H), 1.39–1.31 (m, 1H), 1.14–1.03 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.6, 103.3, 91.9, 80.5, 80.1, 76.0, 73.7, 57.0, 51.9, 51.6, 45.4, 42.3, 40.5, 20.2, 20.0, 19.4, 18.3; IR (KBr) 2850, 1760, 1440, 1180, 1060 cm^{-1}. Anal. Calc. for $C_{17}H_{24}Cl_2O_5$: C, 53.83; H, 6.38. Found: C, 53.92; H, 6.44%; ESI-HRMS: calc. for $C_{17}H_{24}Cl_2O_5$ + H 379.1079, found 379.1073. **6d**; colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.09–4.04 (m, 2H), 4.0–3.97 (m, 1H), 3.67 (s, 3H, OMe), 3.56 (s, 3H, OMe), 3.34 (s, 3H, OMe), 2.98–2.91 (m, 1H), 2.87–2.82 (m, 1H), 2.52–2.43 (m, 1H), 2.29–2.2 (m, 1H), 2.21 (dd, 1H, J = 14.4, 4.2 Hz), 1.73–1.67 (m, 2H), 1.59–1.53 (m, 2H), 1.42–1.32 (m, 1H), 1.27–1.09 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.5, 103.1, 91.9, 80.4, 79.8, 76.8, 73.7, 57.2, 51.8, 51.6, 44.8, 42.5, 41.3, 20.2, 19.9, 19.2, 18.0; IR (neat) 2850, 1740, 1440, 1200, 1060, 960 cm^{-1}. Anal. Calc. for $C_{17}H_{24}Cl_2O_5$: C, 53.83; H, 6.38. Found: C, 53.85; H, 6.63%. **14c**; white solid; mp 120 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.26–4.22 (m, 2H), 3.86 (d, 1H, J = 3.4 Hz), 3.65 (s, 3H, OMe), 3.58 (s, 3H, OMe), 3.57 (s, 3H, OMe), 3.3 (s, 3H, OMe), 3.25 (dd, 1H, J = 12.4, 4.8 Hz), 2.71 (t, 1H, J = 3.6 Hz), 2.69–2.65 (m, 1H), 2.17 (dd, 1H, J = 13.3, 4.7 Hz), 2.0 (dd, 1H, J = 13.1, 5.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.9, 171.4, 104.7, 88.9, 79.3, 78.1, 74.0, 71.1, 57.6, 52.8, 52.4, 51.1, 46.1, 36.8, 35.8; IR (KBr) 2850, 1770, 1730, 1440, 1350, 1290 cm^{-1}. Anal. Calc. for $C_{15}H_{20}Cl_2O_7$: C, 47.01; H, 5.26. Found: C, 47.05; H, 5.43%. **14d**; white crystals (CH_2Cl_2–hexane); mp 124–125 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.20–4.17 (m, 1H), 4.11–4.08 (m, 2H), 3.68 (s, 3H, OMe), 3.63 (s, 3H, OMe), 3.60 (s, 3H, OMe), 3.33 (s, 3H, OMe), 3.28 (dd, 1H, J = 12.3, 4.8 Hz), 2.69 (t, 1H, J = 12.9 Hz), 2.63 (dd, 1H, J = 13.2, 2.2 Hz), 2.28–2.22 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.9, 171.3, 104.6, 89.1, 80.0, 78.3, 75.4, 72.4, 56.7, 52.8, 52.3, 51.1, 46.1, 36.3, 35.3; IR (KBr) 2850, 1780, 1710, 1430, 1360, 1290 cm^{-1}. Anal. Calc. for $C_{15}H_{20}Cl_2O_7$: C, 47.01; H, 5.26. Found: C, 47.26; H, 5.37%.

§ CCDC 649155–649159. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b708268a

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