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Solid-phase oxoalkylation of pyridines and quinolines with 1-methylcycloalkanols under the action of lead tetraacetate*

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A new procedure was developed for the introduction of the oxoalkyl fragment into *N*-heteroaromatic compounds of the pyridine and quinoline series. The procedure is based on the solid-phase reactions of lead tetraacetate with aromatic *N*-heterocycles and tertiary cycloalkanols.

Key words: *N*-heteroaromatic compounds, oxidative decyclization, oxoalkyl-substituted *N*-heterocycles, solid-phase oxoalkylation, lead tetraacetate, tertiary cycloalkanols.

In the last decade, considerable attention has been given to solid-phase reactions of organic compounds and reactions in the absence of solvents involving simultaneously liquid and solid reagents.[2,3] These reactions are of interest for several reasons. First, some solid-phase processes are ecologically more promising. Second, they often provide higher regio- and stereoselectivity in solving synthetic problems. In the solid-phase organic synthesis, reactions on polymeric supports are of special interest. These reactions gained wide acceptance in the combinatorial chemistry.[4]

In our previous studies, we have carried out for the first time the solid-phase reactions involving $Pb(OAc)_4$ in the absence of solvents. 1-Alkylcycloalkanols were oxidized under the action of the $Pb(OAc)_4$—metal halide systems to give ω-haloketones.[5] The reactions with naphthalene afforded 1-mono and 1,4-dihalonaphthalenes.[6] Oxidation of alkan-1-ols with this system gave a unique result. Thus, the reactions in the solid phase proceeded by a different mechanism to give esters[7] rather than 4-haloalkan-1-ols, which were obtained in the liquid phase. The experiments were carried out under the conditions of mechanical activation using a vibration mill (a steel cylinder filled with steel balls as the reactor).

In the present study, we observed for the first time the formation of the C—C bond in a solid-phase reaction proceeding under the action of $Pb(OAc)_4$ and found that these processes can take place without mechanical activation. We examined the oxoalkylation reactions of pyridine (**1a**), methylpyridines **1b**,**c**, quinoline (**2a**), 4-methylquinoline (**2b**), and isoquinoline (**3**) with 1-methylcycloalkanols **4—6**. The liquid-phase version of this reaction has already been tested and gave positive results.[8] The results of our investigation are presented in Scheme 1 and Table 1. The results of analogous experiments, which were carried out at 80 °C in the liquid phase with the use of a solvent (AcOH), are given in Table 1 for comparison.

The solid-phase oxoalkylation was preceded by the formation of a solid composition upon mixing of heterocyclic compound **1—3**, 1-methylcycloalkanol **4—6**, $Pb(OAc)_4$, and benzoic or 2-chlorobenzoic acid. The latter reagents served as protonating agents with respect to *N*-bases, which were converted into solid onium salts. The initial step of the reactions with cycloalkanols **4** and **5** proceeded rather rapidly (~80% of $Pb(OAc)_4$ decomposed during the first 2 h; ~90% of the reagent decomposed during 4 h) and the reactions were completed in ~20 h. Oxoalkylation with 1-methylcyclohexanol (**6**) proceeded ~2.5 times more slowly. In the first step, oxidation of 1-methylcycloalkanol gave rise to the 1-methylcycloalkoxyl radicals, which underwent isomerization accompanied by the ring opening to form the (ω-1)-oxoalkyl radicals. Because of the nucleophilic character, these radicals readily added to the protonated heterocycle bearing a positive charge. The adduct radicals thus generated were oxidized by the Pb^{IV} or Pb^{III} ions to give products of the replacement of the hydrogen atom in the heterocycle by the oxoalkyl fragment (Scheme 2).

In pyridine and quinoline, the replacement occurred at position 2 or 4, the ratio of isomers formed in the solid and liquid phases being only slightly different (runs 1—4 and 18—20). A slight enhancement of the regioselectivity in the solid phase was observed in the oxoalkylation of isoquinoline, which afforded the 1- and 3-positional isomers in a ratio of 95—98 : 5—2 (86 : 14 in solution) (runs 21—23). In 4-methylpyridine (**1b**), 2,4-dimethylpyridine (**1c**), and 4-methylquinoline (**2b**), the replacement occurred only at position 2.

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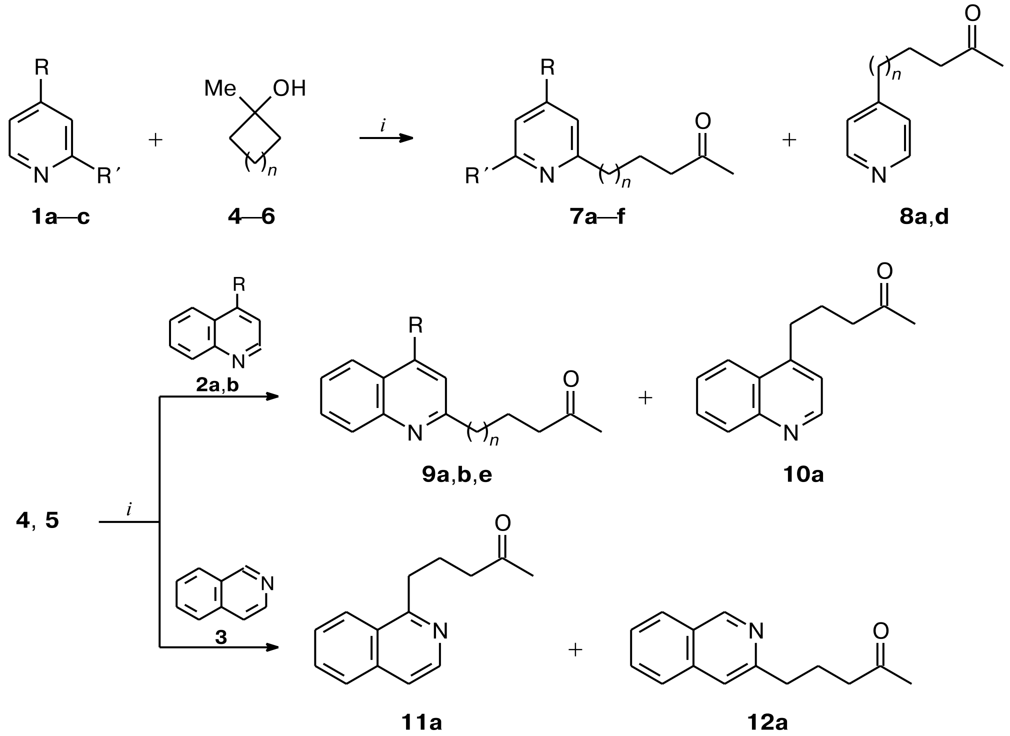
Scheme 1

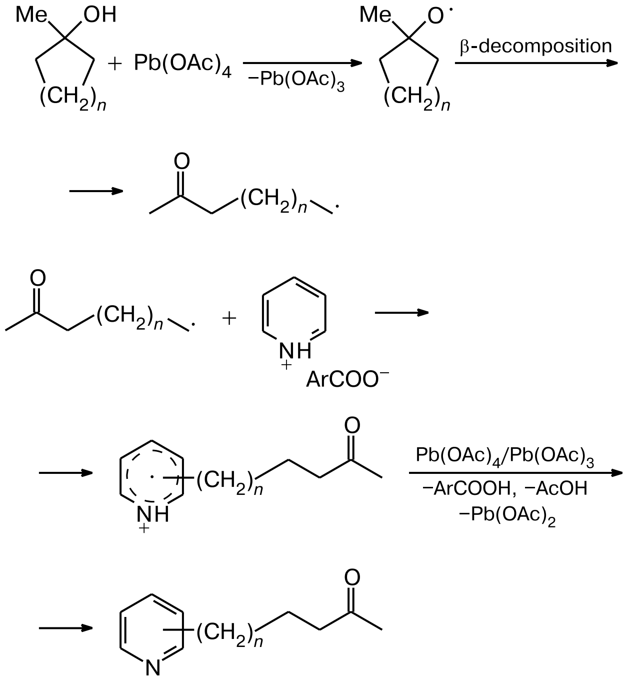


1, **2**, **7**—**12**	**a**	**b**	**c**	**d**	**e**	**f**
R	H	Me	Me	H	Me	Me
R′	H	H	Me	H	H	H
n	1	1	1	2	2	3

n = 1 (**4**), 2 (**5**), 3 (**6**)

Reagents and conditions: *i*. $Pb(OAc)_4$, $PhCO_2H$, or $2-ClC_6H_4CO_2H$, 20 °C.

Scheme 2



The main difference between the solid- and liquid-phase reactions is that the conversion of 1-methylcycloalkanols **4**—**6** in the solid-phase reactions achieved upon the 100% conversion of $Pb(OAc)_4$ was always 20—50% higher than that obtained in the liquid-phase reactions. As a consequence, the oxoalkylation products in the solid-phase reactions were generated in higher yields and with higher selectivity. The advantages of the solid-phase process were demonstrated most clearly by the reaction of 4-methylpyridine (**1b**) with 1-methylcyclohexanol (**6**). When the conversion of the latter was equal to 51%, oxoalkylation product **7f** was obtained in high yield, whereas this reaction in the liquid phase (AcOH, 80 °C) did not proceed at all (runs 12 and 13).

Hence, $Pb(OAc)_4$ is consumed more advantageously in the solid-phase oxidation of cycloalkanols **4**—**6** and intermediate adduct radicals, while side redox transformations of $Pb(OAc)_4$ into $Pb(OAc)_2$ are less pronounced than those in the correspoding processes in solution. The surprising thing is that the conversions of Pb^{IV} acetate into Pb^{II} acetate, which were achieved after ~20 h in the $Pb(OAc)_4$—**1b**—**4**—2-chlorobenzoic acid and $Pb(OAc)_4$—**1b**—2-chlorobenzoic acid compositions, were only slightly different. In other words, the oxidizing agent

Table 1. Solid-phase oxoalkylation of *N*-heterocycles (**1—3**) with 1-methylcycloalkanols (**4—6**) under the action of $Pb(OAc)_4$

Run	Reagents		Acid	Molar ratio[a] **4—6** : Pb(IV) : **1—3** : acid	Conversion[b] of **4—6** (%)	Products	
	1—3	**4—6**				Ratio of positional isomers (%)	Yield[c] (%)
1	**1a**	**4**	PhCOOH	1 : 2 : 4 : 4	98	2 (78), 4 (22)	86/88
2	**1a**	**4**	AcOH [d]	1 : 1.5 : 6	75	2 (73), 4 (27)	50/67 [8]
3	**1a**	**5**	2-ClC_6H_4COOH	1 : 2 : 4 : 4	83	2 (61), 4 (39)	74/89
4	**1a**	**5**	AcOH [d]	1 : 1.5 : 6	55	2 (71), 4 (29)	30/55 [8]
5	**1b**	**4**	PhCOOH	1 : 1 : 4 : 4	89	2 (100)	66/73
6	**1b**	**4**	PhCOOH	1 : 2 : 4 : 4	95	2 (100)	87/92
7	**1b**	**4**	2-ClC_6H_4COOH	1 : 2 : 4 : 4	95	2 (100)	84/88
8	**1b**	**4**	AcOH [d]	1 : 1.5 : 6	67	2 (100)	35/52 [8]
9	**1b**	**5**	PhCOOH	1 : 2 : 4 : 4	10	2 (100)	3/30
10	**1b**	**5**	2-ClC_6H_4COOH	1 : 2 : 4 : 4	97	2 (100)	76/78
11	**1b**	**5**	AcOH [d]	1 : 1.5 : 6	49	2 (100)	28/57 [8]
12	**1b**	**6**	2-ClC_6H_4COOH	1 : 2 : 4 : 4	51	2 (100)	45/88
13	**1b**	**6**	AcOH [d]	1 : 1.5 : 6	5	—	—
14	**1c**	**4**	PhCOOH	1 : 2 : 4 : 4	60	6 (100)	53/88
15	**1c**	**4**	2-ClC_6H_4COOH	1 : 1.5 : 4 : 4	73	6 (100)	57/78
16	**1c**	**4**	2-ClC_6H_4COOH	1 : 2 : 4 : 4	75	6 (100)	67/89
17	**1c**	**4**	AcOH [d]	1 : 1.5 : 6	56	6 (100)	30/54 [8]
18	**2a**	**4**	2-ClC_6H_4COOH	1 : 1.5 : 4 : 4	91	2 (51), 4 (49)	85/93
19	**2a**	**4**	2-ClC_6H_4COOH	1 : 2 : 4 : 4	96	2 (52), 4 (48)	91/94
20	**2a**	**4**	AcOH [d]	1 : 1.5 : 6	58	2 (50), 4 (50)	55/95 [8]
21	**3**	**4**	2-ClC_6H_4COOH	1 : 1.5 : 4 : 4	94	1 (95), 3 (5)	88/94
22	**3**	**4**	2-ClC_6H_4COOH	1 : 2 : 4 : 4	100	1 (98), 3 (2)	98/98
23	**3**	**4**	AcOH [d]	1 : 1.5 : 6	51	1 (86), 3 (14)	49/92 [8]
24	**2b**	**4**	PhCOOH	1 : 2 : 4 : 4	77	2 (100)	70/91
25	**2b**	**4**	2-ClC_6H_4COOH	1 : 2 : 4 : 4	95	2 (100)	87/92
26	**2b**	**4**	AcOH [d]	1 : 1.5 : 6	32	2 (100)	21/66 [8]
27	**2b**	**5**	2-ClC_6H_4COOH	1 : 1.5 : 4 : 4	65	2 (100)	58/89
28	**2b**	**5**	2-ClC_6H_4COOH	1 : 2 : 4 : 4	75	2 (100)	70/93

[a] Compounds **4—6** were taken in an amount of 0.005 mol.

[b] The conversion of $Pb(OAc)_4$ was 100%.

[c] The yield is given with respect to the starting/converted 1-methylcycloalkanol **4—6**.

[d] The reaction in a solution in AcOH, 80 °C.

was consumed with almost equal rates. Cycloalkanol **4**, which was added to the $Pb(OAc)_4$—**1b**—2-chlorobenzoic acid reaction mixture, had no noticeable effect on the total rate of the oxidative process, while reacting actively with $Pb(OAc)_4$. Apparently, the high conversion of **4** was attained due to the tight contact between cycloalkanol and the oxidizing agent in the solid composition. It should be noted that in the solid phase, the oxoalkyl radicals were efficiently captured by both mono- and bicyclic compounds **1—3** to give the 1 : 1 adducts. The degree of their involvement in side reactions varies in the range of 5—20% depending on the pair combination of the reagents **1—3** and **4—6**. In the liquid-phase reactions, the similar conversions were achieved only for bicyclic compounds **2—3**. In the case of monocyclic compounds **1a—c**, 35—45% of the oxoalkyl radicals were involved in side reactions (recombination, hydrogen abstraction).[8]

The reactivity of cycloalkanols **4—6** in oxoalkylation changes in the order **4** > **5** > **6**. This conclusion is true for both the solid and liquid phases and follows from a comparative analysis of the conversions of compounds **4—6** in the reactions with 4-methylpyridine (runs 7, 10, and 12), the conversions of compounds **4—5** in the reactions with 4-methylquinoline (runs 25 and 28), and the yields of the oxoalkylation products.

As mentioned above, benzoic and 2-chlorobenzoic acids serve an auxiliary function, *i.e.*, they act as protonating agents with respect to nitrogen bases **1—3** and simultaneously serve as a template in which the reactions proceed. Oxoalkylation of compounds **1b**,**c** and **2b** by cycloalkanol **4** with the use of both acids gave similar results (runs 5, 7, 14, 16, 24, and 25) although preference should be given to 2-chlorobenzoic acid. The reaction of 4-methylpyridine with cyclopentanol **5** produced sharply different results. Thus, the conversion of **5** in the reaction involving benzoic acid was only 5%, whereas an almost quantitative conversion was achieved in the reaction with 2-chlorobenzoic acid (runs 9 and 10). These facts are hardly to be attributed only to the difference in the acid strength. The effect of acidity is manifested in the protonation step and, as a consequence, in the step of interaction of the oxoalkyl radicals with the protonated heterocycles. For the reaction to proceed successfully, the chemical complementarity and structural compatibility of the reagents, which ensure their tight contact, are required. Apparently, the solid composition involving 2-chlorobenzoic acid better satisfies this requirement as compared to that with benzoic acid.

Hence, it can be concluded that the solid-phase oxoalkylation of *N*-heteroaromatic compounds with 1-methylcycloalkanols is characterized by a higher conversion of 1-methylcycloalkanols and higher yields of the target products as compared to the analogous liquid-phase reactions.

Experimental

The GLC analysis was carried out on an LKhM-80 chromatograph equipped with a flame ionization detector and 3 m × 3-mm analytical columns with 5% SE-30 and 5% XE-60 on Chromaton N-AW-HDMS (0.16—0.20 mm). The IR spectra were recorded on a Specord-80 spectrophotometer in a thin layer between NaCl plates. The ^{1}H and ^{13}C NMR spectra were measured on a Bruker AC-200 spectrometer in $CDCl_3$. The mass spectra were obtained on a Finnigan MAT ITD-700 spectrometer at 70 eV (*m/z*, 50—500). The starting 1-methylcyclopentanol (b.p., 53 °C (15 Torr))[9] and 1-methylcyclohexanol (b.p. 67—68 °C (20 Torr))[9] were prepared from the corresponding cycloalkanones and methylmagnesium halides by the Grignard reaction. 1-Methylcyclobutanol, isoquinoline, and 4-methylquinoline were purchased from Aldrich. 4-Methylpyridine, 2,4-dimethylpyridine, benzoic acid, and 2-chlorobenzoic acid were purchased from Lancaster. All commercial reagents were used without additional treatment. Pyridine and quinoline of chemically pure grade were dried over alkali and distilled before use. Lead tetraacetate of reagent grade was washed with glacial AcOH and dried over alkali *in vacuo*.

Solid-phase oxoalkylation of *N*-heteroaromatic compounds (general procedure). A mixture of the heterocycle (**1—3**), 1-methylcycloalkanol (**4—6**) (0.005 mol), $Pb(OAc)_4$, and PhCOOH (or $2\text{-}ClC_6H_4COOH$) (the reagent ratio is given in Table 1) was thoroughly stirred in a weighing bottle for 5—10 min, after which the reaction mixture became liquid and then solidified. For 1-methylcyclobutanol and 1-methylcyclopentanol, the reaction time (complete conversion of $Pb(OAc)_4$) was ~20 h. In the case of 1-methylcyclohexanol (with the use of $2\text{-}ClC_6H_4COOH$), the reaction time was ~50 h. After completion of the reaction, $CHCl_3$ and ether were added to the reaction mixture. The conversions of the starting heterocycles **4—6** and the yields of the reaction products **7—12** were determined by GLC. The conversion of the oxidizing agent was determined by iodometry.[10] To isolate the reaction products, the organic layer was treated with 3% aqueous HCl, washed with a saturated solution of Na_2CO_3, and dried with Na_2SO_4, and then the solvent was distilled off. Compounds **7—12** were isolated from the residue by either distillation or preparative GLC (2 m × 10-mm copper column with 5% SE-30 on Chromaton N-AW-HDMS, 0.25—0.36 mm). Compounds **7a—d**, **8a**,**d**, **9a**,**b**,**e**, **10a**, **11a**, and **12a** have been identified by us previously.[8] In the present study, additional characteristics of these compounds are reported.

A mixture of **2-(4-oxopentyl)pyridine (7a)** and **4-(4-oxopentyl)pyridine (8a)**. IR, ν/cm^{-1}: 1716 (C=O). According to the ^{1}H and ^{13}C NMR spectra, compounds **7a** and **8a** are identical with those described previously.[8]

A mixture of **2-(5-oxohexyl)pyridine (7d)** and **4-(5-oxohexyl)pyridine (8d)**. IR, ν/cm^{-1}: 1715 (C=O). Found (%): C, 74.65; H, 8.44; N, 7.89. $C_{11}H_{15}NO$. Calculated (%): C, 74.58; H, 8.47; N, 7.91. According to the ^{1}H and ^{13}C NMR spectra, compounds **7d** and **8d** are identical with those described previously.[8]

2-(4-Oxopentyl)-4-methylpyridine (7b), b.p. 62—63 °C (10 Torr). IR, ν/cm^{-1}: 1716 (C=O). According to the ^{1}H and ^{13}C NMR spectra, the compound is identical with that described previously.[8]

2-(5-Oxohexyl)-4-methylpyridine (7e), b.p. 67—68 °C (10 Torr). IR, ν/cm^{-1}: 1715 (C=O). ^{13}C NMR ($CDCl_3$), δ: 20.56 ($C(4)H_3$); 29.47 ($C(1)H_3$); 23.07, 28.85, 37.48, 43.10 (CH_2); 120.77 (C(3)); 123.29 (C(5)); 146.97 (C(4)); 148.50 (C(6)); 161.07 (C(2)); 208.44 (C=O). The ^{1}H NMR spectrum of compound **7e** is identical with that described previously.[8]

2-(6-Oxoheptyl)-4-methylpyridine (7f). IR, ν/cm^{-1}: 1712 (C=O). Found (%): C, 76.44; H, 9.06; N, 6.99. $C_{13}H_{19}NO$. Calculated (%): C, 76.10; H, 9.27; N, 6.83. ^{1}H NMR ($CDCl_3$), δ: 1.34 (m, 2 H, CH_2); 1.62 (m, H, CH_2); 2.11 (s, 3 H, CH_3CO); 2.32 (s, 3 H, $C(4)H_3$); 2.42 (t, 2 H, CH_2CO, $J = 3.7$ Hz); 2.75 (t, 2 H, $C\underline{H}_2CH_2CH_2CH_2CH_2$, $J = 3.8$ Hz); 6.95 (d, 1 H, H(5), $J = 4.6$ Hz); 6.97 (s, 1 H, H(3)); 8.39 (d, 1 H, H(6), $J = 4.5$ Hz). ^{13}C NMR ($CDCl_3$), δ: 21.03 ($C(4)H_3$); 23.56, 28.81, 29.82, 37.69, and 43.55 (CH_2); 29.54 ($\underline{C}H_3CO$); 122.13 (C(3)); 123.09 (C(5)); 147.91 (C(4)); 148.02 (C(6)); 161.59 (C(2)); 209.01 (C=O). MS, *m/z* (I_{rel} (%)): 206 $[M + H]^+$ (37); 162 $[M - MeCO]^+$ (6); 148 $[M - MeCOCH_2]^+$ (7); 134 $[M - MeCOCH_2CH_2]^+$ (18); 120 $[M - MeCOCH_2CH_2CH_2]^+$ (21); 107 $[MeCCHCHNHC(=CH_2)CH]^+$ (100).

2,4-Dimethyl-6-(4-oxopentyl)pyridine (7c). IR, ν/cm^{-1}: 1712 (C=O). According to the ^{1}H and ^{13}C NMR spectra, the compound is identical with that described previously.[8]

A mixture of **2-(4-oxopentyl)quinoline (9a)** and **4-(4-oxopentyl)quinoline (10a)**. IR, ν/cm^{-1}: 1720 (C=O). According to the ^{1}H and ^{13}C NMR spectra, compounds **9a** and **10a** are identical with those described previously.[8]

A mixture of **1-(4-oxopentyl)isoquinoline (11a)** and **3-(4-oxopentyl)isoquinoline (12a)**. IR, ν/cm^{-1}: 1712 (C=O). Found (%): C, 78.85; H, 7.11; N, 6.32. $C_{14}H_{15}NO$. Calculated (%): C, 78.87; H, 7.04; N, 6.57. According to the ^{1}H and ^{13}C NMR spectra, compounds **11a** and **12a** are identical with those described previously.[8]

2-(4-Oxopentyl)-4-methylquinoline (9b). IR, ν/cm^{-1}: 1720 (C=O). Found (%): C, 79.42; H, 7.51; N, 6.27. $C_{15}H_{17}NO$. Calculated (%): C, 79.30; H, 7.49; N, 6.17. According to the ^{1}H and ^{13}C NMR spectra, the compound is identical with that described previously.[8]

2-(5-Oxohexyl)-4-methylquinoline (9e). IR, ν/cm^{-1}: 1712 (C=O). Found (%): C, 79.62; H, 7.86; N, 5.78. $C_{16}H_{19}NO$.

Calculated (%): C, 79.67; H, 7.88; N, 5.81. ^{1}H NMR ($CDCl_3$), δ: 1.69 (m, 4 H, CH_2); 2.06 (s, 3 H, CH_3CO); 2.43 (t, 2 H, CH_2CO, J = 3.5 Hz); 2.63 (s, 3 H, C(4)H_3); 2.93 (t, 2 H, $C\underline{H}_2CH_2CH_2CH_2$, J = 3.7 Hz); 7.11 (s, 1 H, H(3)); 7.46 (t, 1 H, H(7), J = 3.6 Hz); 7.64 (t, 1 H, H(8), J = 3.7 Hz); 7.90 (d, 1 H, H(6), J = 4.1 Hz); 8.08 (d, 1 H, H(9), J = 4.1 Hz).

Liquid-phase reaction of $Pb(OAc)_4$, 4-methylpyridine (1b), and 1-methylcyclohexanol (6). A mixture of cycloalkanol **6** (0.005 mol), $Pb(OAc)_4$ (0.0075 mol), and pyridine **1b** (0.03 mol) in glacial AcOH (10 mL) was vigorously stirred at 80 °C until $Pb(OAc)_4$ was completely converted (test for KI, the duration of the reaction was ~4 h). The conversion of the starting cycloalkanol **6** was determined by GLC with the use of the internal standard.

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