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Comparative Reactions of Nitrogen Compounds with the Isoelectronic Series Mercury(II), Thallium(III), and Lead(IV) Acetates. Principles of Oxidation Reactions

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Contents

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I. *Introduction*

The compounds mercuric acetate (Hg2A), thallium triacetate (TTA), and lead tetraacetate (LTA) are widely used as reagents in organic synthesis. Their reactions include two- and one-electron reductions of the metal, and the variety of pathways by which this can occur includes both ionic and free radical mechanisms. These may involve intra- and intermolecular nucleophiles including solvent molecules thus leading to a broad and interesting chemistry for the reagents. Substitution and addition reactions in which the metallic oxidation state does not change are also observed. There are some thousands of papers in the literature on the uses and behavior of these three reagents, and this high level of interest has resulted in many major reviews. These include accounts of the chemistry of the individual reagents with special functional groups. Thus, for mercury(II) acetate, reviews include oxymercuation of alkenes,[1–5] aromatic mercurations,[6,7] and reactions of mercuric acetate with fatty acids.[8] There are several excellent reviews of the reactions of organic compounds in general with TTA,[9,10] LTA,[11–13] and Hg2A.[14] Special reviews dealing with LTA include oxidations of alkenes,[15] alcohols,[16] carboxylic acids,[17] and sugars.[18]

While most of the general reviews mentioned[9–14] include some discussion of reactions with organic nitrogen compounds, there have been but a few reviews devoted specially to this field and these have been confined to LTA. Aylward[19] has discussed the reactions of LTA with organic nitrogen compounds in general, and the reactions of LTA with substituted azomethines ($>C{=}N{-}$) have been discussed in this journal.[20] Specialized reviews of the reactions of LTA with substituted oximes,[21] hydrazones,[22] heteroallylic systems,[23] and in oxidative cyclizations of carbonylhydrazones[24] have also

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been published. A review of inorganic mercury–nitrogen compounds[25] contains an interesting discussion on the nature of the mercury–nitrogen bond.

This paper is concerned specifically with the behavior of the reagents toward organic nitrogen compounds. Particular emphasis is placed on the comparative chemistry involved since this approach provides useful insights into the factors which determine often widely diverse product control in apparently similar oxidation reactions. Extensive accounts of the reactions of many nitrogen compounds with LTA[12,13] and Hg2A[14] have been provided recently and these preclude repetition herein other than for the stated comparative purposes of this review. Throughout the review the term "acetoxylation" implies the introduction of the elements of an acetoxyl group ($C_2H_3O_2$) to a molecule in any form, not necessarily a compact acetoxyl group. The term *metalation* (e.g., mercuration) means a *substitution* of the group $M(OAc)_{n-1}$ (e.g., –HgOAc) for a proton in a molecule. This review does not include aminomercurations and solvomercurations in general where the main reaction of the electrophile is with an olefin moiety followed by secondary involvement of an external nitrogen compound or solvent, as a nucleophile. An extensive review of these types of reactions has been provided recently.[14] The following abbreviations are used throughout the review: LTA, $Pb(OAc)_4$; LDA, $Pb(OAc)_2$; TTA, $Tl(OAc)_3$; TTN, $Tl(NO_3)_3$; TA, TlOAc; Hg2A, $Hg(OAc)_2$ (Hg is preferred over M for mercury, since for example an abbreviation such as "MDA" would not distinguish it from common magnesium or manganese salts); TFA, CF_3COO; Ac, CH_3CO.

II. The Reagents

A. Preparation

The three reagents are available commerically but the claimed purity of commercial samples should be carefully checked. Hg2A may be easily prepared by heating metallic mercury with peracetic acid in acetic acid solution.[26] The peracetic acid may be generated in situ to simplify the process. Thus the reagent may be prepared by slow addition of 50% hydrogen peroxide (60 g) to a stirring mixture of Hg (150 g), glacial acetic acid (450 g), and nitric acid (7 g) at 40 °C.[27] A white suspension of HgOAc forms after about 30 min. The mixture is then heated to 80 °C and stirred to give a clear solution. When the mixture is cooled and fractionally evaporated, Hg2A is obtained in high yield.[27] LTA and TTA are best prepared from the metal oxides. LTA can be readily obtained by slow addition of red lead oxide (Pb_3O_4) in ca. 20-g quantities to a mixture of acetic acid (550 g) and acetic anhydride (185 g) at 60–80 °C. When the mixture is cooled, white needles of LTA separate.[28-30] Anhydrous TTA may be prepared by prolonged heating of thallium(III) oxide under reflux in acetic acid containing 20% (v/v) of added water to convert the oxide first to the hydroxide, which is more efficiently converted to the acetate,[31] followed by crystallizing the product from acetic anhydride.[32]

LTA is hydroscopic and turns brown due to lead dioxide formation on exposure to air. It is best stored in the dark at 5 °C and moistened to a paste with acetic acid containing a trace of acetic anhydride. Commercial samples may contain up to 10% acetic acid and usually require recrystallization from acetic acid before use. Dry samples may be obtained by washing the paste under suction with small quantities of dry diethyl ether or by azeotropic distillation with benzene immediately before use. The surface of pure dry samples begins to turn brown from lead dioxide formation after a few minutes of exposure to the atmosphere. LTA may be estimated by standard sodium thiosulfate titration after treatment with excess potassium iodide using starch indicator. Pure TTA is also rapidly discolored to the oxide by moisture. It also may be estimated by sodium thiosulfate titration after treatment with excess 5% potassium iodide solution using starch indicator.[31] However, this estimation is more complicated than for LTA due to the formation of $Tl_2(OAc)_4$ from TTA and TA in solution.[31] Hg2A can be estimated in aqueous solution by standard thiocyanate titration after treatment with nitric acid. In acetic acid solution Hg2A can be titrated against chloride or bromide salts by using indicators such as sodium nitroprusside,[33] diphenylcarbazone,[33] or dithizone.[34]

TABLE I. Characteristics of the Reagents

property	$Pb(OAc)_4$	$Tl(OAc)_3$	$Hg(OAc)_2$
mp, °C	175 (D)[a]	75–80 (D)[a]	(D)[a]
$E°$, $M^{n+} + 2e^- \rightarrow M^{(n-2)+}$	1.6–1.75[b]	1.25[b]	0.85[c]
E, LUMO (ev), M^{n+}		–3.37[d]	–4.64[d]
dissociation, K (HOAc)	*e*	1.38×10^{-12}[f]	3.75×10^{-9}[g]

[a] Decomposition. [b] Reference 35. [c] Reference 36. [d] Reference 52. [e] Negligible dissociation reported (cf. text). [f] 25°C, Ref. 32. [g] Reference 42.

B. Structure and Properties

The three reagents contain isoelectronic metal atoms having the electronic configuration $[Xe]4f^{14}5d^{10}$. The oxidation states of the metal are reflected in the decreasing standard reduction potentials (Table I) Pb(IV) > Tl(III) > Hg(II).[35,36] The molecular formulas suggest decreasing coordination of the metal from lead to mercury and this is illustrated by the crystal structures. In crystalline LTA the metal atom is fully coordinated with the four acetate groups exhibiting eightfold coordination around the central lead atom with a distorted cubic geometry.[37] The space group is $P2_{1/c}$ and the unit cell containing eight molecules of LTA is monoclinic with dimensions a, 13.01, b, 26.59, c, 7.86 Å and β, 105° 36′. The structure is built of independent sets of molecules, and there are no bridging atoms between the lead atoms so that each group of four acetate ions belongs to one lead atom only.[37] The packing arrangement gives a coordination polyhedron of oxygen atoms around each lead atom which is a flattened dodecahedron.[37] Carboxylate anion stretching appears at 1520–1540 cm^{-1} and 1400–1410 cm^{-1} and no ester-type carbonyl bands are detected in Nujol or benzene solutions since the oxygen atoms are equivalent.[38] Lead salts of this type show a UV band at 220–270 nm due to an O → Pb charge transfer.[38] Crystalline TTA is monoclinic and a member of the space group $C_{2/c}$ with unit cell dimensions of a, 15.540, b, 8.630, c, 7.848 Å and β, 113.92°.[39] The calculated d value is 2.57 for $Z = 4$ (number of gram formula weights per unit cell). The thallium atom lies on a twofold axis achieving irregular eightfold coordination (Figure 1a) with shortest bonds

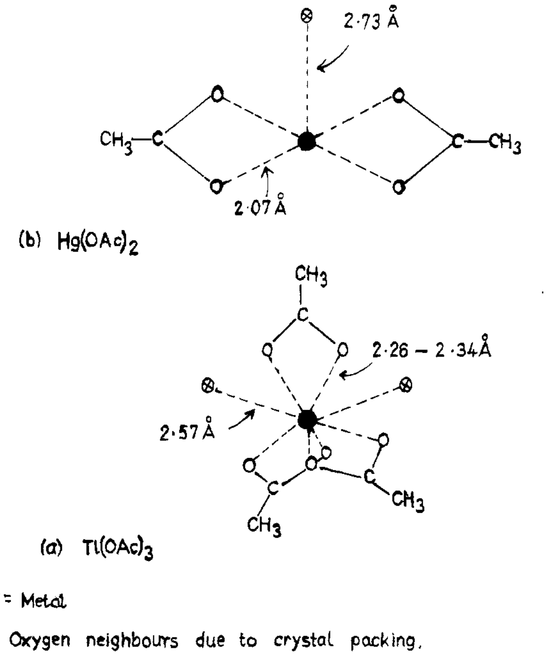
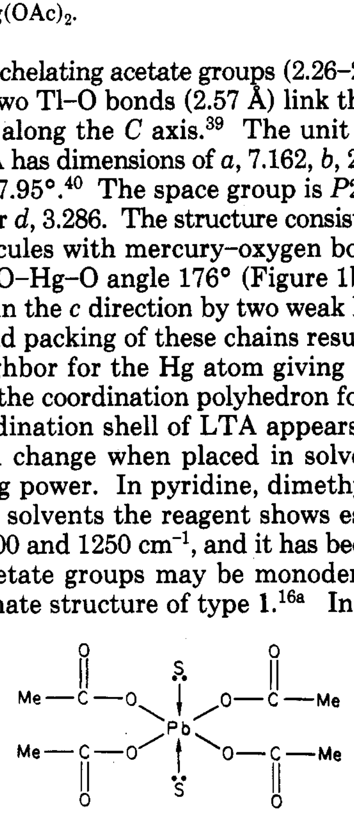


Figure 1. Metal coordination in (a) crystalline $Tl(OAc)_3$ and (b) crystalline $Hg(OAc)_2$.

to the three chelating acetate groups (2.26–2.34 Å). The remaining two Tl–O bonds (2.57 Å) link the molecules into chains along the *C* axis.[39] The unit cell of crystalline Hg2A has dimensions of *a*, 7.162, *b*, 20.13, *c* 4.627 Å and *β*, 107.95°.[40] The space group is $P2_{1/a}$ with a *Z* value of 4 for *d*, 3.286. The structure consists of isolated Hg2A molecules with mercury–oxygen bond distance 2.07 Å and O–Hg–O angle 176° (Figure 1b).[41] Chains are formed in the *c* direction by two weak Hg–O bonds of 2.73 Å and packing of these chains results in a fifth oxygen neighbor for the Hg atom giving a tetragonal pyramid as the coordination polyhedron for mercury.[41]

The coordination shell of LTA appears to undergo a structural change when placed in solvents of high coordinating power. In pyridine, dimethyl sulfoxide, and alcohol solvents the reagent shows ester-type IR bands at 1700 and 1250 cm^{-1}, and it has been suggested that the acetate groups may be monodentate with a hexacoordinate structure of type **1**.[16a] In solutions of acetic acid and more basic solvents the coordination shells of Hg2A and TTA are probably also completed by solvent molecules occupying the vacant coordination sites. In reactions with nucleophilic nitrogen compounds it is likely that for these reagents the early stages should involve replacement of coordination acetic acid or solvent molecules by the nitrogen substrate.



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The reagents exhibit little or no dissociation in solution (Table I). Low dissociation constants have been reported for LTA[32] and Hg2A.[42] Solutions of LTA in acetic acid show virtually no electrical conductivity[43,44] and crysocopy suggests no dissociation of the compound in solution.[45] In hydroxyl and carboxylic acid solvents, at ambient temperatures there is a rapid exchange of acetate groups between the metal coordination shell and the bulk solvent. This has been confirmed by isotopic labeling for LTA[46] and by variable-temperature ^1H NMR for TTA[47] when the normal methyl singlet (δ 2.02) reversibly split into a doublet showing long range Tl–H coupling (J_{Tl-H}, 26.3 Hz) at temperatures below −65 °C in methanol. In solid-state ^{13}C CP/MAS spectra of crystalline Hg2A ^{13}C–^{199}Hg couplings have also been observed.[48] These are absent in solution ^{13}C NMR spectra due to the rapid exchange of acetate groups with the bulk solvent.[48] In solutions of strong acid all or some of the acetate groups may be replaced. For example, when treated with hydrogen chloride or hydrogen bromide in tetrahydrofuran LTA is converted to $Pb(OAc)_2X_2{\cdot}2THF$[49] and in sulfuric acid it is converted $H_2Pb(HSO_4)_6$.[50,51] A number of reagents of the type $Pb(OAc)_{4-n}(X)_n$ are now in general use, the most notable being where X is a fluoride or an azide group. Other salts of the metals such as trifluoroacetates and nitrates (of Tl(III)) are also commonly used in synthesis and these will be referred to in the context of the acetates.

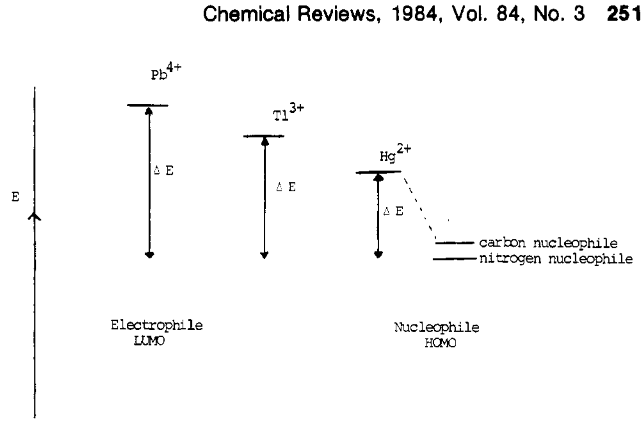


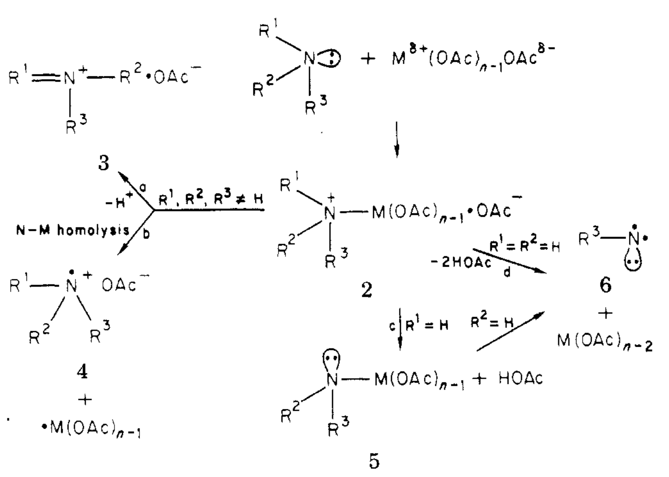
Figure 2. Relative HOMO–LUMO separation for a given nucleophile with the reagents.

The reagents are soft electrophiles with softness decreasing toward Pb(IV). The energies of the empty frontier orbitals calculated by Klopman[52] showed Tl^{3+} and Hg^{2+} at the lower extremity of 25 cations (Table I). Hard electrophiles such as Al^{3+} and Fe^{3+} had LUMO energies of 6.01 and 2.22 eV compared to −4.64 eV for Hg^{2+}. Although these values refer to aqueous solutions, they are important since some nitrogen substrates are borderline soft ambident nucleophiles with relatively high energy HOMOs (Figure 2). Orbital interactions could therefore play a significant role in the reactions of some nitrogen compounds with these metallic acetates although the reactions appear to be mainly charge controlled.

C. Toxicity and Handling

The three reagents are cumulative poisons and need to be handled with respect. The metals are resorbed through the skin from solutions, and the skin threshold limit values are 0.1–0.2 mg/L.[53,54] Solutions of the reagents should not be spilled or allowed to come in contact with the skin. In the case of poisoning from LTA the metal tends to be stored in the liver and brain and causes a disorder of the central nervous system which reaches a climax 6 weeks after exposure. Lead is subsequently excreted through the kidney and intestine.[53] When applied to the rabbit hypothalamus, Hg2A evoked brain seizure by blocking Na transport

SCHEME I

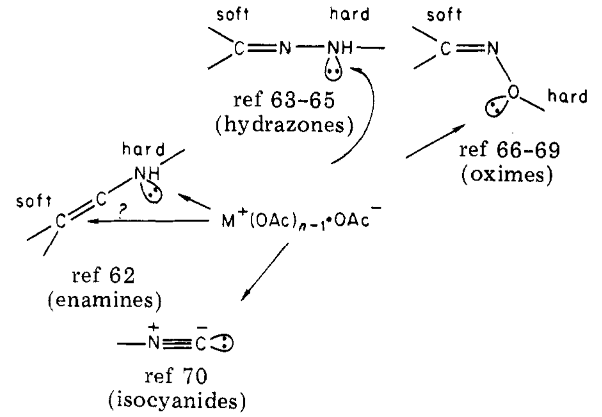


due to inhibition of the membrane ATPase.[55] Hg2A ingested by rats caused severe kidney damage and the metal was also distributed to the brain and testes. Storage of mercury in the liver and kidney was 10–20 times higher for Hg2A ingestion than for other organomercury compounds.[56–58] The major route for excretion of mercury after Hg2A ingestion was in the urine whereas mercury excretion from phenylmercuric acetate was via bile and the intestinal tract.[59] Thallium is excreted particularly slowly from the body.[60] The reagents merit extra precautions during pregnancy. Hg2A is embryopathic and caused delayed growth of animal fetuses as well as weight loss, kidney lesions, diarrhea, tremors, and somnolence in the maternal system.[61] Exposure to small quantities of the reagents over long periods may result in symptoms such as loss of appetite, insomnia, tremor of hands, loss of memory, falling out of hair, weakness of limbs, and irritability. Anyone suspecting of poisoning from the reagents should cease working with them, seek medical advise, and undero urine tests. When these reagents are being used, rubber gloves should be worn and work should be carried out in a restricted controlled area such as a fume hood with good ventilation. The work area should be scrubbed clean regularly to remove dust arising from minor spillage or unwashed vessels. Such precautions which are normal should in fact be applied to most chemicals and represents nothing more than good laboratory management. Small quantities of the salts may be disposed of by running to waste with very high aqueous dilution. Larger quantities should be stored, accumulated; and finally mixed with 10–20 times their weight of sand and buried in an approved place.

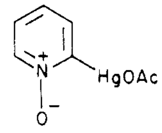
III. Mechanism: General Discussion

A. The Early Stage

SCHEME II



The early stage of the reaction of the metallic acetates with organic nitrogen compounds involves penetration of the metal coordination shell followed by electrophilic attack[9–14] on the HOMO of the nucleophile probably giving the species 2 (Scheme I). This stage appears to be charge controlled,[52] since with ambident systems there is *little* evidence of attack at the softer site and many reactions have been explained in terms of electrophilic attack at the harder sites (Scheme II).[62–68] Orbital control[71a] would be most likely to arise with the softest reagent Hg2A. Orbital control of Hg2A attack on carbon nucleophiles has been suggested with pyridine *N*-oxide where mercuration occurs at the softer 2-position giving compound **7**.[71b] Correlations of the reaction rates of Hg2A, TTA, and LTA with ionization potentials of alkenes and with the inverse of the HOMO–LUMO gap have been noted suggesting significant orbital control.[72] In this context it is of interest that the reaction of Hg2A with phenylhydrazones gave the products **8** in a regiospecific reaction[73] which is quite different from those of TTA and LTA. However, it is relevant that metallo intermediates can sometimes be isolated from Hg2A reactions with nitrogen compounds and in these the mercury is generally bonded to the harder site. Detailed knowledge of the early stages of the reactions with nitrogen compounds is relatively sparse and possible correlations of rates with ionization potentials and FMO gaps do not appear to have been tested. While the reactions are mainly charge controlled, *orbital effects appear to significantly influence* the reactions of mercuric acetate with some nitrogen substrates where the HOMO–LUMO separation is appropriate (Figure 2). Further work is required in this area.



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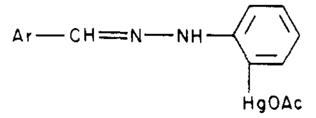

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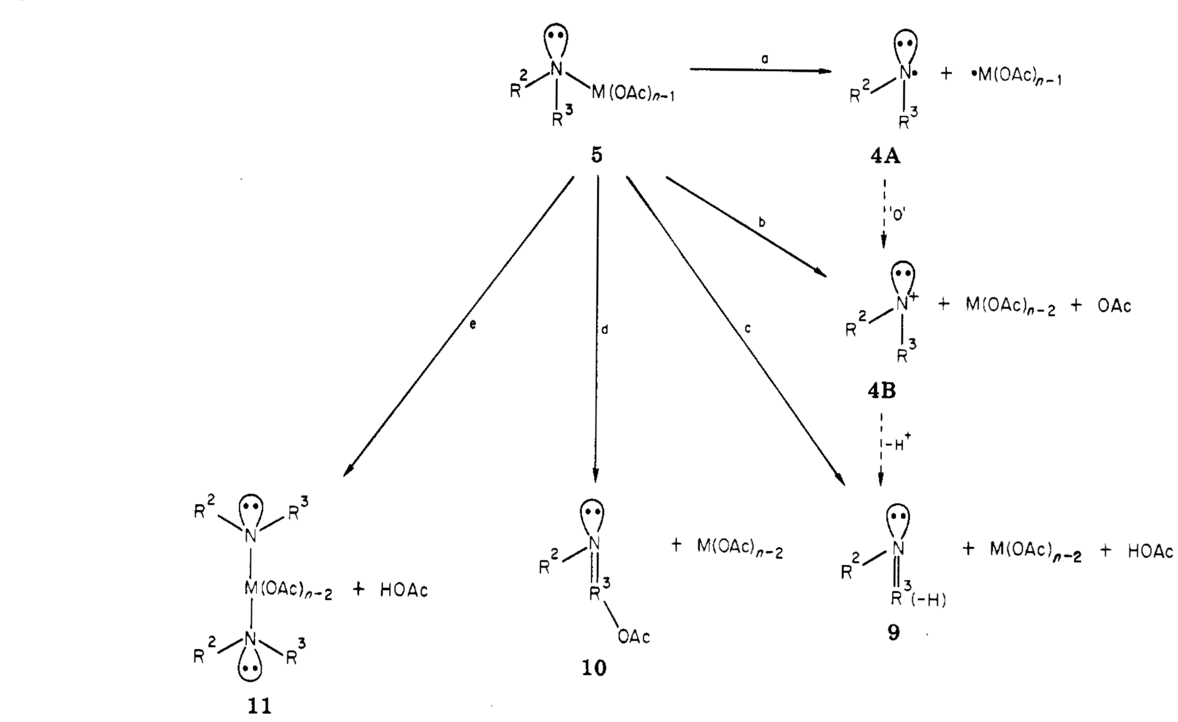
B. Reactive Intermediates

1. Tertiary Nitrogen (>N–)

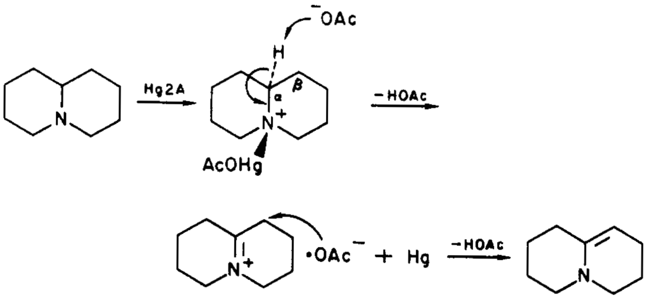
After the initial collision which gives rise to the species 2 the reaction may proceed through a variety of pathways (Schemes I and III). The preferred course depends on a number of factors which include (i) the nature of the substrate and the substituents R^1, R^2, and R^3, (ii) the lability of the nitrogen–metal bond, (iii) the reduction potential of the metal (Table I), and (iv) the nature of the medium and the solvation of the metal ion.

The nature of the substrate is of fundamental importance, and if the nitrogen is tertiary ($R^1, R^2, R^3 \neq$ H), *the intermediate* (**2**) may cleave by paths a or b (Scheme I) giving the iminium ion (**3**) or the cation radical **4**. It is not necessary to invoke an intermediate such as **2** as a precursor to the cation radical (**4**), and

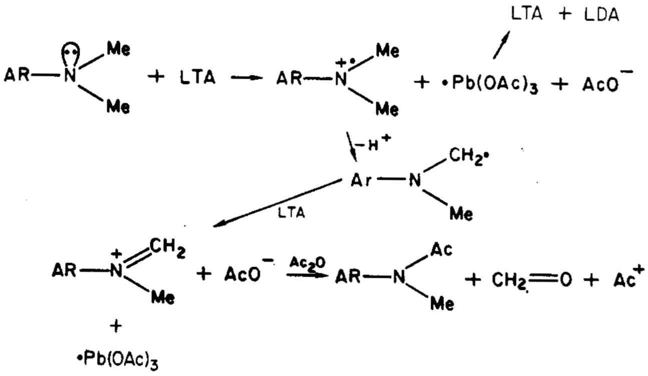
SCHEME III



SCHEME IV

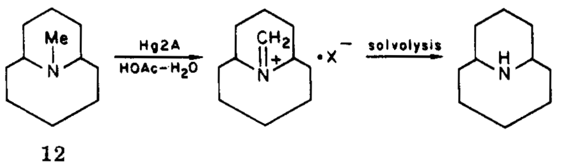


SCHEME V



some workers appear to prefer a direct one-electron transfer to the electrophile. However, in the absence of some outside source of excitation such as irradiation, the most plausible way by which this could occur is via a molecular collision which implies an N–metal bond, however short-lived.

Path a appears to be preferred when the metal is Hg(II). In an extensive study 25 years ago Leonard[74-78] showed that the reaction of excess Hg2A with tertiary amines involved rapid Hg(II) attack on the N atom giving the sequence outlined in Scheme IV. The reaction involved a rate-determining H abstraction from the α-carbon, and the order of Cα–H bond cleavage was tertiary > secondary > primary.[74] The Cα–H bond which was cleaved preferentially was trans coplanar to the N–Hg bond and the reaction was an E_2-type elimination giving an iminium salt[75] (Scheme IV). A subsequent proton abstraction from the β-carbon gave enamine products (Scheme IV). With substrates where the geometry was chosen to preclude a trans elimination of the tertiary Cα–H bond, for example compound 12, the proton loss occurred from the N–Me group where a trans elimination could still occur giving a demethylation. The cationic species in these reactions may also be attacked by nucleophiles,[76] and addition of H_2O to give alcohols has been noted.[79]



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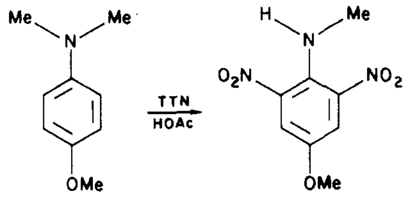
Demethylation (and dealkylation) of *N*-methyl tertiary amines is a common reaction with the series of metallic acetates in which the dealkylated group is ejected as an aldehyde. In the reaction of aryldialkylamines with LTA demethylation was preferred over dealkylation.[80] The reactions with TTA and LTA are dominated by the cation radical species 4 (Scheme I). These have been directly detected by ESR spectra of flow systems of aromatic amines and LTA in dichloromethane–trifluoroacetic acid mixtures.[81] The mechanism outlined in Scheme V has been proposed from a kinetic study of the oxidation of aryldimethylamines with LTA in chloroform–acetic anhydride medium.[82-84] The Hammett ρ value was −2.7 and the reaction was first order in LTA and amine. With TTA as oxidizing agent in the same medium, differences were noted as the Hammett ρ value was −3.5: the reaction showed zero-order dependence on TTA and oxygen became involved in the process by capturing the radicals.[84] When the reagent was TTN in acetic acid, nitration of the ortho positions of the aromatic ring accompanied demethylation. Thus treatment of compound **13** with TTN in acetic acid gave the product **14** in 59% yield.[85] The aromatic nuclear substitutions by ligands, which accompanied the oxidative dealkylations, were sensitive to the solvent and were also observed with secondary aromatic amines (cf. Scheme IX).



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The lability of the metal–nitrogen bond in species such as **2** (Scheme I) of **5** (Scheme III) decreases in the order Pb(IV)–N > Tl(III)–N ≫ Hg(II)–N paralleling the relative reduction potentials of the metal ions. Compounds containing Hg(II)–N bonds are well-known and some intermediates in Hg2A oxidations containing the moiety N–HgOAc have been isolated. Compounds containing the Tl(III)–N and Pb(IV)–N bonds are relatively rare and none appear to have been isolated from TTA and LTA oxidations. The Pb(IV)–N bond in known compounds of the type R_3–Pb–N has been reported[86] to be extremely labile. The Hg(II)–N bond on the other hand is stable, and in compounds of the type CH_3–Hg–NH_3^+ it is reported[25,87,88] to have a strong covalence, a bond length of 2.05–2.11 Å and a higher force constant (3.00 mdyn/Å) than a range of other metal–nitrogen bonds. While steric effects in species of types **2** and **5** might lengthen the bond altering these parameters, such an effect should be less for N–HgOAc than for N–Tl(OAc)$_2$ and N–Pb(OAc)$_3$ thereby adding further to the relative stability of the mercury–nitrogen bond in these intermediates. Hence in competitive fragmentations of species **2** and **5** the mercury–intermediate should be the longest lived and the most selective in choosing interactions with the more suitable nucleophile. This type of selectivity should decrease from Tl(III) to Pb(IV). In general this seems to be the case with nitrogen compounds, although the balance between the thallium(III) and lead(IV) cases is small and the selectivity order could be reversed in some reactions as it is with some carbon substrates. In general the redox fragmentation of Pb(IV)–N intermediates tends to be rapid and intramolecular, occurring within the coordination sphere of the metal and not involving external nucleophiles. With Tl(III)–N intermediates there often tends to be sufficient time for external nucleophiles, and in particular the solvent, to get involved in the redox process, and Hg(II)–N intermediates there is time for the best external nucleophile to become involved, often attacking the Hg(II) which stays in this oxidation state. This pattern represents a broad general trend which is evident in the reactions described in section IV but there are exceptions and each reaction needs to be assessed on its own right.

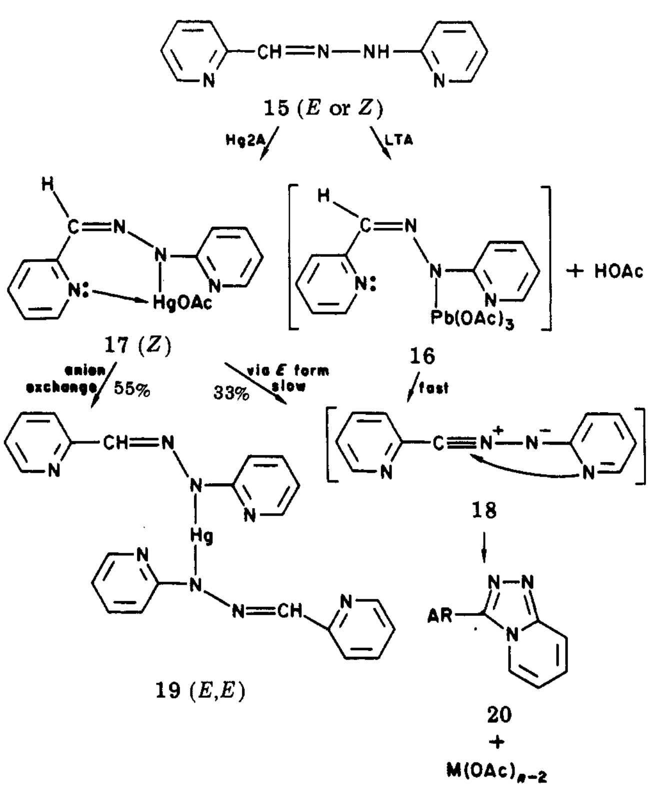
2. *Secondary and Primary Nitrogens (>NH; –NH$_2$)*

When there is at least one hydrogen on the nitrogen atom of species **2** (R^1 = H), the above reactions may still occur with the NH bond intact or more likely the NH proton may be rapidly removed by the acetate ion as a molecule of acetic acid generating the reactive neutral covalent N-metallo intermediate **5** (Scheme I, path c). Such intermediates have been directly detected and isolated from reactions with Hg2A. Their presence has been inferred from kinetic data with the other metals but they have not been isolated. The reactivity of species of type **5** appears to follow the order of lability of the N–metal bond or the related reduction potential of the metal. The main pathways followed by these *N*-metallo intermediates are summarized in Scheme III.

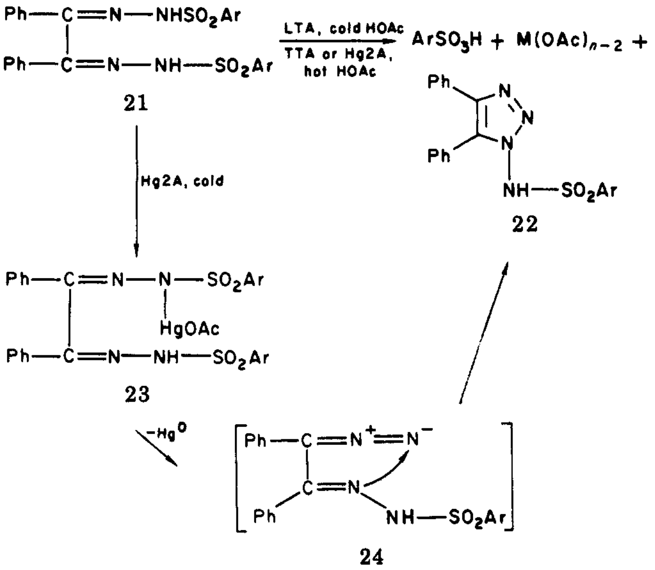
The homolysis of the N–metal bond can lead to amino radicals (**4A**) (path a, Scheme III). This radical is isoelectronic with the cation radical (**4**) (Scheme I) and may exist in equilibrium with this protonated form (**4**, R^1 = H). A redox heterolysis of the *N*-metallo bond in **5** could give rise to the amino cation (**4B**) (Scheme III, path b) and this cation (**4B**) could also arise from a secondary oxidation of the amino radical (**4A**). Paths c and d (Scheme III) represent intramolecular redox processes in the intermediates (**5**). The former involves loss of a proton from one of the nitrogen substituents, R^3, and the latter involves migration of an acetoxy group to an unsaturated site on one of the nitrogen substituents, e.g., R^3, giving products of type **10**. Such behavior is common in reactions between LTA and appropriate substrates. Attack by a nucleophile on the species (**5**) may also occur in the redox step. Thus nucleophilic attack may occur on an appropriate site in one of the nitrogen substituents of the intermediate (**5**) and products of type **10** could arise from acetic acid solvent attack on an unsaturated site in R^3 which is activated by the adjacent metal atom. If the intermediate (**5**) is stable and relatively long-lived, selective attack on the metal by the parent nitrogen compound may also occur (path e, Scheme III). This appears to arise only with Hg2A, and stable products of type **11** are exclusive to this reagent. When the parent nitrogen substrate contains a primary nitrogen atom, –NH$_2$, the intermediate (**2**) will contain two N–H bonds. All of the subsequent pathways mentioned are still possible. An added possibility is the loss of two molecules of acetic acid to give a nitrene intermediate (**6**) (Scheme I, path d). This is a relatively rare pathway which appears to arise mainly with hydrazine and oxyamine substrate compounds in which the bonding site of R^3 has a lone pair, possibily indicating a type of α-effect.

Each of the variety of intermediates possible in these reactions has its protagonsits. Metallo intermediates of type **5** have been isolated in reactions with some hydrazone substrates (Scheme VI and VII). Thus treatment of the heterocyclic hydrazone (**15**) with LTA in acetic acid gave the *s*-triazolo[4,3-*a*]pyridine (**20**) (75–83%). A comparable reaction with Hg2A in hot acetic acid (80 °C) gave compound **20** in 37% yield along with the bis(hydrazone)mercury compound (**19**) (55%).[89] These cyclizations are an example of a general cyclization reaction with LTA[20] in which an intermediate of type **16** is usually postulated as a precursor to a nitrilimine (**18**) which undergoes 1,5-electrocyclization. In the reaction with Hg2A the intermediate **17** was isolated in quantitative yield at ambient temperatures and when this was separately heated at 80 °C in acetic acid it gave the cyclized product **20** and compound **19** in the correct proportions confirming its intermediacy.[89]

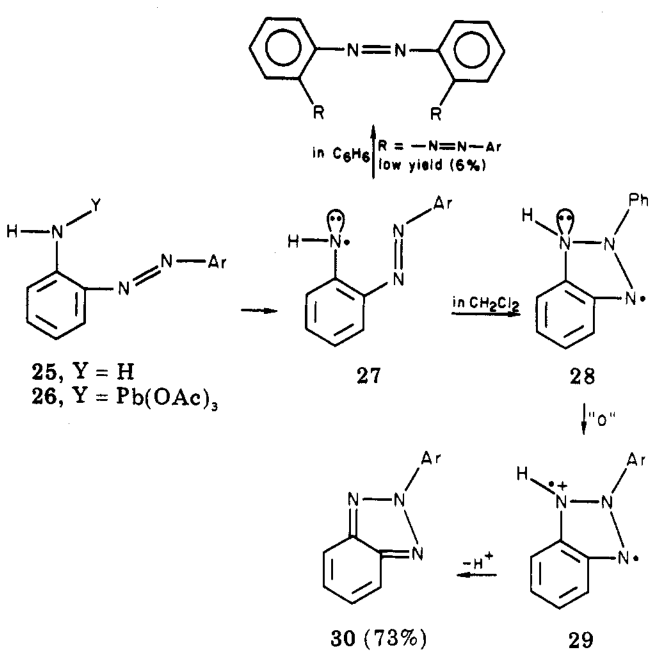
SCHEME VI



SCHEME VII



SCHEME VIII



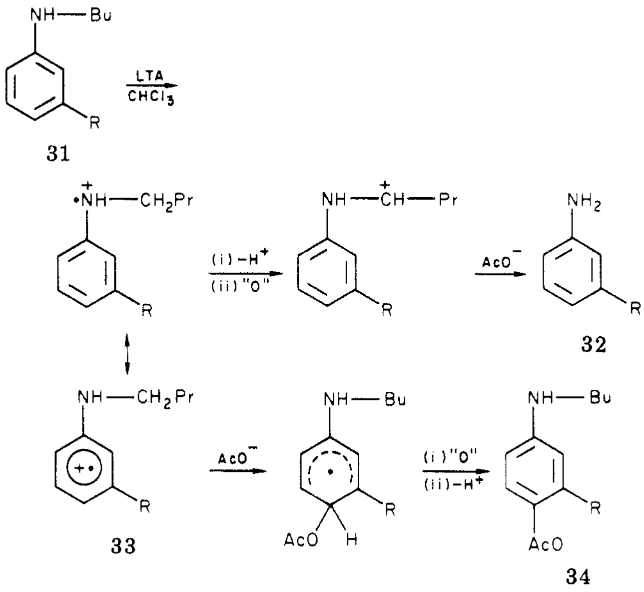
Metallo intermediates have not been isolated from the LTA reactions and compound **17** which had the *Z* configuration, irrespective of the configuration of the starting material, was probably stabilized by coordination of the metal by the pyridine nitrogen.[89] In these reactions the formation of the products (**19**) (cf. path e, Scheme III) arose by an anion exchange between two molecules of the metallo intermediate. Products of type **19** and **11** can also readily arise from an attack by a molecule of the starting nitrogen compound on the metallo intermediate and they may be formed in high yields when the mole ratio of substrate to Hg2A is 2:1. In the conversion of species **17** to **20** (Scheme VI) it is of interest that the *Z* structure of compound **17** changed to the *E* form, as monitored by ^{1}H NMR before the signals of the product (**20**) began to appear and the nitrilimine species (**18**) was too short-lived to be detected.[89] The formation of a nitrilimine species in this reaction represents an example of path c, Scheme III, involving hydrogen abstraction from an adjacent site in the N-substituent. The reactions outlined in Scheme VII represent one of the few cases where treatment of a substrate (**21**) with either of the three reagents, LTA, TTA, or Hg2A, gave the same reaction product (**22**) (80–90%). The metallo compound (**23**) was isolated as an unstable intermediate from the Hg2A reaction.[90,91] Evidence for a pathway involving process **24** has been presented.[91]

The presence of radical intermediates **27** (representing path a, Scheme III) in the oxidative cyclization of the ortho amino arylazo compounds (**25**) to the triazoles (**30**) with LTA has been proposed by Dyall[92] (Scheme VIII). The reaction was explained in terms of a direct one-electron transfer or the *N*-metallo intermediate (**26**) undergoing homolysis to the radical (**27**) which may have been in equilibrium with its protonated form. Cyclization and a secondary oxidation gave rise to the products (**30**).[92] The possibility that amino cations or nitrenes were involved as intermediates was ruled out by comparing the products with those formed when such species were generated separately under the same conditions as the LTA oxidation reactions.[92] The presence of an amino cation, $ArNH^+$, has been suggested in the oxidation of 2,4,6-tris(1,1-dimethylethyl)aniline from trapping reactions with acetate ion.[93] Such species are also known from the solvolysis of substituted *N*-chloroanilines assisted by the presence of silver TFA.[94]

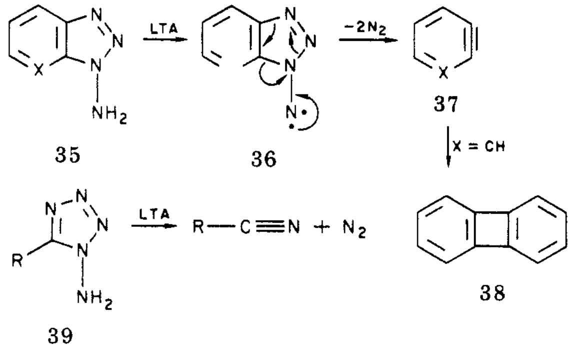
The oxidation of secondary arylakylamines such as compound **31** gives rise to N-dealkylation accompanied by an acetoxylation of the aryl ring which occurs preferentially at the para position giving products of type **32** and **34**.[95] These observations have been explained in terms of the cation radical **33** which is partitioned between nucleophilic attack at the para position and proton loss (Scheme IX).[95]

When there are two hydrogens on the nitrogen atom of the species (**2**) loss of two molecules of acetic acid

SCHEME IX

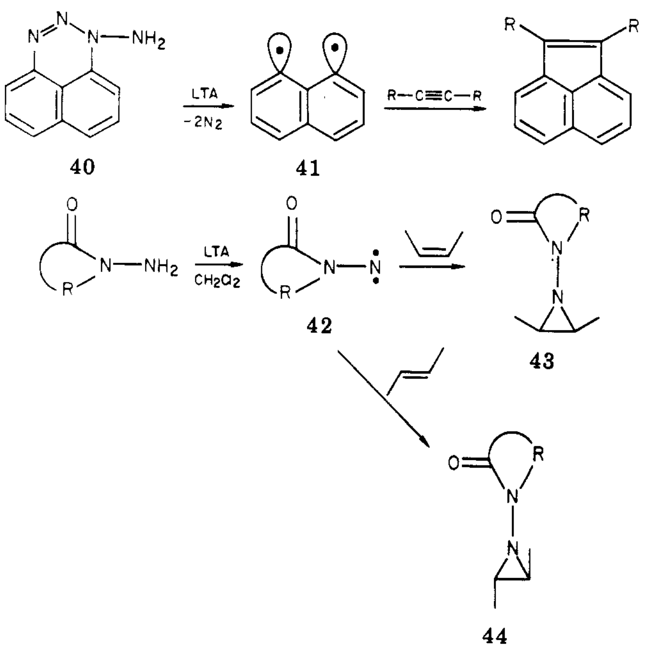


SCHEME X

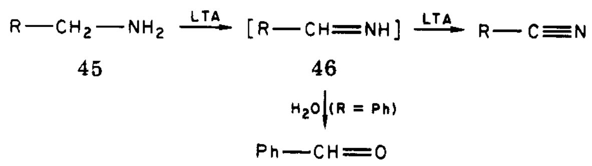


may give rise to nitrene intermediate (6) (Scheme I, path d). This occurs most strikingly in the oxidation of 1,1-disubstituted hydrazines with LTA.[96-101] Thus treatment of the substituted 1-amino-1,2,3-triazoles (**35**) with LTA in dichloromethane gave a nitrene intermediate (**36**) which rapidly lost nitrogen giving benzyne (Scheme X).[96,97] In the absence of trapping agents biphenylene (**38**) was formed in high yield.[97] The reaction has been generalized as a route to a wide range of heterocyclic arynes (**37**)[97-100] and it is also applicable when the 1-amino-1,2,3-triazole moiety is bonded a C=N unit as for example with the substrates (**39**)[101] (Scheme X). The interesting diradical 1,8-dihydronaphthalene (**41**) was generated via the nitrene intermediate in the oxidation of compound **40** with LTA.[102,103] In a range of oxidations nitrenes with the general structure **42** were trapped with olefins. The reactions were stereospecific giving aziridines **43** and **44** (Scheme XI), hence suggesting concerted additions with short-lived nitrenes in the reactive singlet state.[104-106] These nitrene intermediates have only been observed with LTA oxidations and the reactions of comparable substituted hydrazine systems with TTA and Hg2A do not appear to have been reported to date. A full review of the LTA oxidation of substituted hydrazines has recently been provided[12,13] and further discussion herein is confined to cases where comparisons can be made between the reagents.

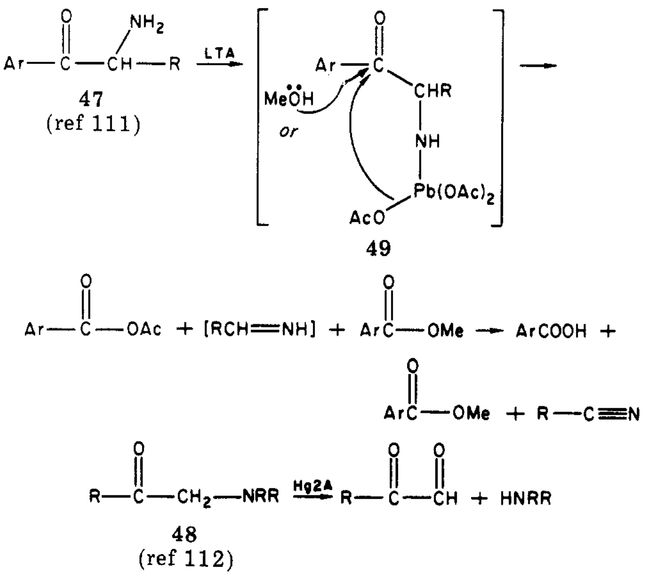
SCHEME XI



SCHEME XII



SCHEME XIII



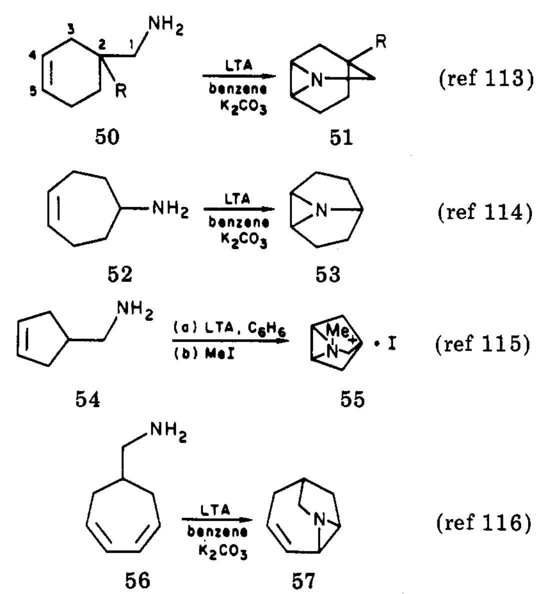
IV. Comparative Reactions with Nitrogen Functional Groups: Synthesis and Mechanism

A. Amines

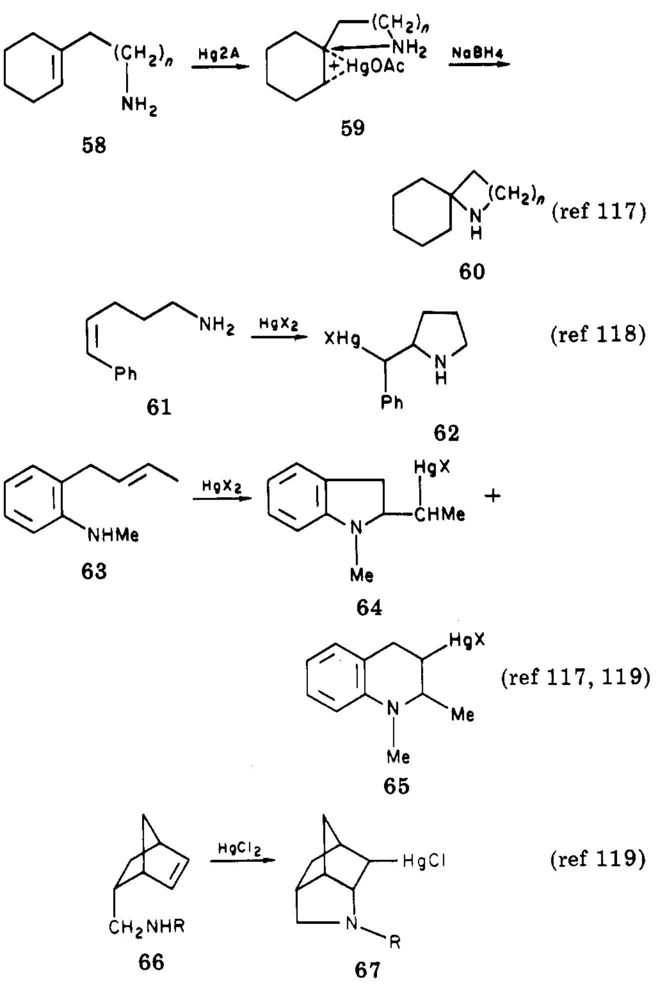
1. Aliphatic Primary Amines

Primary aliphatic amines (**45**) are readily dehydrogenated to nitriles by LTA in boiling benzene[107] (Scheme XII). The reaction consumed 2 mol of LTA and the yields of nitriles were ca. 60%. When 1 mol of LTA was used these yields were halved. The reaction is considered to involve an unstable aldimine interme-

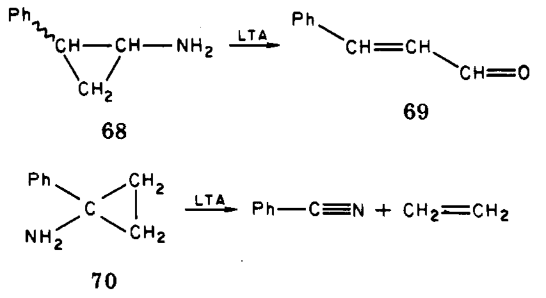
SCHEME XIV



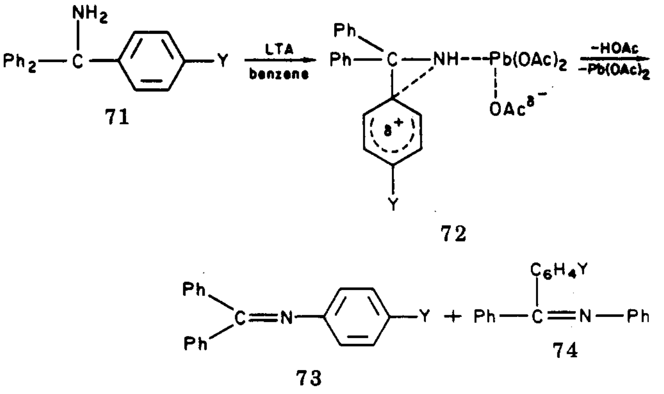
SCHEME XV



SCHEME XVI

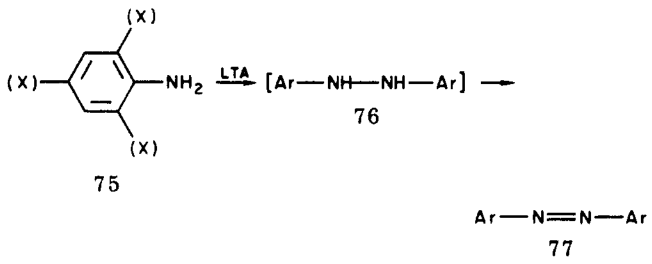


SCHEME XVII



diate (**46**).[107-110] In some cases small quantities of aldehydes were isolated as well as the nitriles and the other byproducts were *N*-alkylacetamides and *N*-alkylamides of the corresponding alkanoic acids.[107] Direct comparisons of the reaction of these substrates with Hg2A and TTA do not appear to be available but a comparison may be drawn with the α-ketoamine substrates **47** and **48** (Scheme XIII), both of which gave C–N bond cleavage on oxidation with LTA and Hg2A. The LTA oxidation of the α-amino ketones (**47**) gave the more complex mixture of products and has been explained in terms of intra- and intermolecular fragmentation of the *N*-metallo intermediate (**47**).[111] Much recent interest in the oxidations of primary aliphatic amine systems has been concerned with neighboring group participations during the oxidation process. LTA oxidation of aliphatic amines containing a 4–5 double bond gives rise to fused aziridine systems, some examples of which are shown in Scheme XIV. Nitrenium ions may be involved in these reactions but nitrene intermediates are not favored since the reactions did not parallel cases where nitrene intermediates were generated by other reliable means. The reaction of Hg2A with primary or secondary amines containing a 4–5 double bond is quite different and involves an intramolecular aminomercuration reaction giving rise to five- and six-membered nitrogen heterocycles, examples of which are shown in Scheme XV. This reaction generally involves an electrophilic Markovnikov attack of the mercury(II) species on the olefinic moiety followed by a trans attack of the nearby nucleophilic amino group, e.g. **59** (Scheme XV). The mercury product is readily demercurated by treatment with sodium borohydride. This reaction is sensitive to the nature of the mercury salt and the solvent. For example treatment of the substrate (**63**) with Hg2A in pyridine gave mainly the fused pyrolidine product (**64**, X = OAc) while the tetrahydroquinoline derivative (**65**, X = Cl) was the major product from the reaction with mercuric chloride in acetone. With these substrates the softer mercury(II) reagent attacks the softer olefinic nucleophile while the harder lead(IV) reagent appears to attack the harder amino nucleophile. Further examples of these reaction types are reviewed separately in ref 12 and 13. Other interesting recent oxidations of primary amines include fragmentations of cyclopropylamines (Scheme XVI) and rearrangements of triarylmethylamines (Scheme XVII). Thus treatment of

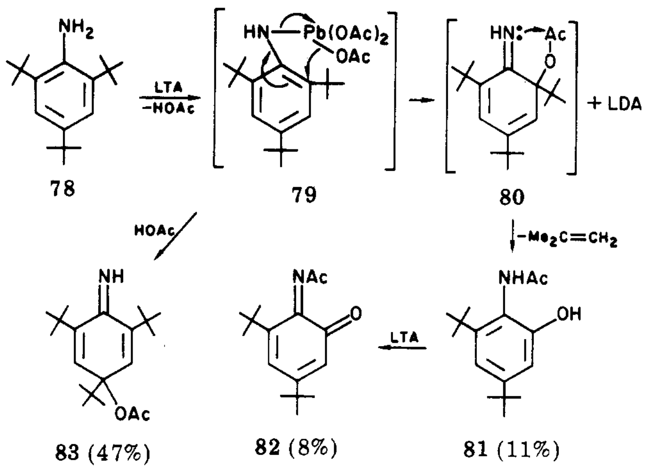
SCHEME XVIII



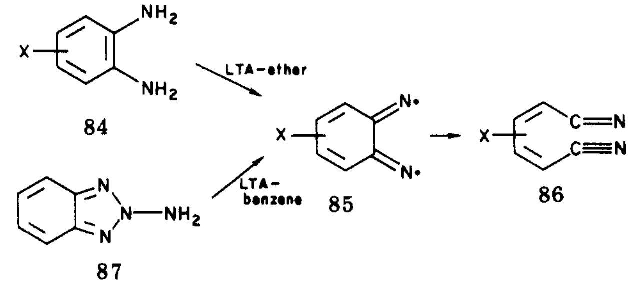
either *cis*- or *trans*-2-phenylcyclopropylamine (**68**) with LTA in dichloromethane at -78 °C gave *trans*-cinnamaldehyde (**68**) in 79–84% yields.[120] Similar oxidations of 1-phenylcyclopropylamine (**70**) gave benzonitrile (69%) and ethylene.[120] Treatment of triarylmethylamines (**71**) with LTA in benzene under reflux gave the rearranged products **73** and **74** (Scheme XVII).[121] The relative migratory aptitudes for p-Y-C_6H_4 and Ph varied from 0.39 for p-NO_2 to 152 for p-MeO and a pathway (**72**) involving a concerted electron deficient migration of the aryl group with elimination of lead diacetate and acetate ion from an *N*-lead intermediate has been proposed.[121] Free radical or nitrene-type intermediates were not detected in this reaction. The reaction is similar to the Hoffmann degradation of amides and is a common type of rearrangement observed in LTA oxidations. For example a similar rearrangement is observed on LTA oxidation of triarylmethanols[122,123] and also on LTA oxidation of amides (section IVB). It arises presumably because of the high redox instability of the *N*-metallo intermediate and might also be expected with TTA in inert solvents. It does not occur with Hg2A for amide substrates because the *N*-metallo compound is stable (Section IVB).

2. Aromatic Primary Amines

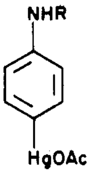
SCHEME XIX



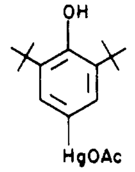
SCHEME XX



Oxidation of substituted aromatic amines (**75**) with LTA leads to arylazo compounds (**77**) in varying yields.[124–126] The reaction is generally considered to involve hydrazo compounds (**76**) as intermediates which are rapidly oxidized further (Scheme XVIII). Hydrazo compounds in general are readily oxidized to azo compounds by LTA.[124,127,128] They could arise from aromatic amines via dimerization of anilino radicals[129] or by attack of amino cation radicals ArN^+H_2, on the parent amine. Such cation radicals have been detected by ESR spectroscopy when solutions of aromtic amines in methylene chloride were mixed with solutions of LTA in methylene chloride–trifluoroacetic acid.[130] The reaction may take a different course when special ortho substituents are present. Thus treatment of 2,4,6-tri-*tert*-butylaniline (**78**) with LTA in benzene at 5 °C gave products **81**–**83** (Scheme XIX).[131] An *N*-metallo intermediate (**79**) could account for these interesting products and it is relevant that similar products, with higher yields of ortho derivatives, are formed in the LTA oxidation of the oxygen analogue, 2,4,6-tri-*tert*-butylphenol.[132] In this case the ortho–para ratio of acetoxylation was considerably higher than for methoxylation (in methanol solvent), in agreement with an intramolecular redox process of type **79**. When the ortho substituent is another amino group ring, fragmentation to muco nitriles (**86**) occurs on oxidation with LTA (Scheme XX).[133,134] This reaction is considered to involve a dinitrene intermediate (**85**) and interestingly the same product (**86**, X = H) was obtained when compound **87** was treated with LTA.[135] These varied reactions which arise from attack by the Pb(IV) electrophile on the nitrogen atom contrast with those of Hg2A where the attack occurs at the benzene carbon atoms giving aromatic mono- and polymercurations. Thus treatment of aniline and *N*-alkylanilines with dilute solutions of Hg2A gave high yields of p-(acetoxymercuri)anilines (**88**).[136,137] The reaction of ortho and para toluidines with Hg2A gave high yields of mixtures arising from mono- and diacetoxymercuration at positions ortho and para to the amino group and the reaction of phenols with Hg2A also resulted in ring metallation. Compound **89** was obtained in 95% yield from the reaction of 2,6-di-*tert*-butylphenol with Hg2A in 75% acetic acid.[139] The formation of aromatic lead–carbon bonded species, $Ar-Pb(OAc)_3$, is common in the reactions of LTA with aromatic hydrocarbons[12] and the contrast in the reactions of LTA and Hg2A with aromatic amines may therefore further illustrate ambident selectivity where the softer Hg(II) electrophile attacks the softer carbon sites while the harder Pb(IV) species attacks the harder nitrogen sites. When the active ring sites are occupied as for example in the reaction of 2,4,6-trimethylaniline with Hg2A a 1:1 complex (**90**) has been reported[138] in which the mercury is bonded to the nitrogen atom. A 1:1 complex of Hg(II) with aniline was also detected spectrophotometrically in aqueous $NaClO_4$–$HClO_4$ solutions.[140]



88



89

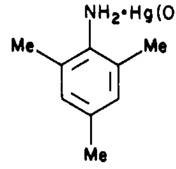


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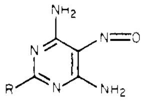
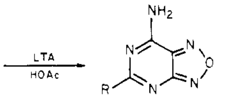
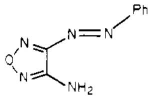
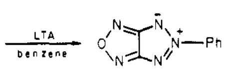
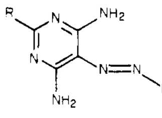
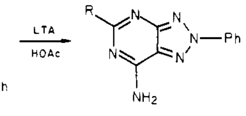
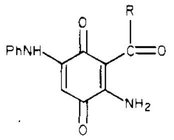
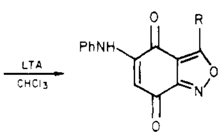
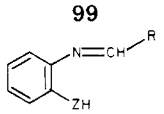
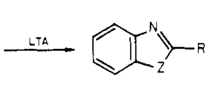
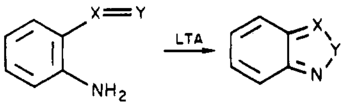
TABLE II. LTA Oxidative Cyclization of Ortho-Substituted Aromatic Amines

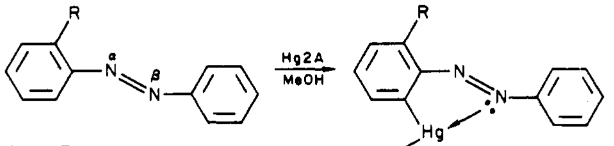
substrate	product (yield %)	ref
 **93a**	 **94** (>75)	141
 **95**	 **96** (28)	142
 **97**	 **98** (>75)	143
 **99**	 **100** (>65)	144
 **101**, Z = O, NH, S	 **102** (50-60)	145-148

Much recent interest in the oxidation of aromatic primary amines has centered around compounds of type **91** containing an unsaturated X=Y ortho substituent.



91 **92**

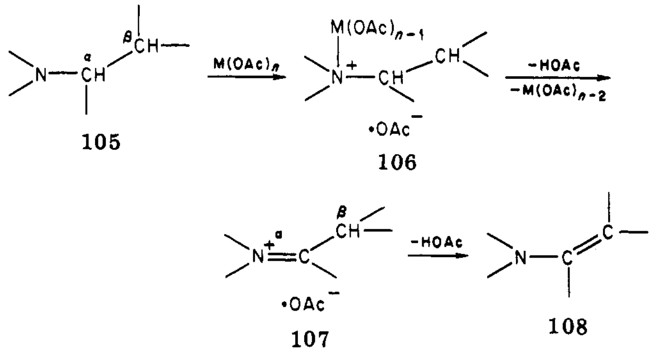
Oxidation of these substrates with LTA gives a general cyclization to products to type **92** and the generality of the reaction is illustrated by the examples listed in Table II. The reaction has been considered to involve radical or cation radical intermediates and the mechanism is discussed above for Scheme VIII. The substrates **101** (Table II) also fit the general reaction scheme although they are slightly different insofar as an exocyclic dehydrogenation is possible in this case without loss of the aromatic closed shell of the parent heterocyclic ring. The cyclization **101** → **102** (Table II) is an older reaction, known since the late 1940s,[145] which also occurs with —OH and —SH groups ortho to the —N=CHR moiety, and its mechanism may be different from those of the others in Table II. At present these reactions appear to be exclusive to LTA and information on the behavior of these substrates with TTA and Hg2A is not readily available. However, it is of interest that ortho-substituted azobenzenes **103** react readily with Hg2A to give a cyclometallation reaction regioselectivity at the ortho position via a mechanism involving complexation of the incoming $HgOAc^+$ electrophile by the n electrons of the β-azo atom giving the products **104**.[149,150]



103, R = alkyl, halogen, CN, NO_2

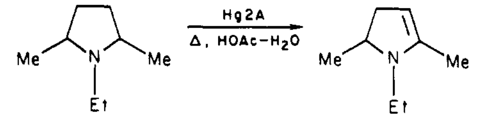
104

SCHEME XXI

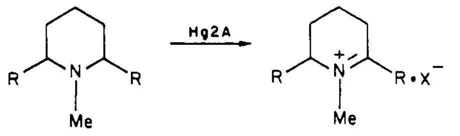


3. Tertiary and Secondary amines

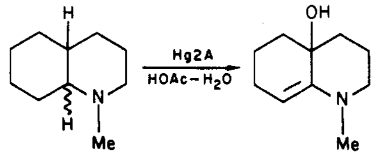
The various reactions pathways which are possible between tertiary amines and the metallic acetate reagents have been described in section IIIB1. One of the most common involves the formation of an iminium salt of type **107** by proton loss from the α-carbon (Scheme XXI). If the β-carbon contains a proton, this may also be eliminated in the presence of base hence resulting in an overall dehydrogenation at the α–β bond of the tertiary amine (Scheme XXI). This type of reaction appears to be common to all of the reagents, but the iminium ion may possibly arise by different pathways (cf. Scheme V) and there are relatively little data on TTA reactions. Examples of such reactions with Hg2A include dehydrogenations of a wide range of 1-alkylpyrrolidines, such as compound **109**, to the corresponding Δ^2-pyrrolines,[151] and oxidations of 1,2,6-trialkylpiperidines (**111**) to the inimum salts (**112**).[76] These dehydrogenation reactions when carried out in aqueous acetic acid may also be accompanied by hydroxylations. Thus treatment of the 1-methyldecahydroquinolines (**113**) with 4 mol of Hg2A in 5% acetic acid at 90 °C gave the hydroxyl derivative (**114**) in 54% yield,[152] and oxidation of compound **115** gave a mixture of the cis and trans isomers of the hydroxy derivatives **116**.[153] Oxidation of either of the isomers of compound **117** with LTA gave the iminium salt **118** and this on



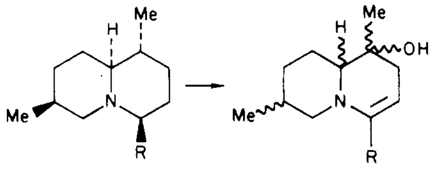
109 **110**



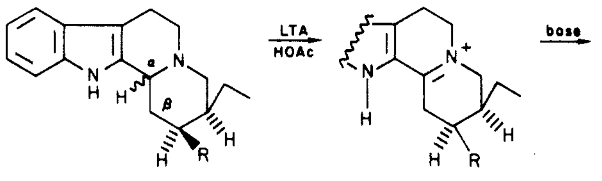
111 **112**



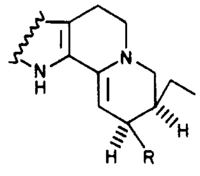
113 **114**



115 116



117 118

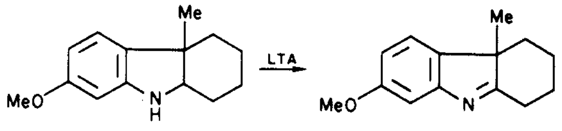


119

treatment with base lost a proton from the β-carbon giving the product 119.[154,155]

When one of the substituents on the tertiary nitrogen is a methyl group or an acyclic group, dealkylations are observed [cf. compound 12). Thus treatment of *N*-alkylhydrazone derivatives (**120**) with LTA resulted in dealkylation to the monosubstituted hydrazones (**123**) and the aldehyde of the alkyl group in a reaction involving the iminium species (**122**) (Scheme XXII).[156,157] Other systems which have been demethylated with LTA include *N*,*N*-dimethylglycine,[158–160] a range of alkaloids containing the *N*-methylindolenine moiety,[161–163] and the *N*-dialkylanilines already discussed (Scheme V).

There is a paucity of information on the comparative reactions of the three reagents with secondary amines but reactions with LTA have been reported. With substrates containing an α-H atom the reaction involves a dehydrogenation to an imine (Scheme XXIII). Thus LTA oxidation of dibenzylamine (**124**) gave *N*-benzylidenebenzylamine (**125**) along with a range of other products derived from further oxidation or cleavage of this first-formed product (Scheme XXIII)[107] (cf. also Scheme XLII). LTA oxidation of compound **126** and related gardneria alkaloids gives a ready dehydrogenation of the secondary amine.[164] Similar dehydrogenations of more complex alkaloid systems have been reported and are accompanied by rearrangements and ring transformations.[165,166] The reaction of secondary *N*-alkylanilines with LTA has already been discussed (Scheme IX) and the reaction with Hg2A involves ring mercuration giving products of type **88**.

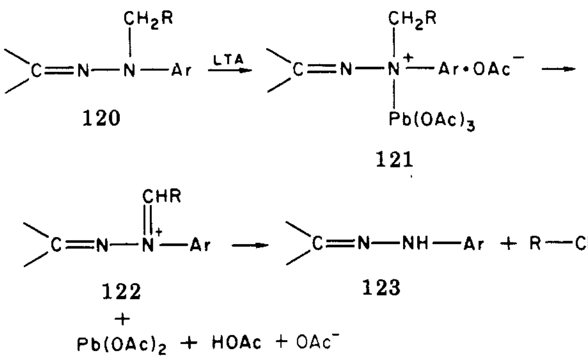


126 127

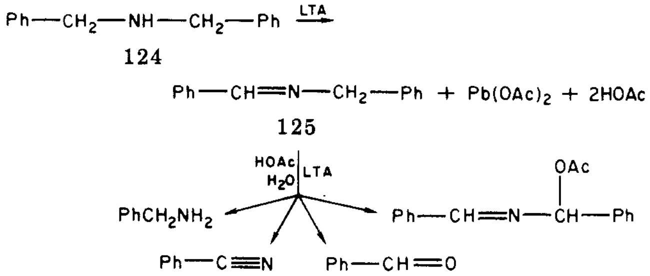
B. Amides and Hydrazides

The marked contrast in the reactions of amide substrates with the reagents further illustrates some of the principles described in section III. Hg2A forms stable mercury(II) compounds with amides arising from displacement of one or both acetates from the Hg2A. Treatment of acetamide with Hg2A gave stable AcNH-HgOAc.[167,168] Infrared spectra of the compound were interpreted in terms of chelate bonding of both the amido nitrogen and oxygen atoms with the mercury atom,[169] but the X-ray structure showed mercury–nitrogen bonding in the solid state,[170] with chains formed via hydrogen bonding as in structure **128** (Scheme XXIV). In contrast, the reaction of amides with LTA involves a 1,2-C → N shift similar to the Hofmann rearrangement giving isocyanates **131** (Scheme XXIV).[171,172] The amide carbonyl substitutent R migrates with retention of configuration[171] and the reaction may involve an unstable intermediate (**129**), with a labile N–Pb(IV) bond, which undergoes a rapid redox process (**130**) generating an electron-deficient nitrogen with concomitant migration of the amide substituent (Scheme XXIV). The isocyanate products (**131**) are readily isolated in aprotic solvents.[171,172] The reaction, when carried out in benzene containing alcohol or in alcohol alone, provides an efficient route to good yields of N-substituted carbonic acid esters (**132**).[172] Good yields of substituted ureas (**133**) may be obtained from this reaction in dimethylformamide containing primary amines,[171] and when the reaction was carried out in benzene containing a carboxylic acid the main products were the acylamines (**134**) (30–70%) along with lesser yields of ureas (**135**) (5–12%).[172]

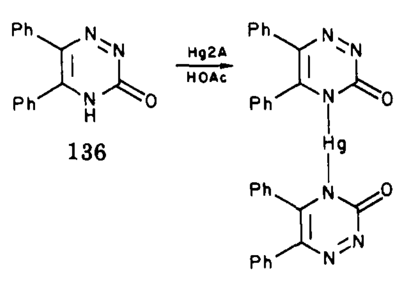
SCHEME XXII



SCHEME XXIII



A similar comparative reactivity is evident with cyclic amides and is illustrated by the behavior of the related amide triazinone substrates **136** and **138**. Treatment of compound **136** with Hg2A in acetic acid gave a quantitative yield of the stable bis(triazinone)mercury derivative (**137**).[173] In contrast treatment of compound **138** with LTA in boiling benzene gave 86% yield of the ring-contracted benzotriazole (**139**).[174] This could arise via an initial 1,2-N → N rearrangement of an amido N–Pb(IV) intermediate with involvement of acetate ion or acetic acid followed a 1,4-O → N acetyl migration in a species of type **138A**.



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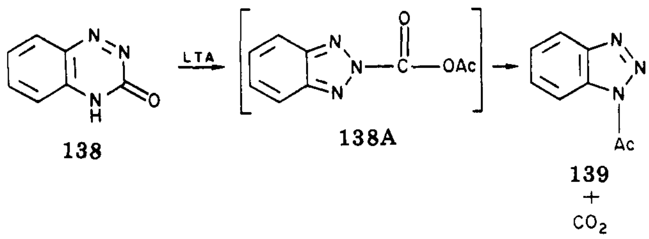

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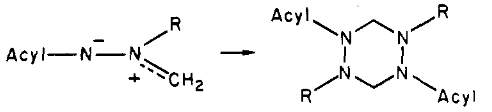
138A

139

Oxidation of *N*-methyl hydrazides of type **140** with LTA gives rise to 1,3-dipoles of the general type **144**



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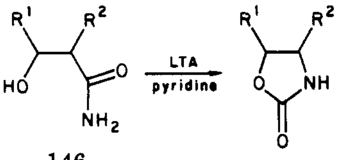
which readily dimerize to tetrazines **145**.[175-177] Oxidation of the hydrazide (**140**) with LTA in dichloromethane at 25 °C gave the intermediate dipole (**141**) which was readily trapped with styrene giving compound **142**. In contrast treatment of compound **140** with mercuric oxide gave the bis(hydrazido)mercury compound **143**.[178] Subsequent heating of this mercury compound at 135 °C resulted in oxidative degradation to the dipolar species **141** (Scheme XXV).

Intramolecular cyclizations of amides containing an adjacent functional group are common in LTA oxidations. Oxidation of β-hydroxy primary amides (**146**) in



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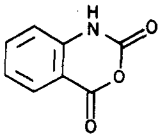
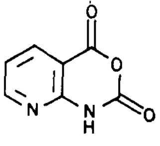
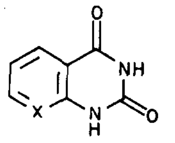
pyridine gave high yields (>70%) of the 2-oxazolidinones (**147**).[179] LTA oxidation of ortho-substituted aromatic amides gave a range of bicyclic dioxoazines. Thus treatment of phthalamic acid, 2-carbamoylnicotinic acid, phthalamide, and pyridine-2,3-dicarboxamide with LTA in benzene gave compounds **148–151**, respectively,[180] and the reaction has also been used as a route to dihydrouracils from acyclic diamide substrates.[180,180a] These reactions involve Hofmann-



148 (44%)

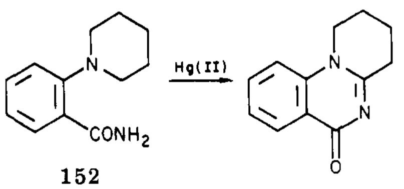


149 (75%)



150, X = CH (81%)
151, X = N

type rearrangements to isocyanate intermediates. An interesting cyclization of the amide (**152**) to the quinazolinone (**153**) by Hg(II)-EDTA oxidation has recently been reported.[181] An oxidation of haloacetamides, e.g. $Cl\text{-}CH_2CONH_2$, with Tl(III) in aqueous perchlorate medium has also been reported recently.[182] The reaction involved a degradation and the products were the corresponding halomethanol, ammonia, and carbon dioxide.[182]



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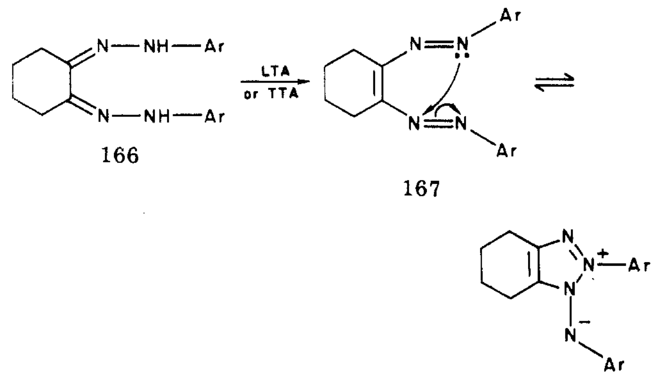
153

C. Nitrogen Chains: Hydrazines, Triazenes, and Tetrazenes

1. Hydrazines

Oxidation of mono- or 1,2-disubstituted hydrazines with LTA involves a dehydrogenation of the —NH—NH— unit generating an azo group, —N=N—. This reaction has been widely used in synthesis with LTA as oxidant, but there are relatively few reports of the employment of TTA and Hg2A for the same purpose although they should be expected to work readily because of the low oxidation threshold of the NH—NH unit. Thus LTA oxidation of arylhydrazines (**154**) involves a dehydrogenation of aryldiimides (**155**) which leads ultimately to aryl diazonium ions at low temperatures and aryl radicals at ambient temperatures (Scheme XXVI).[183,184] A kinetic study of the oxidation of some substituted phenylhydrazines with Tl(III) in acid chloride medium has recently been reported.[185] The reaction was considered to involve an initial complexation of Tl(III) with the hydrazine, and ortho nitro substituents are reported to have a rate-enhancing effect due to chelation.

The numerous examples of LTA dehydrogenations of 1,2-disubstituted hydrazines to both acyclic and cyclic azo compounds have been extensively reviewed recently[12,13,19] and repetition herein is unnecessary. The ene–hydrazine system (**158**) represents a case where a dehydrogenation is readily effected by LTA or Hg2A giving the stable conjugated azo compounds (**159**)[186] (Scheme XXVII). These compounds (**159**) contain a trans olefinic linkage unfavorable for a cyclization of the conjugated azo system. When dihydrazones of acyclic 1,3-diones such as **160** are oxidized, the reaction again occurs via the ene–hydrazine forms (**161**). These are easily dehydrogenated with LTA or Hg2A to the reactive cis-conjugated azo olefins (**162**) which cyclize in situ to the pyrazoles (**164**), probably via an intermediate of type **163**[186] (Scheme XXVII). When the tautomerism to the reactive ene–hydrazine form of the 1,3-dihydrazone is prevented as in the substrates **160** (R^1, $R^2 \neq$ H), the products of LTA oxidation are the azopyrazolines **165**,[187,188] and oxidation by Hg2A will not occur unless forcing conditions are employed causing decompositions. An interesting parallel is observed in the oxidation of the 1,2-dihydrazones **166** which are readily dehydrogenated to bis(azo) compounds **167** by a variety of oxidizing agents, including LTA and TTA.[189,190] The compounds (**167**) are structurally related to the derivatives **162**. They also undergo ready cyclizations and in fact they exist in equilibrium with the cyclic form (**168**) (comparable to structure **163**).



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167

168

Both forms have recently[189] been detected in equilibrium for compound **167**, Ar=$p{-}NO_2C_6H_4$.[189] These conjugated aza olefinic systems **162** and **167** represent interesting potential nitrogen analogues of the 6π-electrocyclizations common in 1,3,5-hexatriene systems. They contain terminal sp^2 nitrogen atoms in place of sp^2 carbons. However, their cyclizations are not electrocyclizations but 5-exo trig type reactions dominated by the nucleophilic nitrogen n-electrons. Compunds of type **167** and **168** are highly sensitive to acetic acid and they rapidly undergo rearrangements to o-cyclohexylaniline derivatives in the presence of acid, and hence LTA or TTA oxidations are not useful for their isolation.[189]

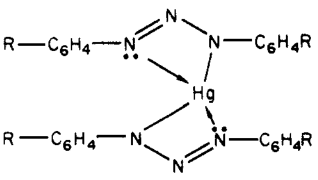
There is a paucity of comparative data on oxidations of 1,1-disubstituted hydrazines with the three reagents despite the fact that extensive work has been reported on LTA oxidations of such substrates. This LTA work has recently been reviewed in detail[12,13] and the general reaction is discussed above (section IIIB2). Many of these LTA oxidations are considered to involve interesting nitrene intermediates which often give rise to useful ring-expansion reactions. Some further recent examples are shown in Scheme XXVIII involving conversion of N-aminodiazoles to triazines.

2. *Triazenes and Tetrazenes*

The relative stability of the mercury(II)–nitrogen and Pb(IV)–nitrogen bond is also illustrated in the reactions of triazenes (diazoamino compounds) with the reagents. Treatment of symmetrical 1,3-diaryltriazenes **169** with

$$R{-}C_6H_4{-}N{=}N{-}NH{-}C_6H_4{-}R \xrightarrow{Hg2A}$$

169



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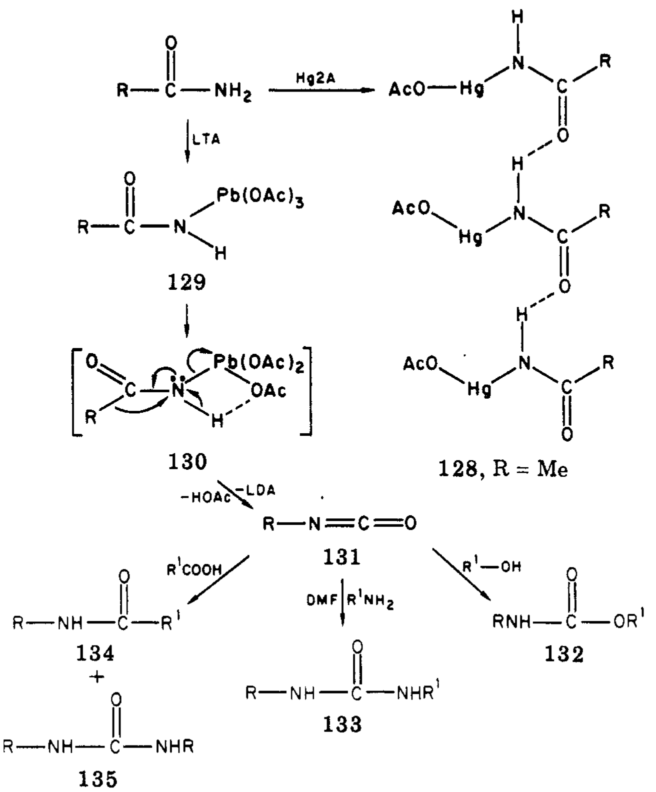
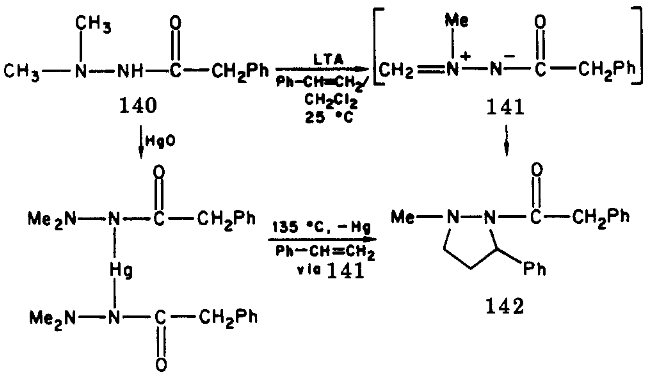
Hg2A in ethanol gave stable bis(triazeno)mercuric compounds **170**.[193] These mercuric derivatives may also be obtained by generating the triazene in situ by diazotization of primary aromatic amines with isoamyl nitrite in the presence of Hg2A.[194,195] Stable triazenes with nitrogen–mercury bonds of the type Ar—N=N—N(HgPh)—Ar are well-known.[196,197] In solution the Ph–Hg group undergoes a rapid exchange between the 1- and 3-nitrogen atoms.[196,197]

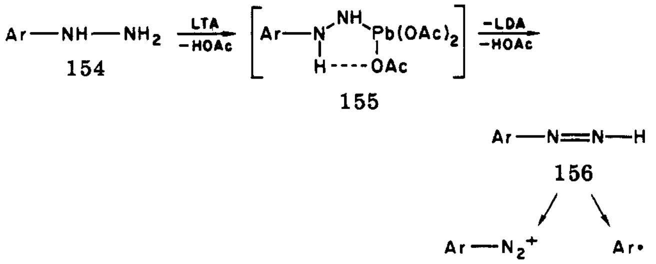
SCHEME XXIV



SCHEME XXV

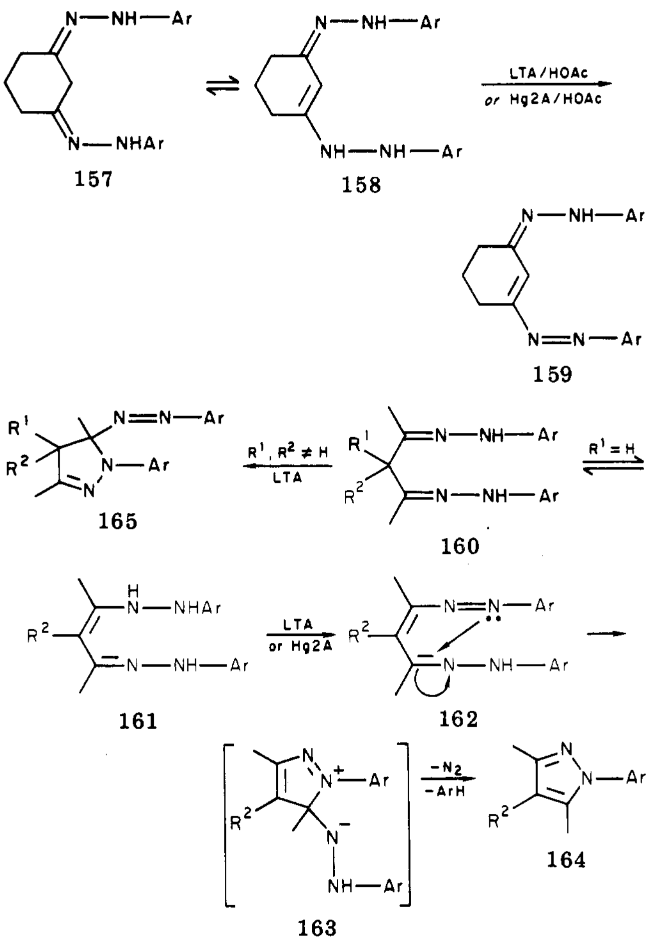


SCHEME XXVI

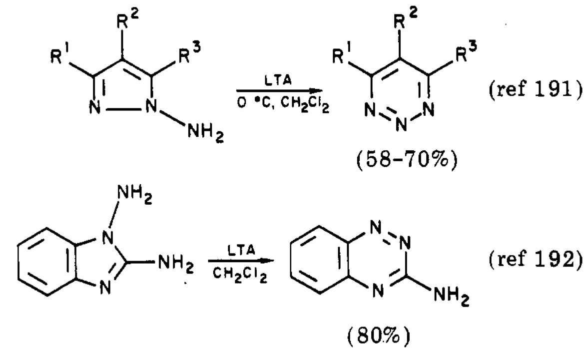


The reaction of LTA with 1,3-diaryltriazenes is more complicated and may give mixtures of products. With monosubstituted benzenes as solvents the products were azo compounds (**173**) and biaryls (**174**) derived from the solvent.[198] The isomeric ratios of the biaryls showed that they were formed from aryl radicals and a rapid homolysis of the species (**171**) seems likely. The ESR spectrum of the reaction mixture of 1,3-diphenyltriazene with LTA exhibited a triplet with coupling constant 10 G which could be due to a triazenyl radical

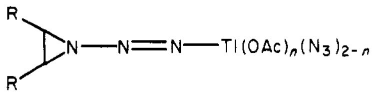
SCHEME XXVII



SCHEME XXVIII



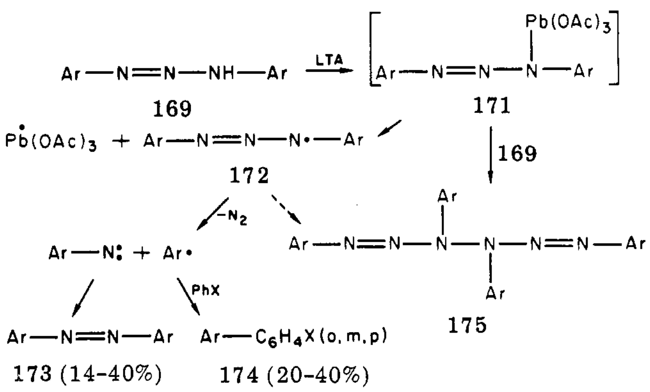
(172)[198] (Scheme XXIX). In some cases the reaction of 1,3-diaryltriazenes with LTA may give good yields of hexaaza-1,5-dienes, e.g., compound **175**, which could arise from dimerization of the radicals (**172**) or from attack by the parent molecule on the Pb(IV) intermediate (**171**).[199] These reactions reflect the lability of the N-Pb(IV) bond in the triazene system (**171**). The corresponding reactions with TTA do not appear to be reported but the triazenyl-type thallium(III) derivatives (**176**) have recently been obtained from the reactions



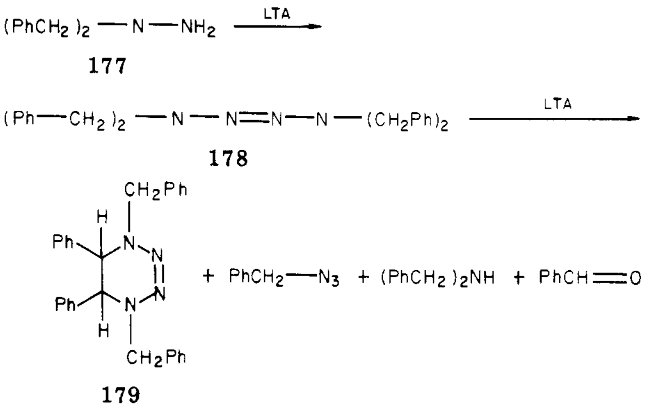
176, $n = 0$-2

of thallium(III) acetate–(trimethylsilyl azide with olefins.[200]

SCHEME XXIX



SCHEME XXX

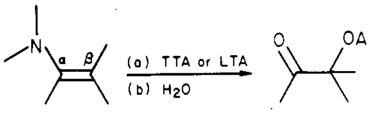


There is little information on the reactions of tetrazenes with the three reagents except for LTA. Oxidation of 1,1-dibenzylhydrazine (**177**) with LTA gave the tetrazene (**178**).[201-203] The methylene groups of this were rapidly acetoxylated by further in situ LTA attack resulting in cleavage to benzyl azide, benzaldehyde, and dibenzylamine (Scheme XXX).[201-203] Small quantities of the unique cyclic tetrazene **179** were also obtained from the separate LTA oxidation of tetrazene **178**.[202]

D. Heteroallylic Systems: $>C{=}X{-}\ddot{Z}{-}$

1. Enamines

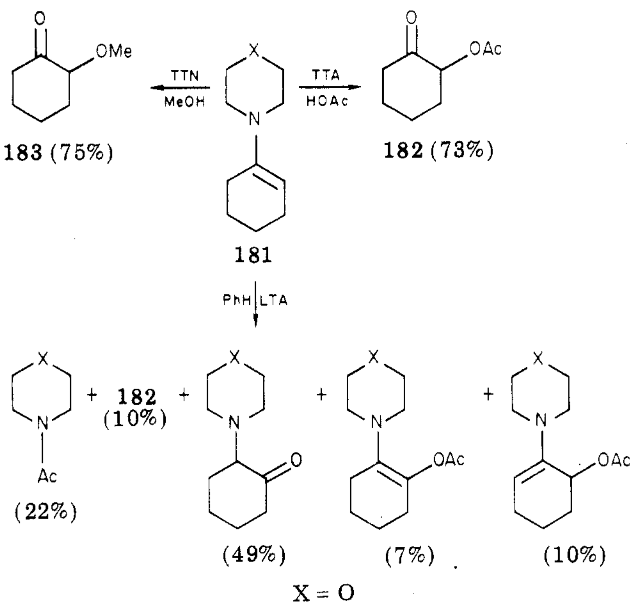
The reaction of enamines containing a tertiary nitrogen with TTA[204] or LTA[205] gives rise to α-acetoxy ketones **180** in varying proportions. The TTA reaction



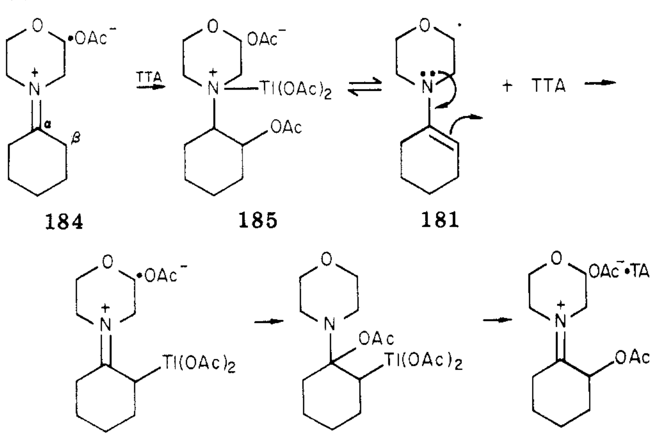
180

is cleaner and of more synthetic value. The LTA reaction gives complicated mixtures in which products of type **180** may be minor components. Thus cycloalkanone enamines of type **181** gave high yields of the α-acetoxy ketone (**182**) on treatment with TTA in acetic acid.[204] The α-methoxy derivative (**183**) was obtained when TTN in methanol was used.[206] Oxidation of the substrates (**181**) with LTA in benzene[205] gave the complicated mixture of products shown (Scheme XXXI). The essential mechanistic differences between these reactions is not well established and strong evidence for the initial sites of attack and the nature of the metallo intermediates is not available. Kuehne and Giacobbe[204] have established that in acetic acid the enamine exists in the iminium salt form **184** which adds TTA to give

SCHEME XXXI[a]



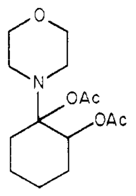
SCHEME XXXII



184 185 181

186 187 188

species 185. The oxidation however occurred through a slow equilibrium back to the free enamine and thallic cation (Scheme XXXII) and was envisaged in terms of the key intermediate 186 containing a carbon–thallium bond. An intramolecular displacement of thallium by its ligand bonded at the α-carbon (or by the nitrogen atom) in species 187 was postulated to give rise to the iminium salt (188), the precursor to the α-acetoxy ketone products (Scheme XXXII).[204] In the Pb(IV) oxidation the diacetoxyl derivative (189) was postulated as the key intermediate.[205] None of the data presented would appear to exclude mechanism 190 as a competitive route to the α-acetoxy ketones and the strong steric effects and preference for axial acetoxylation reported would be compatible with it. The route to α-substituted cycloalkanones has been effectively extended to aryl derivatives such as compound 191 by using using aryllead(IV) tricarboxylates as oxidants.[207]



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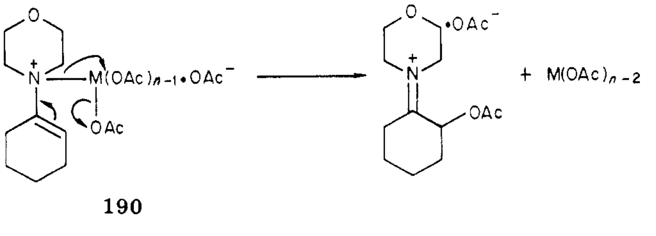

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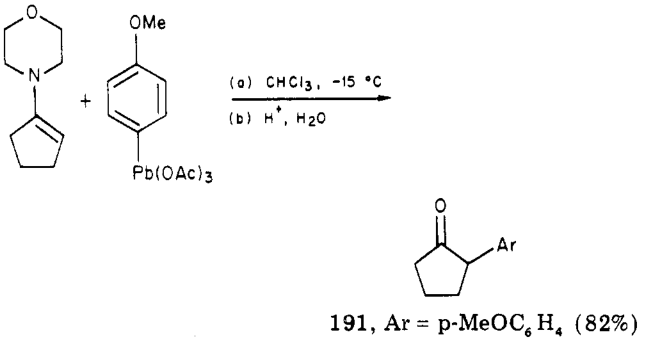
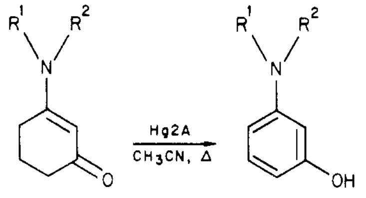


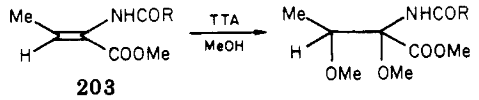
191, Ar = p-MeOC$_6$H$_4$ (82%)

The reaction of Hg2A with tertiary enamines is also reported to give β-acetoxyiminium salts,[78] but these reactions usually need to be carried out in boiling solvents and overoxidation and decompositions are the main features of the relatively sparse reports. Recently the enamines 192 were treated with Hg2A in acetonitrile under reflux and the products were the *m*-aminophenols 193.[208]



192 193

Some interesting oxidation reactions have been reported for enamines containing a secondary nitrogen atom. For example, the enamide compound 194 underwent a β-acetoxylation when treated with LTA in benzene giving the product 195.[209,210] In acetic acid this rearranged to the enamide form 196 and when this was further treated with LTA β-acetoxylation again occurred giving the product 197 (Scheme XXXIII).[209,210] LTA oxidation of *N*-alkyl- and *N*-arylenamines of type 198 gave rise to mixtures of dimeric products (Scheme XXXIV).[62,211,212] Evidence has been presented in favor of initial dimerization via an activated N–Pb(IV) intermediate (199).[62,211] A C–Pb(IV) intermediate has also been postulated as the active species.[211b] Interesting bicyclic structures also arose from further attack of species 199 on the pyrroles 202 and attempts to trap 1,3-dipoles which could have arisen from a 1,3-dehydrogenation of the substrates 198 proved negative.[62] Such a pathway is common with other heteroallylic systems such as aldehyde hydrazone and oxime derivatives. In contrast to the LTA reactions treatment of acyclic enamides (203) with TTA in methanol gave a diastereomeric mixture of α,β-dimethoxy derivatives[212] (cf. also Scheme XLIII). Oxidation of the enamides 204 with TTN in methanol gave a ring expansion which is



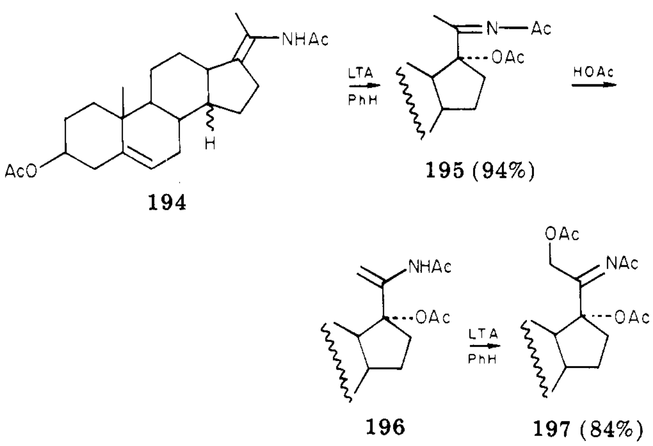
203

TABLE III. Comparative Kinetic Data for Reactions of Substituted Phenylhydrazones with Metallic Acetates in Acetic Acid

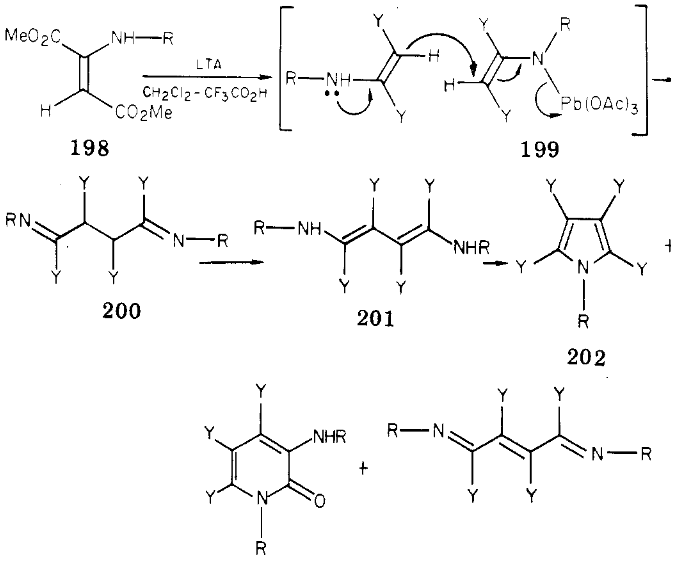
oxidant	relative rates[a]	Hammet ρ values		ΔH_{act}, K·cal·mol^{-1}	ΔE_{act}, K·cal·mol^{-1}	ΔS_{act}, cal·K^{-1}·mol^{-1}
		c-phenyl	N-phenyl			
LTA	1[a]	$-0.6(\sigma^{n})^{d,e}$	-1.95^{f}	g	g	g
TTA[b]	1×10^{-2}	$-1.05(\sigma^{+})^{d}$	-3.6	17.2	17.9	-14.6
Hg2A[c]	1×10^{-3}	$-1.02(\sigma^{+})^{d}$	-2.99	16.9	17.5	-14.1

[a] Approximate values. [b] All data in HOAc at 25 °C from ref 214a. [c] All data in HOAc at 25 °C from ref 73. [d] For correlation with substituent constants indicated in parentheses. [e] From ref 219. [f] From ref 63. [g] Not reported.

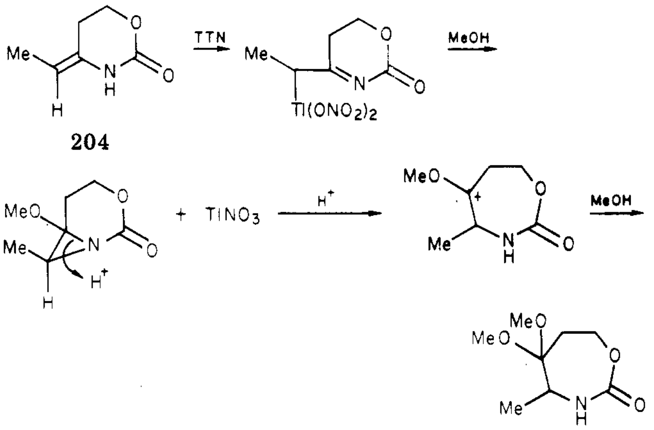
SCHEME XXXIII



SCHEME XXXIV



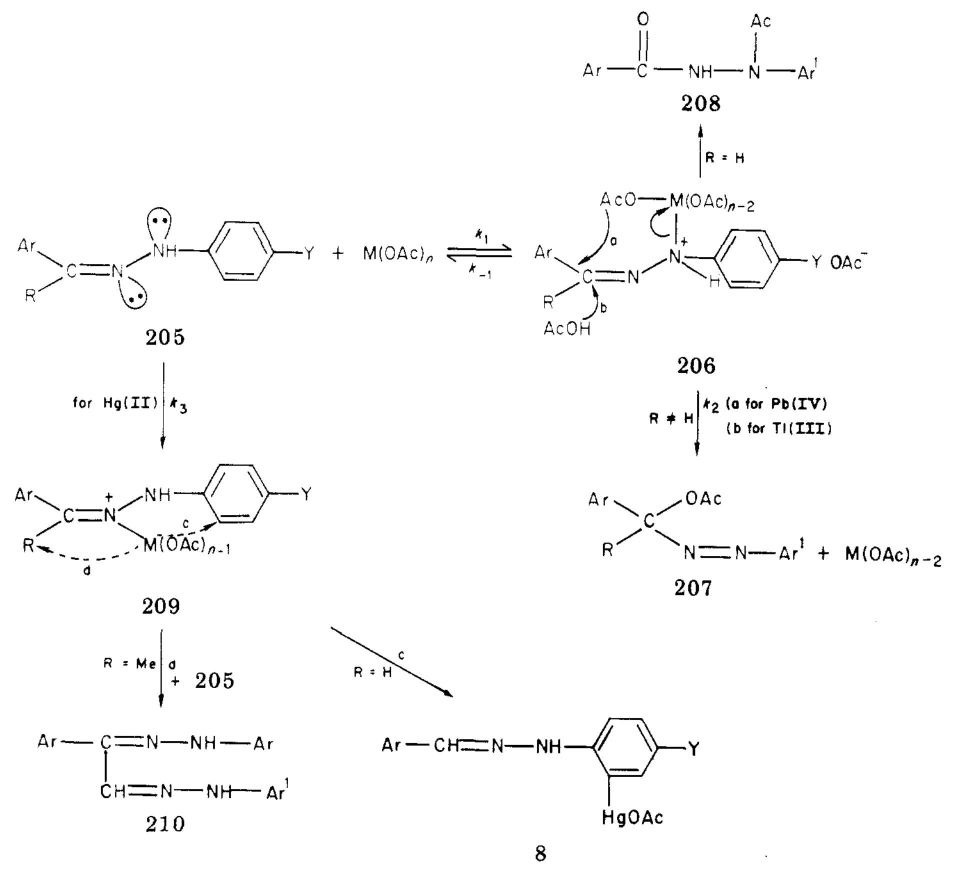
explained in terms of a Tl(III) attack at the β-olefinic carbon.[213]



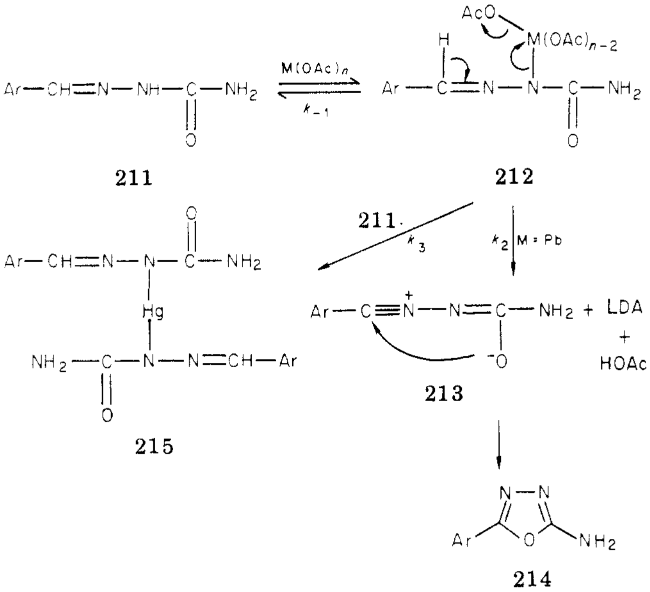
2. Hydrazones

a. N-Substituted Hydrazones. Substituted phenylhydrazones (**205**) represent a class of substrate where comparative data are available for the three reagents. When treated with LTA in anhydrous acetic acid, ketone hydrazones (**205**, $R \neq H$) gave the azo acetates[63] (**207**). A similar reaction with TTA gave the same products (**207**) along with small quantities of the osazones (**210**),[214a] while with Hg2A as oxidant the compounds **210** were the main products.[214b] Oxidation of aldehyde hydrazones (**205**, R = H) with LTA and TTA in acetic acid gave the diacylhydrazines (**208**), while the reaction with Hg2A gave almost quantitative yields of ortho acetoxymercuri derivatives (**8**)[73,215] (Scheme XXXV). Comparative kinetic data for the three reactions are summarized in Table III. The relative rates are described as approximaate because the LTA data were measured under conditions slightly different to the others. The reactions are related by the key N-metallo intermediates (**206**) (Scheme XXXV). When the metal is Pb(IV), this intermediate is highly reactive and undergoes an intramolecular redox with an acetoxy migration to the methine carbon giving the products **207**.[63,64] This occurs readily in solvents such as CH_2Cl_2–Et_3N, where external acetic acid is not present.[214] When the metal is Tl(III), the N-metallo intermediate is longer lived and the azo acetates (**207**) are formed by solvent attack at the methine carbon.[214] Thus the azo acetates are not formed from the Tl(III) reaction in dichloromethane–triethylamine where external acetic acid is not available and with TTN in methanol the products are azo methyl ethers (**207**, Me for Ac) derived from methanol solvent involvement.[66] When the metal is Hg(II) the N-mercuri compound is stable and does not proceed further (and can be isolated).[73] In this case a competitive attack at the methine imino nitrogen (**209**) takes over. Mercury migration to the adjacent alkyl group R activates this group generating a carbocation which, after involvement of another molecule of starting hydrazone, ultimately gives rise to the osazones (**210**) (thereby providing a simple one-pot preparation of such derivatives without the difficulty of synthesizing a reactive α-keto aldehyde).[214] When the original substrate was an aldehyde hydrazone, the mercury migrated instead to the ortho position of the N-phenyl ring giving the products **8** (Scheme XXXV).[73] The important controlling factors in the overall sequence are the relative magnitudes of the rate constants k_2, k_{-1}, and k_3 (Scheme XXXV).[214] For Pb(IV) $k_2 \gg k_{-1}$ and the reaction proceeds rapidly. With aldehyde hydrazones a rapid dehydrogenation occurs giving a nitrilimine, $Ar{-}C{\equiv}N^{+}{-}N^{-}{-}Ar$, LDA, and HOAc. Addition of acetic acid to the nitrilimine gives the products **208**. For Tl(III) k_2 is still faster than k_{-1} but significantly less than k_2 for Pb(IV).[214] Hence the N-thallium intermediate is sufficiently long-lived for involvement with external nucleophiles and a small

SCHEME XXXV

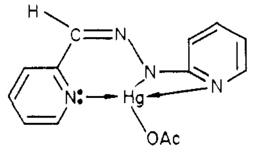


SCHEME XXXVI



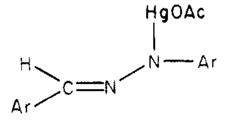
amount of competition from k_3 is also evident. The products **208** in this case are formed by solvent attack at the methine carbon followed by tautomerism in **207** (R = H) and a 1,4-O → N acetyl migration (Scheme XXXV). For Hg(II) $k_{-1} \gg k_2$; hence k_3 dominates the reaction and the reactions of Hg$_2$A with hydrazones differ dramatically from those of LTA. This will always be the case as long as k_{-1} is much greater than k_2 (Scheme XXXV) and there is an alternative pathway (k_3) available. Thus Hg2A fails to oxidize hydrazone substrates and remains in the Hg(II) state. One of the most common patterns observed in the reactions of Hg(II) with hydrazone substrates is outlined in Scheme XXXVI. Semicarbazones (**211**) are rapidly cyclized to oxadiazoles (**214**) on brief treatment with LTA at room temperature.[216] This is an example of the general LTA cyclization of *N*-acyl aldehyde hydrazones[217,218] and heterocyclic hydrazones[20,219] which is widely used in synthesis.[20] It is generally considered to involve a nitrilimine intermediate of type **213** which can undergo a 1,5-electrocyclization or a 5-endo dig type process. Such cyclizations of semicarbazones are not observed with Hg2A (or TTA) and the products from Hg2A are the bis(hydrazono)mercuri derivatives (**215**),[220] the formation of which represents k_3, i.e., an alternative pathway by which mercury can remain as mercury(II).

When structural constraints are imposed to reduce the value of k_{-1} relative to k_2 (Scheme XXXV), then Hg2A may give similar reactions to LTA. Such is the case with hydrazones of 2-pyridylcarboxaldehyde where the intermediate **17** (cf. Scheme VI) is stabilized by extra coordination of the Hg(II). In acetic acid solution the mercurihydrazone (**216**) rapidly cleaved to parent hydrazone and Hg2A,[73] but compound **17** was stable in acetic acid at ambient temperatures,[89] thus confirming that k_{-1} is much larger for species **216** than for **17**. Compound **17** is the only reported case to date where Hg2A effects a dehydrogenative cyclization of a substituted hydrazone giving, on heating, the product **20** (Scheme VI) and that only as a minor product since the



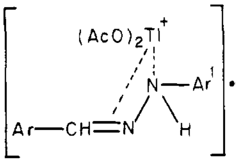
17

vs.



216

main reaction gives compound **19** (Scheme VI).[89] The marked divergence between the reaction products for Hg(II) and the other reagents contrasts with the close similarity between the kinetics of Hg(II) and Tl(III) reactions (Table III). However, these kinetic similarities are deceptive and we believe they arise from a significant but different involvement of the metal with imino group in the slow step in both cases. In the Tl(III) case a transition state (**217**) involves the imino π-electrons whereas in the Hg(II) case the imino n-electrons as in structure **218** are involved. Each interaction is dominated by delocalization of positive charge into the methine aryl ring and the kinetics could not distinguish between these close situations but the subsequent course of the reaction does.



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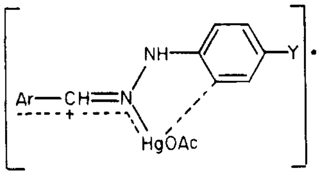
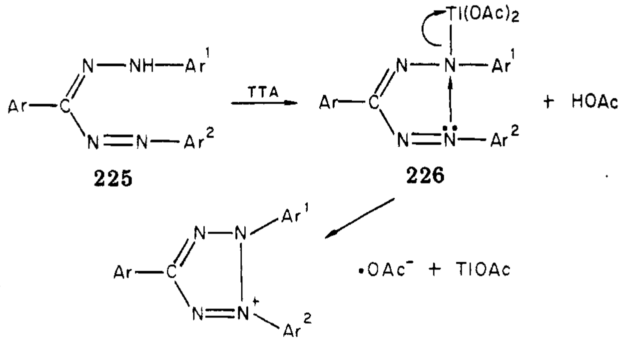


218

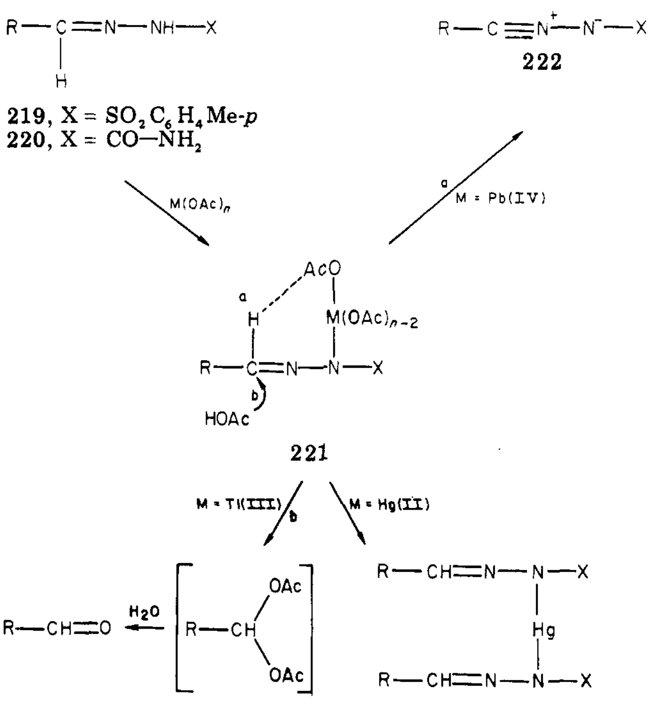
One of the consequences of the different mechanisms is that TTA emerges as unique among the three reagents for regenerating *aldehydes* from (tolylsulfonyl)hydrazones (**219**) and semicarbazones (**220**). Ketones are easily regenerated from (tolylsulfonyl)hydrazones with LTA[221] because the azo acetate products are readily hydrolyzed. However LTA will not regenerate aldehydes from hydrazones since these are rapidly dehydrogenated to nitrilimines (**222**) in an internal redox (**221**) (Scheme XXXVII, path a).[222] With TTA however the redox is intermolecular involving solvent giving a diacetyl acetal species (**223**) when X is a good leaving group. Hence aldehydes are regenerated by TTA from compounds **219** and **220**.[222,223] The comparisons described herein apply to reactions carried out in pure acetic acid or in organic solvents. The thallium(III) reactions appear to be particularly sensitive to solvent and oxidation of substituted benzaldehyde phenylhydrazones with TTA in acetic acid–water mixtures containing added chloride ion, which complexed with Tl(III) are reported to give monophenylhydrazones of benzil in a reaction involving a hydrazone dimerization which may be free radical in character.[224]

Formazans (**225**) are readily oxidized by LTA[225–229] and TTA[230] to tetrazolium salts (**227**). The mechanism is probably similar in both cases. A recent kinetic study of the thallium(III) reaction supports an intramolecular cyclization in the N–Tl(III) intermediate (**226**).[230] A similar reaction is the LTA oxidation of hydrazone derivatives of 2-acylpyridines (**228**) to 8-azaindazolium salts (**229**).[231] This cyclization works readily for both the *E* and *Z* forms of the hydrazones (**228**),[232] although it was reported earlier[231] that only the *Z* form of the hydrazone was cyclized.

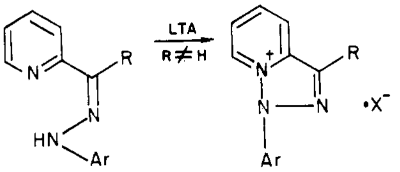


225 **226** **227**

SCHEME XXXVII



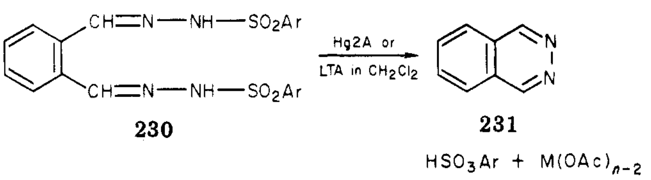
219, X = $SO_2C_6H_4Me$-*p*
220, X = CO—NH_2
222
221
223 **224**



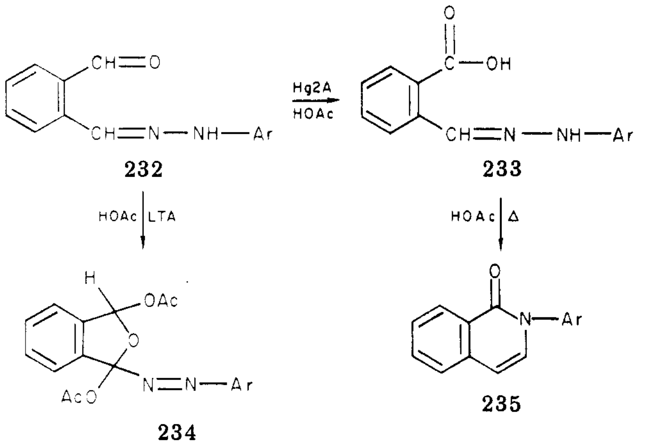
228
(*Z* form)
(E form also)

229

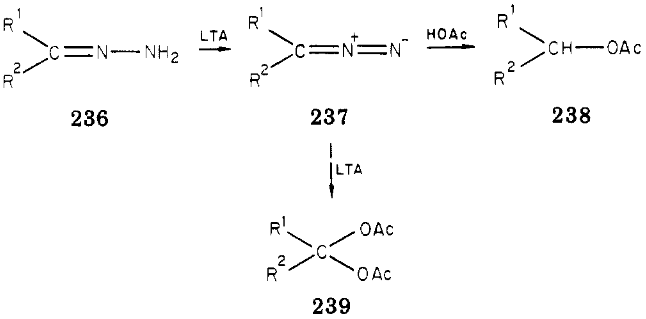
The reaction of 1,2-bis((*p*-tolylsulfonyl)hydrazones) (Scheme VII) represents a case where the reagents behaved similarly because of the high reactivity and leaving ability of the N-substituent. Bis((arylsulfonyl)hydrazones) of 1,4-dicarbonyl compounds (**230**) also behaved similarly with LTA and Hg2A giving an interesting fragmentation to phthalazine (**231**).[233] Oxidation of the *o*-carboxaldehyde *N*-arylhydrazones (**232**) with Hg2A occurred at the site of lowest oxidation threshold, the aldehyde group giving the products **233** which cyclized in acetic acid.[233] In the LTA oxidation of compounds **232** the hydrazone chain was also attacked giving the products **234**.[233] The extensive reactions of the wide variety of substituted hydrazone types of LTA, which have been comprehensively reviewed elsewhere,[12,13,20] have not yet been extended to TTA. Many interesting reactions can be expected from Tl(III) in this area.

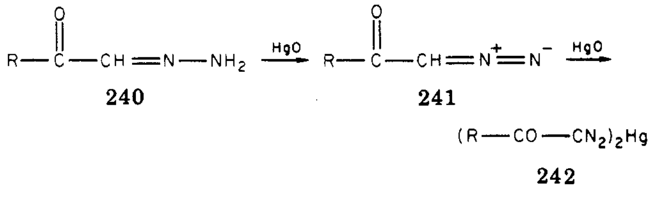


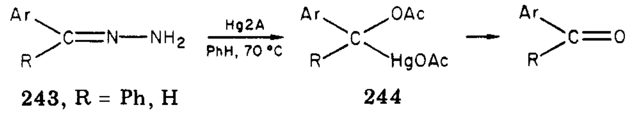
230 **231**



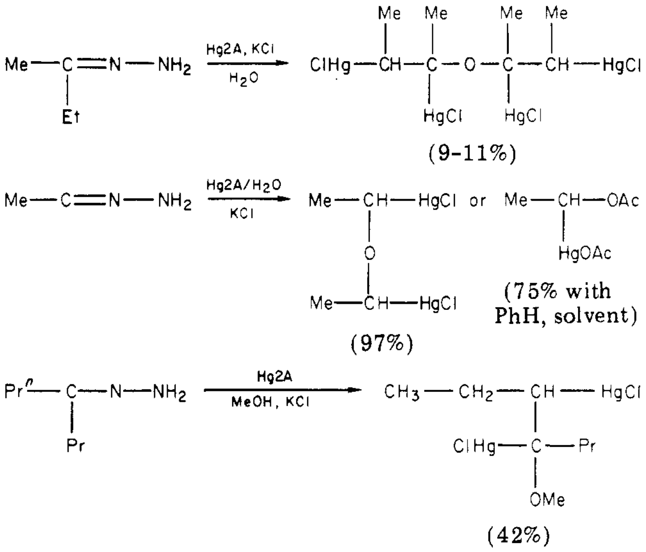
b. N-Unsubstituted Hydrazones. LTA oxidation of unsubstituted hydrazones **236** gives a dehydrogenation to diazoalkanes **237**.[234,235] The isolation of the compounds (**237**) depended on their stability, and when the substituents R^1 and R^2 were both CF_3,[236,237] CN,[238] or benzenesulfonyl groups,[239] the diazo compounds were stable. The diazo products (**237**) may react further with LTA to give *gem*-diacetoxy compounds **239** and in acetic acid they are converted to monoacetoxylalkanes **238**.[234,235] Methyl phenyldiazoacetate[240] and α-aryl- and α-cyanodiazoacetic esters[241] have also been obtained as stable products from the oxidation of the corresponding hydrazones with LTA. Similarly the α-diazo ketones (**241**) were obtained from mercuric oxide oxidation of the α-carbonylhydrazones (**240**).[242] Further treatment of the compounds (**241**) with mercuric oxide gave bis(diazo)mercury derivatives **242**.[242] The reported reactions[243-245] of unsubstituted hydrazones with Hg2A gave more complicated products which are generally mercuri derivatives not containing nitrogen. Thus oxidation of benzophenone or benzaldehyde hydrazones (**243**) with Hg2A in benzene gave the products **244** which reverted to the original carbonyl compound on standing or on treatment with base.[243] In general this reaction with dry benzene as solvent resulted in the introduction of OAc and HgOAc groups bonded to the methine carbon with loss of the nitrogen of the hydrazone chain,[243] probably via a diazo precursor. In the presence of water and halide ions more complicated dimeric products have been reported (Scheme XXXVIII).[244,245]







SCHEME XXXVIII

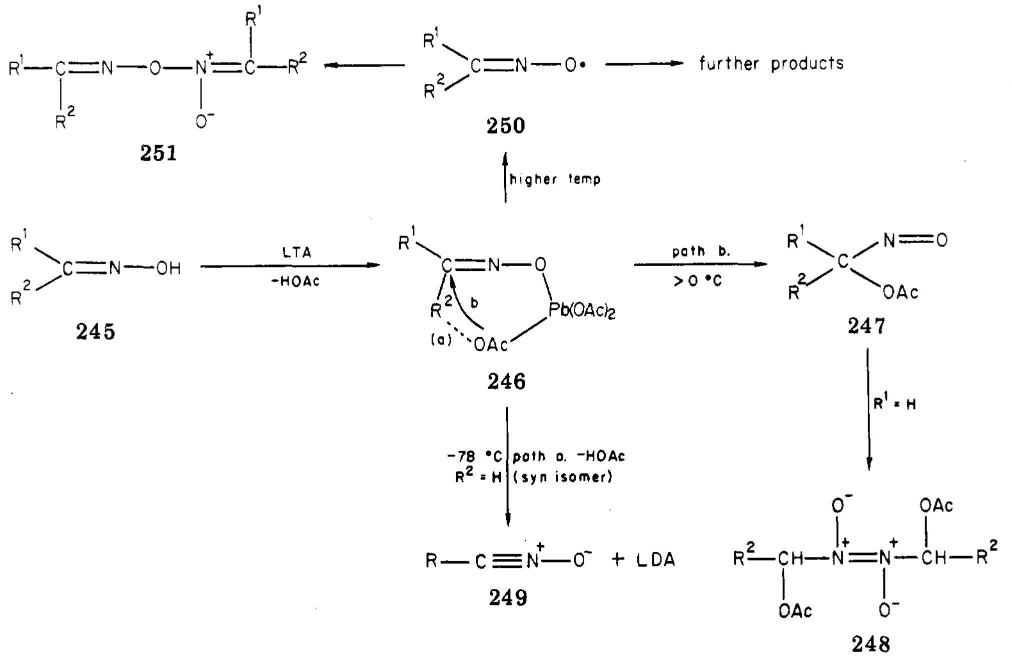


In oxidation of hydrazones derived from cycloalkanes with LTA olefins may also be formed most likely via carbocations, R_2CH^+, generated from protonation of precursory diazo intermediates.[245] This also occurs in Hg2A oxidations and for example treatment of cyclohexanone hydrazone with Hg2A at 90 °C in an aqueous solution containing a small amount of copper(II) gave 1-acetoxymercuri-1-cyclohexene.[244]

3. Oximes

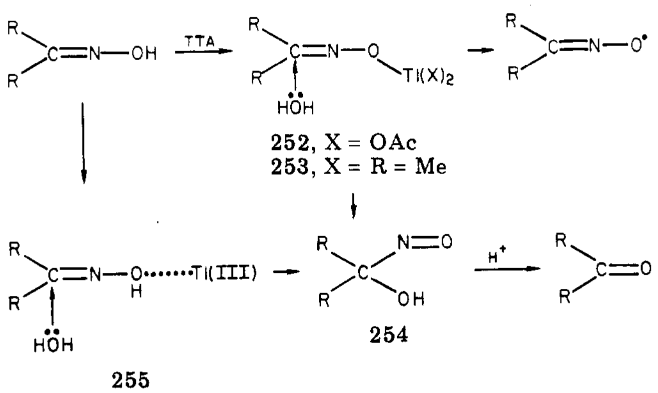
The reactions of oximes (**245**) with LTA and TTA seem to broadly parallel those of hydrazones with the added complexity that there are a number competing pathways operating. The reaction with LTA has been extensively studied and found to vary with (i) structure of the oxime, (ii) ratio of LTA to substrate, (iii) temperature, (iv) solvent, and (v) interference by autoxidation reactions and nitric oxide. When the reaction was carred at 70 °C in a number of solvents, a wide range of oxime types fragmented to regenerate the carbonyl compound in good yields.[247] TTN in methanol has also been recommended for efficient regeneration of carbonyl compounds from oximes when the products of the oxidation are treated with dilute sulfuric acid.[66] The overall reaction with LTA can be represented by the coherent sequence of competitive reactions outlined in Scheme XXXIX. The key intermediate is the *O*-metallo species (**246**). This may react by path b (Scheme XXXIX) to give the *gem*-nitrosoacetates (**247**). These products were isolated from aliphatic[68] and alicyclic ketoximes[248-251] and also from aliphatic *anti*-aldoximes where they dimerized to the compounds **248**.[248,251,252] At low temperatures species **246** from *syn*-aldoximes reacted by path a (Scheme XXXIX) giving nitrile oxide intermediates (**249**)[252,253] in a reaction analogous to the nitrilimine formation with aldehyde hydrazones. A competitive homolysis in species **246** also gives rise to iminoxy radicals **250** which have been directly detected by ESR spectroscopy.[254,25] No fewer than five different types of nitroxide radicals have

SCHEME XXXIX



been identified in oxime–LTA systems.[250,258,259] These radicals arise from secondary reactions which occur after the initial LTA attack.[20] The iminoxy radicals may also dimerize to products of type **251**. With some substrates, including oximes of aromatic aldehydes at 0–5 °C, these may become the major products in yields of up to 50%.[249,252,260]

The reactions of oximes with TTA may also involve an intermediate of type **252**.[66] The related compound **253** has been prepared by treatment of oximes with trimethylthallium.[66] As with substituted hydrazones, the Tl(III) redox process appears to be intermolecular involving nucleophilic solvent molecules giving rise to hydroxy nitroso compounds **254** in aqueous environments, which are the precursors to the regenerated carbonyl compounds.[66,67,261,262] Iminoxyl radicals have also been detected in oxime–Tl(III) systems.[66,261,262] Thus benzophenone oxime with TTN in benzene showed the ESR spectrum of the iminoxy radical,[66] and kinetic studies[261,262] of TTA–oxime reactions have been interpreted in terms of consecutive one-electron oxidations in an outer-sphere Tl(III)–oxime complex giving iminoxy radicals which were further oxidized. A mechanism of type **255** involving solvent attack on an activated Tl(III) complex has also been suggested[67] from kinetic studies. The products (**254**) were found to complex with further Tl(III), thereby inhibiting the carbonyl regeneration.[67]

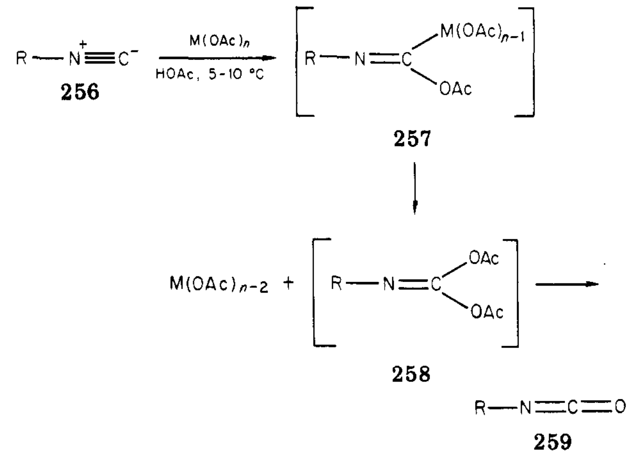


252, X = OAc
253, X = R = Me

254

255

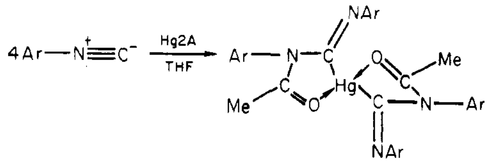
SCHEME XL



E. Other Functional Groups

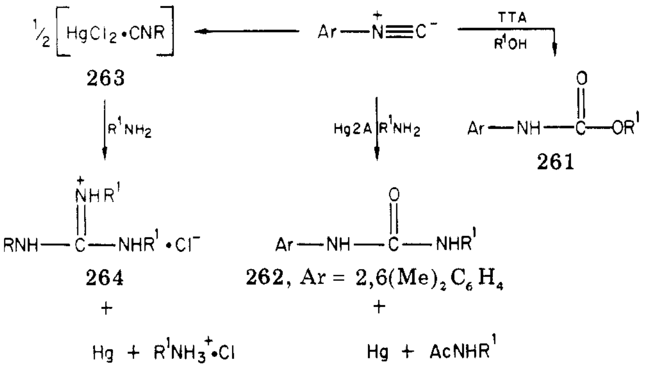
1. *Isocyanides*

The isocyanide group has a low oxidation threshold and like other such functional groups its reactions with the three reagents are the same (Scheme XL).[70] Thus treatment of isocyanides **256** with either LTA, TTA, or Hg2A at 5–10 °C in acetic acid or benzene–acetic acid mixtures gave good yields of isocyanates **259**.[70] The reaction is a two-electron oxidation probably involving the reactive intermediates **257** and **258** (Scheme XL). While the *C*-metallo intermediates have not been directly detected, the presence of a carbon–metal bond is supported by the formation of the unusual compounds **260** in the reaction of Hg2A with aromatic isocyanides in dry tetrahydrofuran.[263] A range of these

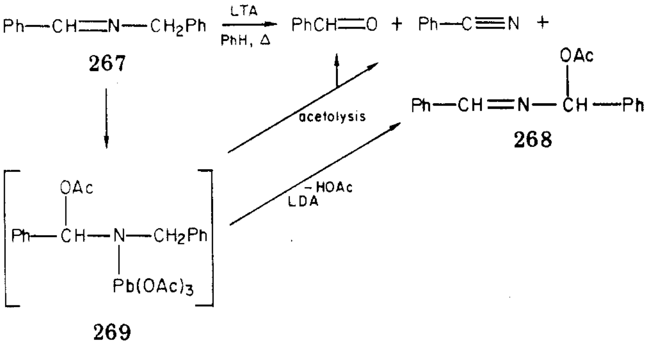


260

SCHEME XLI



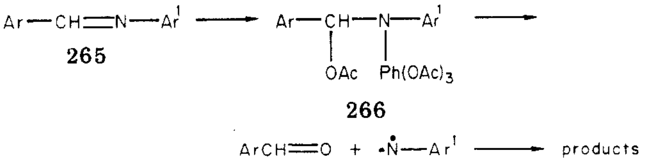
SCHEME XLII



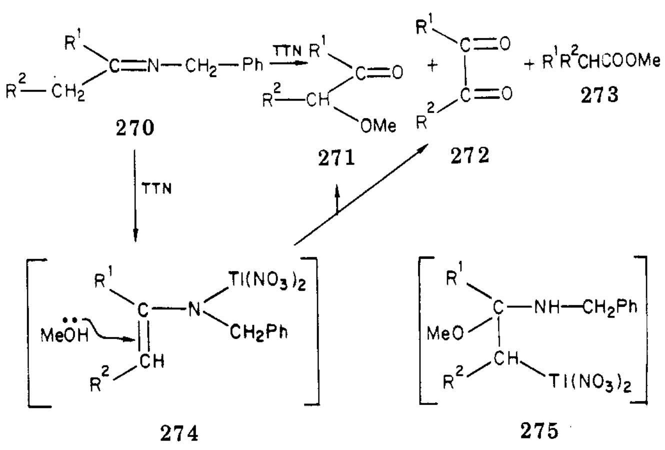
interesting new organomercury compounds has been reported[263] along with X-ray crystal structures. The reactions of Hg(II) and Tl(III) with isocyanides in the presence of amines or alcohols have proved useful for the synthesis of carbamates[70] (**261**) and ureas (**262**)[264,265] (Scheme XLI). Treatment of isocyanide–mercuric chloride complexes **263** with excess quantities of primary amines gave the guanidinium salts **264**, while the reaction with a 1 M quantity of the primary amine in the presence of Et_3N gave carbodiimides.[264] The route to the product (**262**) was unique to Hg2A and with TTA or LTA as oxidant no ureas or guanidines were formed.[264]

2. *Imines and Schiff Bases*

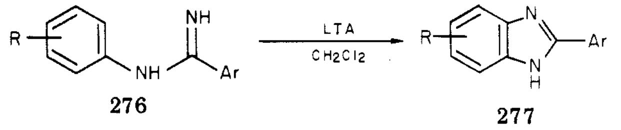
LTA oxidation of aromatic Schiff bases (benzylideneanilines) (**265**) resulted in fragmentation to the parent aldehyde, a substituted azobenzene, and small quantities of the parent amines.[266] The mechanism has been explained in terms of an electrophilic attack on the nitrogen atom giving species **266** which fragments to the aldehyde and a nitrene.[266] LTA oxidation of *N*-benzylidenebenzylamine (**267**) resulted in fragmentation to benzaldehyde and benzonitrile as well as an α-acetoxylation giving compound **268**.[107] Species **269** (**Scheme** XLII) was considered to be the key intermediate.[107] This could give benzaldehyde by acetolysis of $PhCH(OAc)_2$ and benzonitrile by fragmentation to $PhCH_2$-NH-$Pb(OAc)_3$ followed by further oxidation.[107] Oxidation of the tautomeric imines **270** with TTN in methanol gave, after aqueous workup, α-methoxy ketones **271** and α-diketones **272** as main products and in some cases small quantities of esters **273** (Scheme XLIII).[267] The N–Tl(III) intermediate **274** was considered to be a precursor to the products **271** and **272**, while a competitive pathway involving oxymetallation of the >C=C< of the enamine form, giving species **275** followed by an oxidative rearrangement and solvolysis, was the proposed route to compounds **273**.[267] Such an oxidative rearrangement to carboxylic acid derivatives was the main reaction of TTN in methanol with the corresponding ketones.[268]



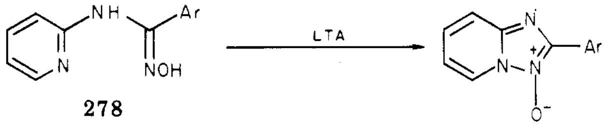
SCHEME XLIII



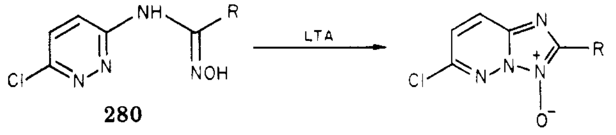
Oxidative cyclizations of ortho-substituted *N*-aryl Schiff bases (**101**) with LTA have already been referred to (Table II, ref 145–148). Other interesting recent cyclizations of imine-type systems with LTA include the substituted amidines **276**[269] and the amidoxime derivatives **278**[270] and **280**.[271]



276 **277**



278 **279**



280 **281**

3. *General*

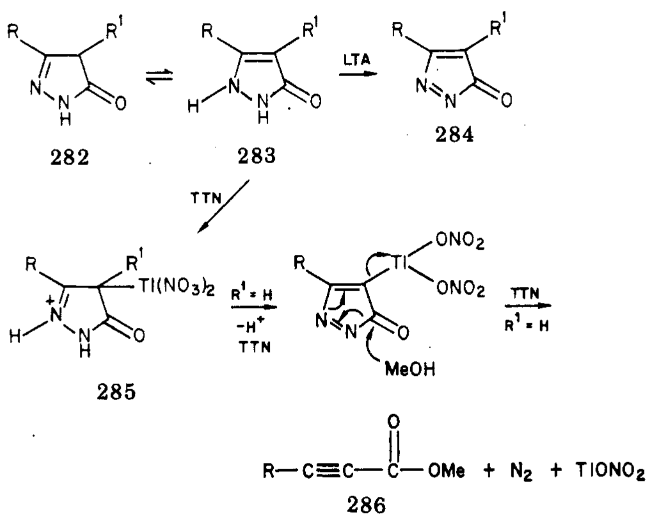
The individual reactions of LTA with a number of other nitrogen functional groups including hydroxylamines, substituted oxyamines, and nitrones have been reported elsewhere.[12,13,19,20]

F. Cyclic Nitrogen Compounds

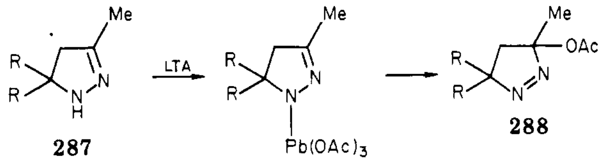
1. *Azoles and Five-Membered Rings*

The contrast in the reactions of LTA, TTA, and Hg2A with azole and azoline systems also illustrates some of the principles described in section III. For example oxidation of the 2-pyrazolin-5-ones **282** with Pb(IV) and Tl(III) occurred via the reactive enamine

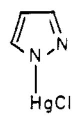
SCHEME XLIV



form (**283**) (Scheme XLIV). The LTA reaction appeared to occur preferentially on the nitrogen atoms and gave a dehydrogenation to the well-known dienophiles (**284**).[272-274] The parent 1-pyrazolin-3-one (**284**, R = R^1 = H) has been isolated at low temperatures from LTA oxidation of the corresponding pyrazolidin-3-one.[275] Generally, however, compounds of type **284** are unstable and are generated in situ for cycloaddition reactions with dienophiles. Oxidation of the substrates **283** with TTN in methanol involved initial Tl(III) attack at the olefinic center giving a species of type **285** (Scheme XLIV).[276,277] This was subsequently oxidized to the azo form followed by a solvolytic degradation giving substituted acetylenes (**286**) in contrast to the products from the LTA reaction.[276,277] The LTA oxidation of the 1*H*-2-pyrazolines (**287**) paralleled that of acyclic ketone hydrazones giving the 3-acetoxy derivatives (**288**) which are the cyclic analogues of the azo acetates (**207**).[278] A wide range of substituted pyrazolines has been oxidized with LTA.[20] The products depended on the substituent pattern in the ring and were generally either acetoxy derivatives or aromatized pyrazoles.[20]



The reactions of Hg2A with azole systems are essentially electrophilic aromatic substitution reactions. These may occur at an NH site or a CH site or at both. For example the reaction of pyrazole substrates with mercuric salts in aqueous media gives products of type **289** and **290**.[279] Many of these mercuric azoles are not well characterized due to difficulties arising from complexation and coordination polymerization as in structure **291**.[280] Treatment of pyrrole with Hg2A gave 2,3,4,5-tetrakis(acetoxymercuri)pyrrole.[281] The reaction of Hg2A with indole in aqueous or ethanolic media gave a bis(acetoxymercuri)indole,[282,283] which as the structure **292**,[284] although a 2,3-disubstituted structure was originally proposed. Oxidation of the substituted indoles (**293**) with TTA gave the dimeric products (**294**).[285] LTA oxidation of the indole-type substrates (**295**) gave the acetoxy derivatives (**296**) which were oxidized further to the pyridinium compounds (**297**).[286] On treatment of 1-*N*-methylindazole with Hg2A mercuration occurred at the 3-position of the pyrazole unit giving 3-acetoxymercuri-1-*N*-methylindazole.[287] The reaction of substituted purines with Hg2A in water or acetic acid gave bis(imidazolo) mercurials of type **298**.[288]



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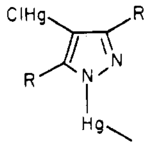

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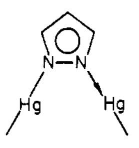

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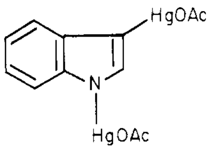

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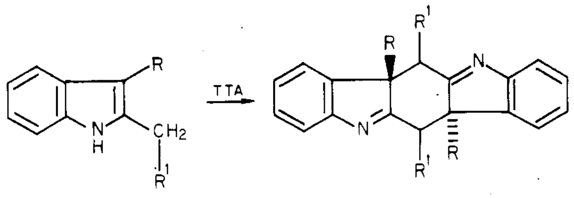
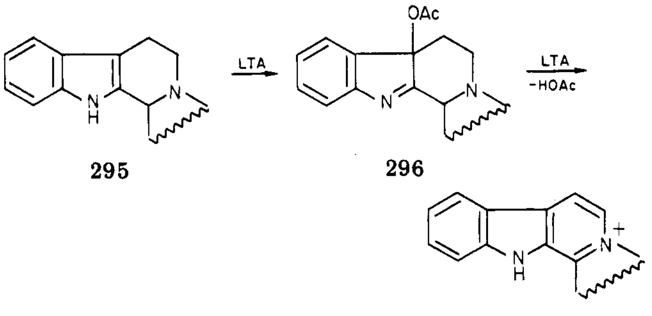
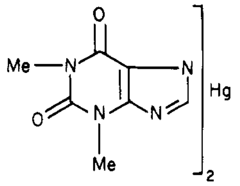
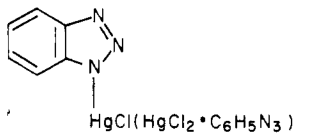






298



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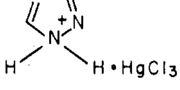
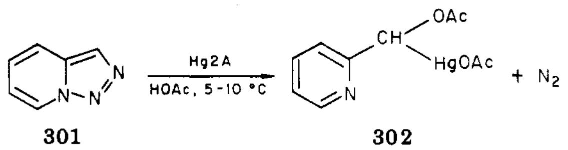
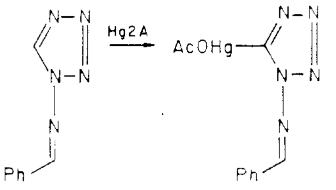


300

Complexes of imidazole with methyl mercury (Me–Hg–) have recently been fully characterized.[289] Complexes **299** and **300** have been reported[279] from the reactions of benzotriazole and 1,2,4-triazole with mercuric chloride. Cleavage of the triazole ring 1,2,3-triazolo[1,5-*a*]pyridine (**301**) occurred on treatment with Hg2A

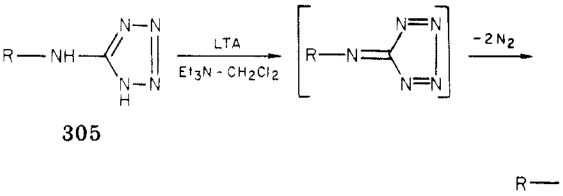


giving the acetoxymercuri product (**302**).[290] Even the deactivated tetrazole ring undergoes ready C-mercuration with Hg2A. The tetrazole derivative **303** on



303 304

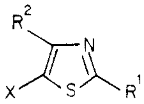
treatment with Hg2A in water gave the ring mercurated product **304** interestingly without interference at the imine moiety.[291] N-unsubstituted tetrazoles, RCN_4H, are nitrogen analogues of the carboxylic acids (RCO_2H) and should form stable salts, $M(OAc)_{n-1}(RCN_4)$, with the reagents in which an acetate group is displaced. We have observed this behavior with LTA and 5-aryltetrazoles which are therefore unreactive to the reagent under normal conditions.[292] However, if the tetrazole 5-substitutent contains a labile H atom allowing for a dehydrogenation to a tetraazafulvene, intermediate destruction of the tetrazole ring may ensue as in the LTA oxidation of the substrates **305** which gives high yield of isocyanides.[293]



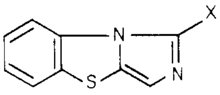
305

306

Some sulfur-nitrogen heterocycles which have been treated with Hg2A to give ring mercuration include the 2,4-disubstituted thiazoles **307** which gave the products



307, X = H
308, X = HgOAc

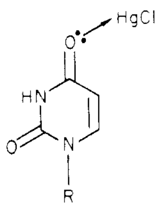


309, X = H
310, X = HgOAc

308[294,295] and the imidazolobenzothiazoles **309** which gave the products **310**.[296]

2. Azines and Six-Membered Rings

Azine heterocycles do L-prolyl-L-proline possess NH bonds and their reactions with the reagents may not directly involve the nitrogen atom. The few reactions which are reported are again of the aromatic substitution type which is outside the scope of this review. For example pyrimidine nucleosides reacted with Hg2A in aqueous solution at 50–70 °C to give C-5 mercurated pyrimidine derivatives.[297] Mercuration of quinoline *N*-oxide in acetic acid or perchloric acid occurred mainly at the 8-position and to a lesser extent at the 3-, 5-, 6-, and 7-positions.[298] N-Monosubstituted 2,4-dihydroxypyrimidines (uracils) interestingly gave three different kinds of products when treated with mercuric salts.[299] Crystalline products, involving coordination of the neutral ligand to the carbonyl oxygen (**311**), where obtained by using aqueous solutions of $HgCl_2$ at pH 4.2 at room temperature. Electrophilic substitution at C-5, giving compounds of type **312**, occurred on treatment of uracil and uridine with Hg2A in aqueous solutions at pH 5 at 50–70 °C.[299] At pH 7–9 the 3-N-mercurated products **313** were formed with uridine and thymidine and these were labile at lower pH values as expected for systems containing a Hg–N bond.[299] These systems provide models for some of the toxic effects associated with mercuric derivatives, e.g., destruction of the DNA regeneration system. Thus at pH 7–9 the reaction of mercury(II) or alkylmercury(II) with native DNA may involve mercury substitution of the important 3-N proton of the thymidine unit (hydrogen bonded to adenosine on the double helix).



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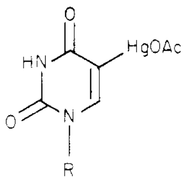

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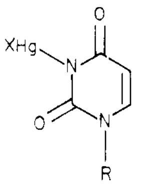
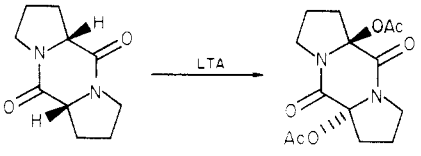
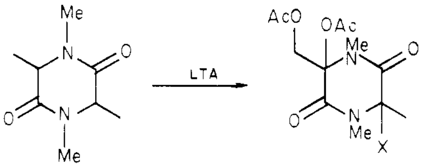


313

LTA oxidation of *L*-propyl-*L*-proline anhydride (**314**) in benzene gave the diacetoxyl derivative (**315**).[300] In a related reaction the substituted piperazinedione **316** gave a mixture of the products **317** and **318** on treatment with LTA in benzene.[301] These reactions probably involve attack on the enol or enamine functions in the tautomeric enol forms of the substrates. Some further examples of reactions with six-membered nitrogen rings have been referred to above including compounds **7**, **136**, and **138**.



314 315

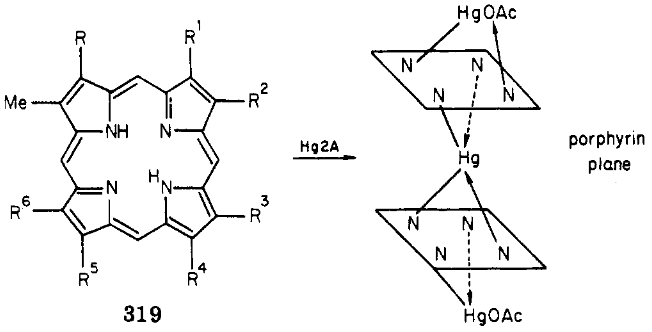


316

317, X = H
318, X = OAc

3. General

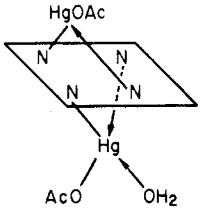
Although discussion of the variety of complexes of these metals which may contain a nitrogen donor atom is outside the scope of this review, mention is made here of some particularly interesting porphyrin derivatives, recently reported, in which the reagents are involved. The "double-sandwich" mercury(II) porphyrin derivatives **320** were obtained on treatment of etioporphyrins **319** with Hg2A in tetrahydrofuran and methylene chloride.[302] Normal 1:1 complexes were observed when pyridine was used as solvent.[303] When the methine bridges of the porphyrin ring contained phenyl substituents as in *meso*-tetraphenylporphyrin, rotation of the phenyl rings almost at right angles to the macrocyclic plane prevented the formation of double-layer complexes, and the product obtained on treatment of *meso*-tetraphenylporphyrin with Hg2A in tetrahydro-



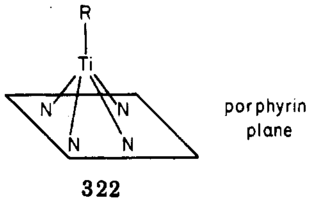
319

320

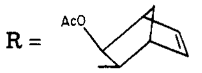
furan–methylene chloride had the structure **321**.[304,305]



321



322



Interesting complexes derived from Tl(III) have also been reported. For example the oxythallated adduct of norbornadiene reacted with tetraphenylporphyrin to give the complex **322**.[306] A number of other similar Tl(III) complexes with R = Me and Cl have also been reported.[307] The structure is characterized by a large displacement of the thallium atom from the porphyrin plane by 0.9 Å.

Registry No. $Hg(OAc)_2$, 1600-27-7; $Tl(OAc)_3$, 2570-63-0; $Pb(OAc)_4$, 546-67-8.

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