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Reactions of Lead Tetraacetate with Substituted Azomethines

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Contents

I. Introduction

This review covers the reactions of lead tetraacetate (LTA) with compounds variously referred to as imines, azomethines, anils, or Schiff bases and which can be designated structurally as RR′C═NR″. Most of the work to date has been concerned with compounds where the bonding site of R″ is a N atom (hydrazones) or an O atom (oximes). In agreement with naming systems used previously, the term *Schiff base* is limited to azomethines where R′ is an aryl group, R is a hydrogen, and R″ is either an alkyl or aryl group. Hydrazones, RR′C═NNR″R‴, are termed unsubstituted when R″ = R‴ = H, monosubstituted when R″ is a group other than hydrogen, and disubstituted when neither R″ nor R‴ is a hydrogen. Compounds are termed aldehyde derivatives when R′ of the azomethine moiety is a hydrogen and keto or ketone derivatives when neither R nor R′ is a hydrogen. Throughout the review the term *acetoxylation* means replacement of a hydrogen atom in a compound by the elements of an acetoxyl group ($C_2H_3O_2$) in any form, not necessarily a compact acetoxyl group.

Previous reviews of LTA chemistry include its reactions with 1,2-glycols,[1] sugars,[2] sterols,[3] hydrazones,[4] and oximes[5] and its general reactions with organic nitrogen compounds.[6] A review of the oxidative cyclization of derivatives of carbonyl compounds with a number of oxidizing agents including LTA has also been published.[7] Since the chemistry of the oxidation of substituted azomethines with LTA has not been covered comprehensively, the review deals with this topic from the introduction of LTA as a reagent about 50 years ago (up to ca. April 1972). The field has expanded rapidly in recent times probably because of the commercial availability of the reagent and a growing recognition of its versatility.

It is hoped that the review will demonstrate the synthetic usefulness of the reagent and also assist in identifying mechanistic ambiguities which prevail and stimulate some further work in this area, particularly kinetic measurements.

II. Reaction Mechanisms

A. With Hydrazones

1. Unsubstituted Hydrazones

The key intermediates in the reaction of LTA with hydrazones (**1**) are the diazoalkanes (**2**) resulting from dehydrogenation of the hydrazone.[8,9] In this respect the oxidation with LTA is similar to that with other oxidizing agents,[10] *e.g.*, MnO_2 and Ag_2O. The products of the reaction depend on the stability of the intermediate (**2**)

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(1) R. Criegee and C. A. Bunton, "Oxidation in Organic Chemistry," K. B. Wiberg, Ed., Academic Press, New York, N. Y., 1965, p 398.

(2) R. S. Perlin, *Advan. Carbohyd. Chem.*, 14, 9 (1959).

(3) K. Heusler and J. Kalvoda, *Angew. Chem., Int. Ed. Engl.*, **3**, 525 (1964).

(4) R. N. Butler, *Chem. Ind. (London)*. 437 (1968).

(5) R. N. Butler, *Chem. Ind. (London)*. 523 (1972).

(6) J. B. Aylward, *Quart. Rev., Chem. Soc.*, **25**, 407 (1971).

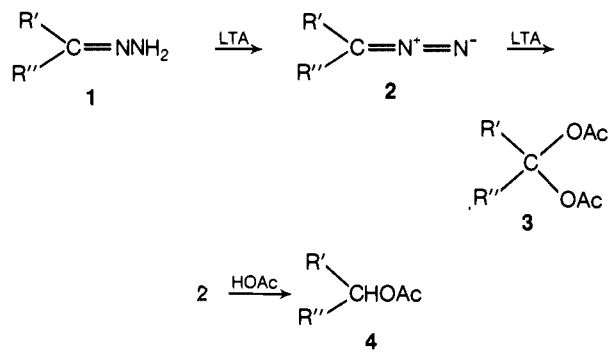
(7) J. Warkentin, *Synthesis*. 279 (1970).

(8) D. H. R. Barton, J. F. McGhie, and P. L. Batten, *J. Chem. Soc. C*. 1033 (1970).

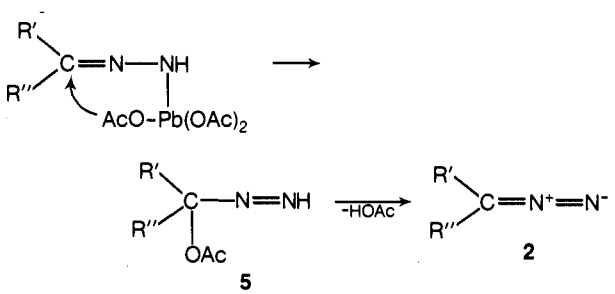
(9) A. Stojiljkovic, N. Orbovic, S. Sredojevic, and M. Lj. Mihailovic, *Tetrahedron*. **26**, 1101 (1970).

(10) O. Meth-Cohn and H. Suschitzky, *Chem. Ind. (London)*. 443 (1969).

and its subsequent reactions with LTA or the medium. This general reaction pathway was established independently by two groups of workers.[8,9] When the substituents R′ and R″ are both CF_3,[11,12] or CN[13] groups, the diazo compounds (**2**) are stable. With benzophenone hydrazone (**1**, R′ = R″ = Ph) the intermediate (**2**) was suggested from a red coloration.[8,9] It was directly detected by trapping with dimethyl acetylenedicarboxylate.[8] Methyl phenyldiazoacetate[14] and α-aryl- and α-cyanodiazoacetic esters[15] have also been obtained as stable products by treating the corresponding hydrazones with LTA. In general, the reaction products are substituted monoacetoxy alkanes (**4**) or diacetoxy alkanes (**3**) resulting from further reactions of the intermediates (**2**).[8,9,16] With alicyclic hydrazones rapid reactions are observed and olefins are formed along with the acetoxylated products.[8,17] The origin of the olefins appears to be a carbonium ion (R_2CH^+) generated from the protonated precursory diazo intermediate ($R_2CHN_2^+$).[8] No evidence for carbene intermediates has been obtained.[8,9]



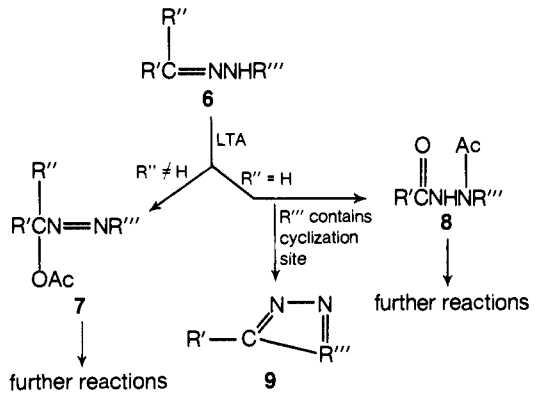
The mechanism of the dehydrogenation **1** → **2** has not been determined, and no kinetic study has been reported. It may involve rapid loss of acetic acid from an intermediate (**5**) analogous to the reaction with substituted hydrazones. Other mechanisms are also possible, and, for example, a nitrene =N—N: intermediate could be involved. LTA oxidations of compounds containing N–NH_2 moieties give rise to products which have been explained in terms of nitrene intermediates.[18-23]



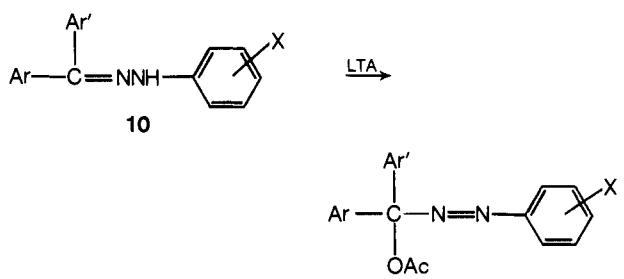
2. Monosubstituted Hydrazones

In general, the reactions of LTA with substituted hydrazones (**6**) follow the pattern outlined in Scheme I. Ketohydrazones yield azoacetates **7**, and aldehyde hydrazones yield acylhydrazines of type **8**. Dehydrogenative cyclization of aldehyde hydrazones also occurs when the substituent R‴ has a suitable cyclization site. Other products may arise from further reactions and minor deviations from this main pathway. For example, with benzaldehyde phenylhydrazone the azoacetate **7** (R′ = R‴ = Ph; R″ = H) was isolated in about 27% yield.

SCHEME I

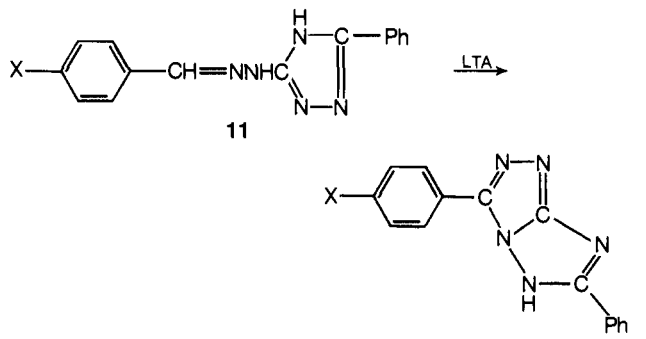


A free-radical mechanism was invoked originally by Iffland[24] and more recently by Gillis[25,26] to explain the reaction with ketone hydrazones. Although free radicals are known to be involved in certain reactions of LTA and iminoxy radicals have been directly detected in the reactions of LTA with oximes (see below), there is no evidence for such intermediates in the reaction with substituted hydrazones. The esr procedures which were used successfully to detect radicals in the LTA–oxime reaction showed no radicals for the hydrazone systems.[27] Systematic kinetic studies have been reported for the LTA oxidation of the ketone arylhydrazones[27] (**10**) and the aldehyde heterocyclic hydrazones[28,29] (**11**).



A Hammett ρ value[30] of −1.95 was obtained for the compounds[27] (**10**). The ρ value obtained for substituent variation in the arylidene ring of the hydrazones **11** was[28,29]

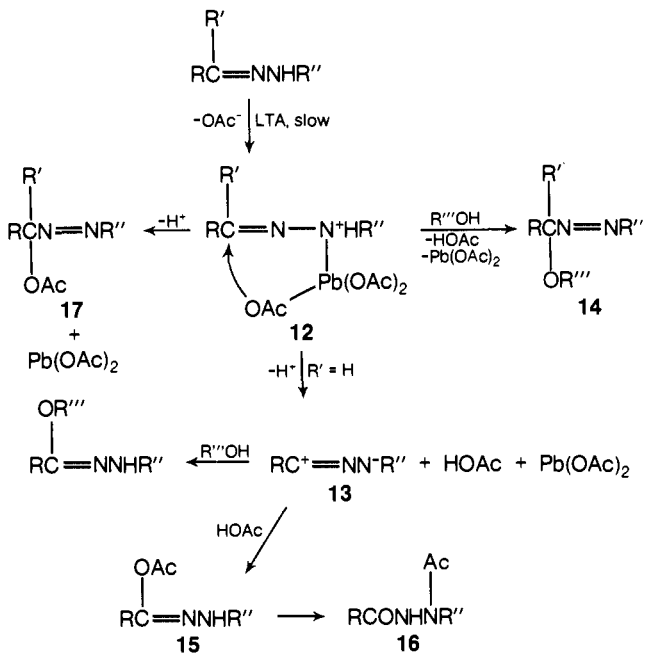
(11) D. M. Gale, W. J. Middleton, and C. G. Krespan, *J. Amer. Chem. Soc.*, **88**, 3617 (1966).
(12) C. G. Krespan and W. J. Middleton, U. S. Patent 3,242,166 (1966); *J. Org. Chem.*, **30**, 1398 (1965).
(13) E. Ciganek, *J. Amer. Chem. Soc.*, **87**, 657 (1965).
(14) E. Ciganek, *J. Org. Chem.*, **30**, 4198 (1965).
(15) E. Ciganek, *J. Org. Chem.*, **35**, 862 (1970).
(16) R. H. Hensel, *Chem. Ber.*, **88**, 257 (1955).
(17) (a) M. Debono and R. M. Molloy, *J. Org. Chem.*, **34**, 1454 (1969); (b) T.-T. Wang, Ph.D. Thesis, Rice University, 1967.
(18) J. W. Barton and S. A. Jones, *J. Chem. Soc. C*, 1276 (1967).
(19) H. E. Baumgarten, P. L. Creger, and R. L. Zey, *J. Amer. Chem. Soc.*, **82**, 3977 (1960).
(20) R. K. Smalley and H. Suschitzky, *Chem. Ind. (London)*, 1338 (1970).
(21) D. J. Anderson, T. L. Gilchrist, D. C. Horwell, and C. W. Rees, *J. Chem. Soc. C*, 576 (1970).
(22) C. D. Campbell and C. W. Rees, *J. Chem. Soc. C*, 748, 752 (1969), and other papers in the series.
(23) G. Koga and J.-P. Anselme, *J. Amer. Chem. Soc.*, **91**, 4323 (1969).
(24) D. C. Iffland, L. Salisbury, and W. R. Schafer, *J. Amer. Chem. Soc.*, **83**, 747 (1961).
(25) B. T. Gillis and M. P. La Montague, *J. Org. Chem.*, **33**, 762 (1968).
(26) B. T. Gillis and M. P. La Montague, *J. Org. Chem.*, **33**, 1294 (1968).
(27) M. J. Harrison, R. O. C. Norman, and W. A. F. Gladstone, *J. Chem. Soc. C*, 735 (1967).
(28) F. L. Scott and T. A. F. O'Mahony, *Tetrahedron Lett.*, 1841 (1970).
(29) T. A. F. O'Mahony, R. N. Butler, and F. L. Scott, *J. Chem. Soc., Perkin Trans. 2*, 1319 (1972).
(30) K. B. Wiberg, "Physical Organic Chemistry," Wiley, New York, N. Y., 1966, pp 396–430.



11

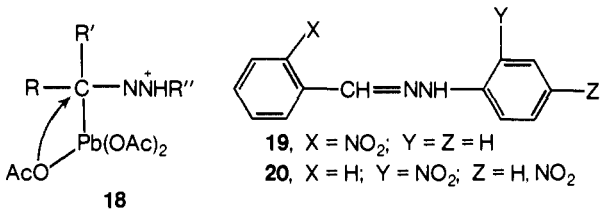
−0.60. The rates of reaction of the hydrazones **10** were sensitive to solvent composition being more rapid in polar solvents.[27] These data suggest a polar mechanism, and both groups of workers[27-29] have interpreted them in terms of a rate-determining displacement on lead(IV) yielding an ammonium species such as **12** (Scheme II).

SCHEME II



The inductive effect of the positive charge enhances the susceptibility of the methine carbon to nucleophilic attack, and the intermediate **12** may yield an azoacetate by intramolecular transfer of an acetoxy group or, in the case of aldehyde hydrazones, a nitrilimine intermediate (**13**) may be formed by a proton abstraction from the methine carbon. Reactions carried out in alcoholic solvents yielded azo ethers (**14**) which arise by an intermolecular displacement of the lead salt in **12** and not by exchange with azoacetates.[27] Gladstone[31] first detected nitrilimine intermediates in the reactions with aldehyde hydrazones by trapping them with acrylonitrile. The presence of these intermediates has been fully confirmed,[32-35] and oxidation of aldehyde hydrazones with LTA is now becoming a standard method of generating nitrilimines for 1,3-dipolar addition reactions. The acylhydrazines (**16**) are now considered to arise from addition of acetic acid to the nitrilimines (**13**) followed by 1,4-acyl migration[36-40] in the resulting hydrazonyl acetates[31,32] (**15**). Hydrazonyl acetates (**15**) were originally considered to arise *via* a tautomerism in the azoacetates **17** (R′ = H), but the isolation of compound **17** (R = R″ = Ph; R′ = H) discounted this since the rate of tautomerism was considerably less than the rate of the LTA oxidation.[31,32] Hydrazonyl ethers, sometimes formed with aldehyde hydrazones in alcoholic solvents, may also arise from solvent addition to the nitrilimines (**13**).

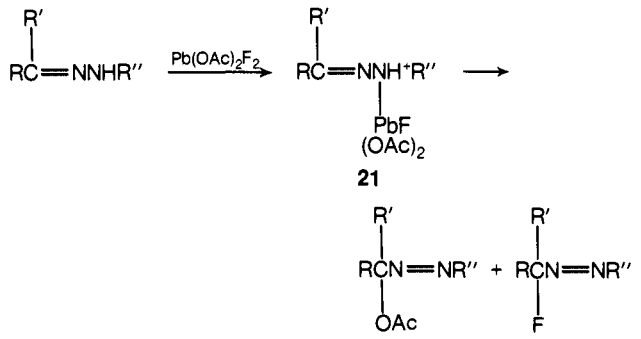
Hence the cohereht mechanistic pathway depicted in Scheme II emerges. Ambiguities, however, exist in relation to the initial site of attack on the hydrazone and the mechanism of cyclization of heterocyclic aldehyde hydrazones, for example, **11**. The mechanistic data could also be explained in terms of an initial attack by Pb(IV) at the methine carbon with dissipation of positive charge toward the *N*-aryl moiety. Such a mechanism was, in fact, proposed[41] for the oxidation of substituted 2-pyrazolines (cyclic hydrazone systems) to substituted 3-acetoxy-1-pyrazolines with LTA. In contrast with this, a mechanism involving initial attack on N-**1** has also been proposed for the LTA oxidation of N-substituted 2-pyrazolines to pyrazoles.[42] Two points seem to argue in favor of a mechanism involving initial N-attack as in Scheme II: (i) the involvement of a five-membered transition state for the acetoxy migration in **12** as against the three-membered transition state required for an intermediate such as **18**; (ii) the reactivity of compound **19** compared with the unreactivity of the compounds **20** suggesting[32] a steric



18

19, X = NO_2; Y = Z = H
20, X = H; Y = NO_2; Z = H, NO_2

protection of the NH site. The former point is valid if the azoacetates arise from an internal acetoxy migration rather than an intermolecular nucleophilic displacement similar to that involved with the azo ethers **14**. Evidence for an intramolecular acetoxy migration is tenuous, being based mainly on a limited preference for azoacetate formation rather than azo ether formation in solutions containing large excesses of alcohol.[27] However, the formation of mixtures of azoacetates and azofluorides on treatment of ketone arylhydrazones with lead(IV) diacetate



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(31) W. A. F. Gladstone, *Chem. Commun.*, 179 (1969).
(32) W. A. F. Gladstone, J. B. Aylward, and R. O. C. Norman, *J. Chem. Soc. C*, 2587 (1969).
(33) T. Sasaki and K. Kanematsu, *J. Chem. Soc. C*, 2147 (1971).
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(35) T. Sasaki, K. Kanematsu, and M. Uchide, *Bull. Chem. Soc. Jap.*, 44, 858 (1971).
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(37) J. M. Burgess and M. S. Gibson, *J. Chem. Soc.*, 1500 (1964).
(38) I. T. Barnish and M. S. Gibson, *J. Chem. Soc.*, 2999 (1965).
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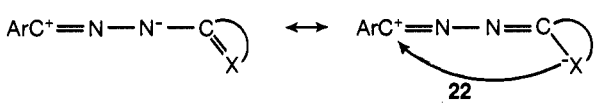
(41) P. Bouchet, J. Elguero, and R. Jacquier, *Bull. Soc. Chim. Fr.*, 4716 (1967).
(42) W. A. F. Gladstone and R. O. C. Norman, *J. Chem. Soc. C*, 1536 (1966).

difluoride in chloroform may also support an internal acetoxy migration.[43,44] Higher yields of the azoacetate are consistent with internal acetoxy migration in an intermediate such as[44] **21**. The second point is ambiguous since it has been found that ortho substituents (X) in the arylidene ring of compounds of type **19** (Y = H; Z = NO_2) provide little steric hindrance to the approach of bromine to the methine carbon,[45] and that the rates of oxidation of hydrazones with bromine are governed by the stereochemical syn–anti forms of the hydrazone.[46] The rate-retarding effect of the substituent Y in compounds **20** could therefore also arise from a "locking" of the molecule in an unfavorable stereochemical form by hydrogen bonding. It has been demonstrated[28,29] that the electronic substituent effects operating for the LTA oxidation of hydrazones are very similar overall to those which apply for attack on hydrazones by electrophiles such as diazonium ion and bromine where methine attack is rate determining. In each case an N-aryl-ρ/C-aryl-ρ ratio of 3.3–3.5 obtains. Hence present data are equally accommodated by initial attack at C or N. Another mode of reaction which merits consideration involves initial and reversible attack at either site followed by irreversible attack at the other.[45,46]

In reactions involving cyclization of heterocyclic hydrazones, e.g., **11**, initial attack may also occur at the C=N site of the heterocyclic substituent. The uncertainty[46a] of the initial site of attack allows for numerous postulations for the subsequent cyclization steps. These may be divided into three general types (i) involving generation of electrophilic character at the methine carbon by loss of a group or groups from the precursory intermediates, the electrophilic center being then attacked by the internal heterocyclic nucleophile; (ii) electrocyclic cyclization of the 1,5-dipolar form of a nitrilimine intermediate,[47] e.g., **22**; (iii) neighboring nucleophilic displacement of a group



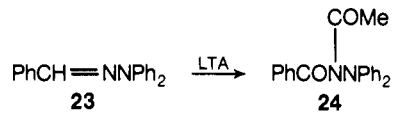
22

X = N, O, S

or groups from the precursory intermediates by the internal nucleophile (heterocyclic ring or methine C=N moiety) with simultaneous ring closure. Attempts to trap nitrilimine intermediates in the reactions of LTA with heterocyclic hydrazones have not been successful.[28,29,48] This could mean that such intermediates are not present or that the internal 1,5-dipolar cyclization is much more rapid than the external 1,3-addition reaction.

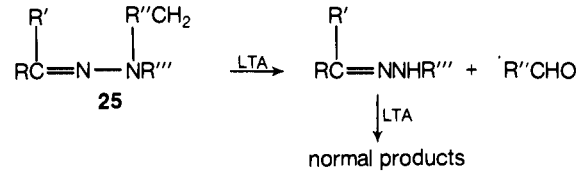
3. N,N-Disubstituted Hydrazones

Replacement of the H atom of the NH moiety of the hydrazone chain by a more bulky substituent might be expected to have an inhibitory effect on the reaction. In general, this has not been the case and new reaction pathways or modifications of the general path outlined are observed. Thus, benzaldehyde diphenylhydrazone (**23**) readily yields the acylhydrazine (**24**) on treatment



23 **24**

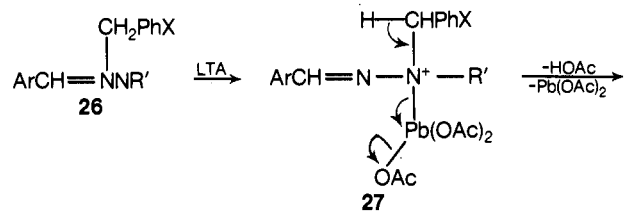
with LTA.[32] A cationic intermediate, generated similarly to a nitrilimine, has been proposed to explain this reaction.[32] With both aldehyde[49] and ketone[50] *N*-alkyl-*N*-arylhydrazones (**25**), a stoichiometry of 2:1 (LTA:hydrazone) operates, the first step of the reaction involving a dealkylation of the hydrazone to the monosubstituted



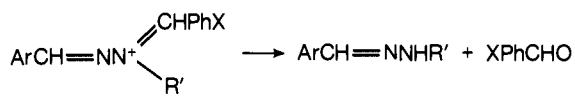
25

normal products

form and a carbonyl derivative (aldehyde for primary and ketone for secondary substituents) of the alkyl substituent. Aylward[49] has observed rate enhancement for electron-donating substituents (X) in the benzyl moiety of the *N,N*-dibenzylhydrazones (**26**) and rate retardation by electron-withdrawing substituents. The dealkylation has been explained[49] in terms of the cationic intermediates **27** and **28**. The monosubstituted hydrazones thus generated undergo normal reactions with the second mole of LTA.



26 **27**



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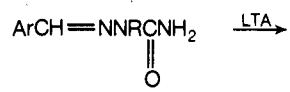
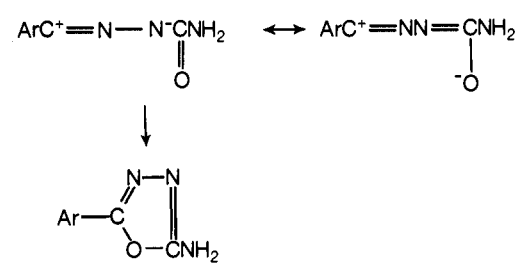
In some cases a decrease in reactivity has been noted on replacement of the H atom of the hydrazone chain by an alkyl group. Thus, for example, the semicarbazones **29** are readily cyclized to oxadiazoles with LTA, whereas the *N*-methyl derivatives **30** are unreactive under the



29, R = H
30, R = CH_3



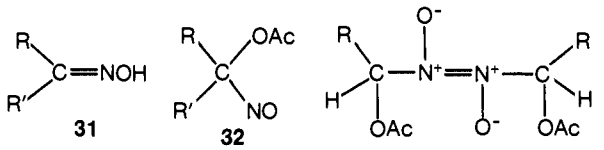
same conditions.[51] However, the inhibitory effect of the methyl group is more likely due to its structural prohibition of a nitrilimine intermediate than to a steric prohibition of the initial Pb(IV) attack.

(43) J. Bornstein and L. Skarlos, *J. Amer. Chem. Soc.*, **90**, 5044 (1968).
(44) J. Bornstein and L. Skarlos, *J. Org. Chem.*, **35**, 1230 (1970).
(45) A. F. Hegarty and F. L. Scott, *J. Chem. Soc. B*, 1031 (1966).
(46) A. F. Hegarty and F. L. Scott, *J. Org. Chem.*, **33**, 753 (1968).
(46a) Note Added in Proof. Recently it has been suggested that the acetyl group in benzaldehyde acetylhydrazone reduces the nucleophilicity of the NH site, thereby causing the initial attack to occur at the imino nitrogen; *cf.* R. O. C. Norman, R. Purchase, C. B. Thomas, and J. B. Aylward, *J. Chem. Soc., Perkin Trans. 1*, 1692 (1972).
(47) H. Reimlinger, *Chem. Ber.*, **103**, 1900 (1970).
(48) R. N. Butler, P. O'Sullivan, and F. L. Scott, *J. Chem. Soc. C*, 2265 (1971).
(49) J. B. Aylward, *J. Chem. Soc. C*, 1494 (1970).
(50) D. C. Iffland and E. Cerda, *J. Org. Chem.*, **28**, 2769 (1963).
(51) T. M. Lambe, R. N. Butler, and F. L. Scott, *Chem. Ind. (London)*, 996 (1971).

B. With Oximes

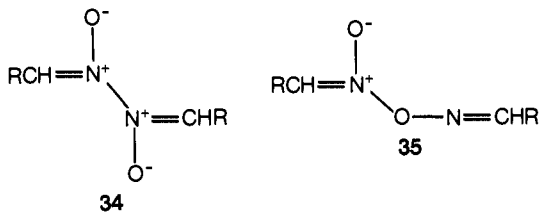
The reaction of LTA with oximes (**31**) is a complicated process giving rise to a range of products, the nature of which depends upon such variables as (a) structure of the substrate, (b) ratio of LTA to substrate, (c) temperature, (d) solvent, and (e) interference by autoxidation reactions and nitric oxide. The reactions are also characterized by the direct detection of quite a number of reactive intermediates.

The main products obtained with ketoximes are the *gem*-nitrosoacetates (**32**) and the parent ketone.[52,53] The nitrosoacetate dimers (**33**) are obtained from aliphatic al-



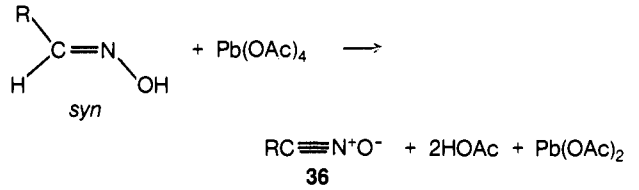
31 **32** **33**

doximes, and products which have been assigned both of the structures **34** and **35** are obtained from aromatic al-



34 **35**

doximes along with the parent carbonyl compound at temperatures above 0°.[54,55] At low temperatures (−78°) all *syn*-aldoximes yield nitrile oxides (analogs of nitrilimines) (**36**) as follows.[55,56]



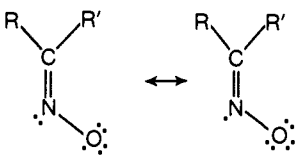
syn

$$RC{\equiv}N^{+}O^{-} + 2HOAc + Pb(OAc)_2$$

36

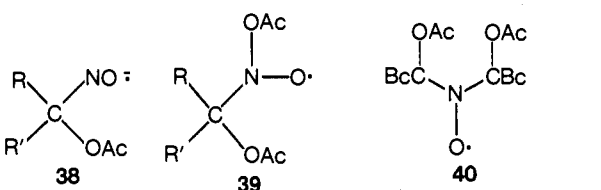
The yields of nitrile oxides decreased with increasing temperature and only when the substituent R had large steric requirements were nitrile oxides obtained at room temperature. With ketoximes (**31**) in which the substituents R and R′ had large steric requirements, the reaction involved a C–C bond fission and also yielded nitrile oxide intermediates (detected spectroscopically and by methyl acrylate trapping).[57]

At least six different radical species (**37–42**) have been identified in LTA–oxime systems by esr spectroscopy. The main intermediates were the iminoxy radicals **37**.[58-68] These are characterized by a large splitting due to nitrogen of $a_N \approx 30$ G, indicating significant spin density on the nitrogen atom in an orbital of s character. The CNO bond angle is about 140° and the unpaired electron is in a π-type orbital, derived from a nitrogen sp^2 orbital and an oxygen p orbital, which lies in the nodal plane of the C–N π bond. This π-type orbital is orthogonal to the molecular system and the radicals are sigma (σ) radicals. Generally both isomers are formed irrespective of the configuration of the oxime used, indicating that the energy barrier to isomerism is lower in the radical than in the oxime. The structure[69-71] and transmission of spin[58-68] in these radicals have been studied extensively, but this aspect of the radicals is outside the scope of this review (see literature cited and, in particular, ref 64, 68, and 70).



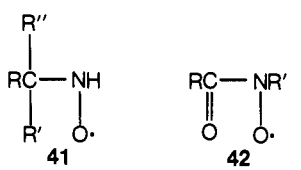
37

Nitroxide radicals of types **38** and **39** were also observed by Lown,[72,73] along with iminoxy radicals. Bicyclic ketoximes yielded the radicals **40**, **41**, and **42** when oxidized with LTA.[74] Mechanistic proposals have been mainly concerned with accounting for these intermediates, and kinetic studies have not been reported.



38 **39** **40**

Bc = bicyclic ring system



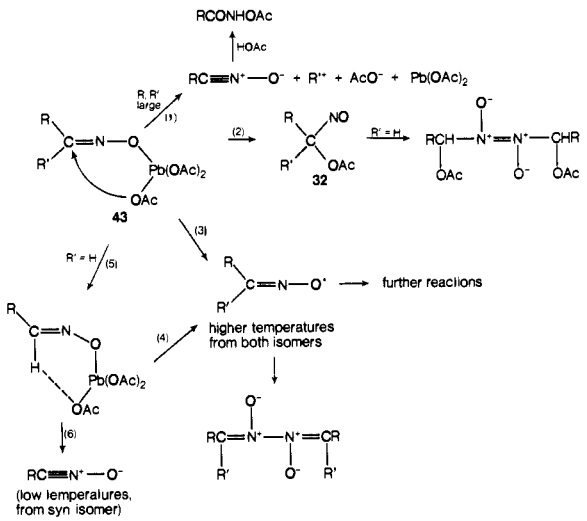
41 **42**

A free radical mechanism involving abstraction of the oxime OH hydrogen atom by an acetoxy radical followed by attack of a second acetoxy radical at the methine carbon has been suggested.[60,61] However, products arising from Me· radicals or radical substitution in aromatic rings have not been isolated, and free acetoxyl radicals may not be involved. Initial attack involving a displacement of the oxime OH hydrogen atom agrees with the failure of oxime *O*-alkyl ethers to react.[75] A concerted mechanism (Scheme III) involving the intermediate **43** has been suggested[53] to account for the nitrosoacetates **32**. The imin-

(52) D. C. Iffland and G. X. Criner, *Chem. Ind. (London)*, 176 (1956).
(53) H. Kropf and R. Lambeck, *Justus Liebigs Ann. Chem.*, **700**, 1 (1966).
(54) H. Kropf and R. Lambeck, *Justus Liebigs Ann. Chem.*, **700**, 18 (1966).
(55) G. Just and K. Dahl, *Tetrahedron*, **24**, 5251 (1968).
(56) G. Just and K. Dahl, *Tetrahedron Lett.*, 2441 (1966).
(57) G. Just and K. Dahl, *Can. J. Chem.*, **48**, 966 (1970).
(58) B. C. Gilbert, R. O. C. Norman, and D. C. Price, *Proc. Chem. Soc., London*, 234 (1964).
(59) B. C. Gilbert and R. O. C. Norman, *J. Chem. Soc. B*, 86 (1966).
(60) H. Lemaire and A. Rassat, *Tetrahedron Lett.*, 2245 (1964).
(61) M. Bethoux, H. Lemaire, and A. Rassat, *Bull. Soc. Chim. Fr.*, 1985 (1964).
(62) B. G. Gilbert and R. O. C. Norman, *J. Chem. Soc. B*, 981 (1967).
(63) B. G. Gilbert and R. O. C. Norman, *J. Chem. Soc. B*, 123 (1968).
(64) B. G. Gilbert and R. O. C. Norman, *J. Phys. Chem.*, 71, 14 (1967).
(65) A. Caragheorgheopol, M. Hartmann, R. Kuhmstedt, and V. E. Sahini, *Tetrahedron Lett.*, 4161 (1967).
(66) A. Caragheorgheopol, U. Grafe, M. Hartmann, V. E. Sahini, and K. Wermann, *Tetrahedron Lett.*, 3035 (1970).
(67) H. Caldararu, N. Barbulescu, L. Ivan, and V. E. Sahini, *Tetrahedron Lett.*, 3039 (1970).
(68) R. O. C. Norman, *Chem. Brit.*, 6, 66 (1970).
(69) M. C. R. Symons, *J. Chem. Soc.*, 1189 (1963).
(70) M. C. R. Symons, *Advan. Phys. Org. Chem.*, 1, 283 (1963).
(71) M. C. R. Symons, *J. Chem. Soc.*, 2276 (1965).
(72) J. W. Lown, *J. Chem. Soc. B*, 441 (1966).
(73) J. W. Lown, *J. Chem. Soc. B*, 644 (1966).
(74) A. Caragheorgheopol, H. Caldararu, T. Constantinescu, and V. E. Sahini, *J. Amer. Chem. Soc.*, **93**, 6766 (1971).
(75) See ref 24, footnote 9.

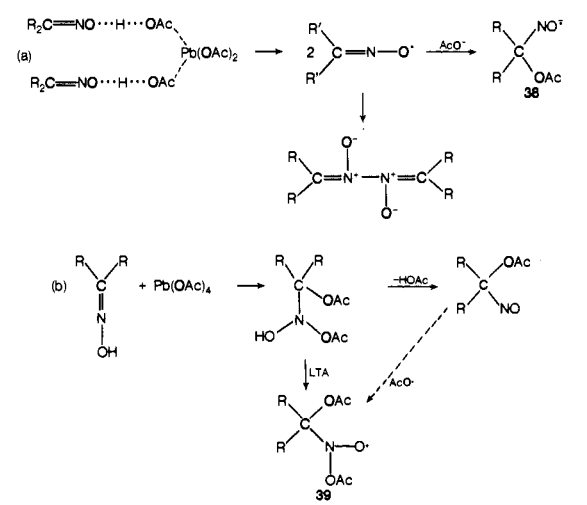
oxy radicals and nitrile oxides obtained from aldoximes have been accounted for[55] in terms of steps 3, 4, and 6 of Scheme III. An alternative mechanism involving a cationic intermediate was also suggested.[54] Scheme III,

SCHEME III



which embodies a number of mechanisms suggested for separate specific reactions, presents a reasonably coherent picture and explains most of the observations to date. Steps 2 and 6 have direct analogs in the reactions with hydrazones and can be identified as a general trend for systems such as >C=NXR (X = O, NH). Radicals of type **40** are considered to arise subsequent to step 2 by a reaction between two nitrosoacetate molecules with loss of NO.[74] Radicals of type **42** are thought to arise subsequent to step **1** after a C-C bond fission which leads ultimately to hydroxamates.[74] In agreement with this, the radicals **40** were mainly detected with nonhindered oximes, whereas the radicals **42** were associated with sterically hindered oximes. Intermediate oximes gave mixtures of both types of radicals.[74] The origin of the radicals **41** is as yet obscure. Lown[72,73] has suggested a mechanism involving two separate reactions (Scheme IV) to account for the radicals **38** and **39**. However, part

SCHEME IV

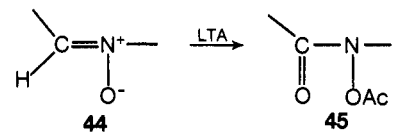


a of this mechanism seems unlikely. Radicals such as **39** could also arise from the nitrosoacetates behaving as spin traps[76-78] for free acetoxy radicals if such were present.

C. With General Azomethines

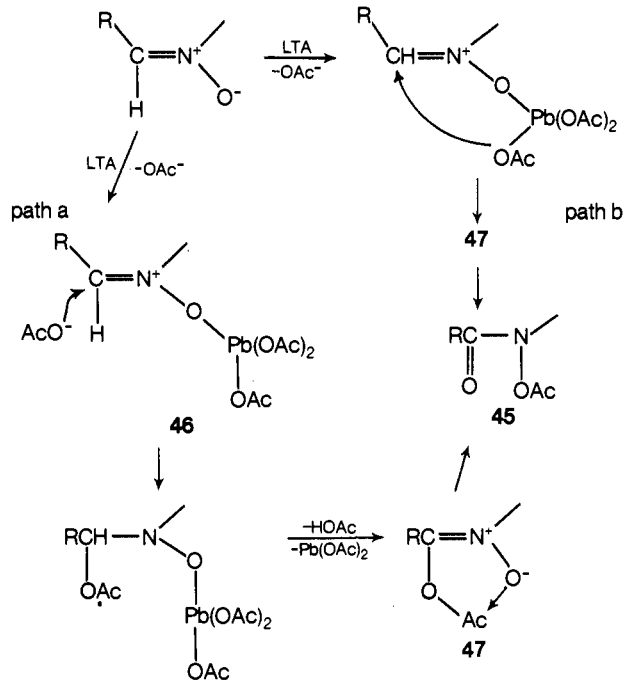
1. Azomethine N-Oxides (Nitrones)

In general, LTA oxidizes azomethine *N*-oxides (**44**) to *N*-acetoxy amides (**45**). No systematic mechanistic stud-



ies have been reported. Electron-donating substituents enhance the reaction with quinoline *N*-oxide.[79,80] A number of workers[79-81] have explained the reaction in terms of addition of acetate ion to the *N*-oxide–LTA adduct (**46**), giving the *O*-acetate **47** which yields the products by a 1,4-acetyl migration (path a, Scheme V). An alternative route to the intermediate **47** *via* an intramolecular acetoxy transfer in **46** (path b, Scheme V) has also been

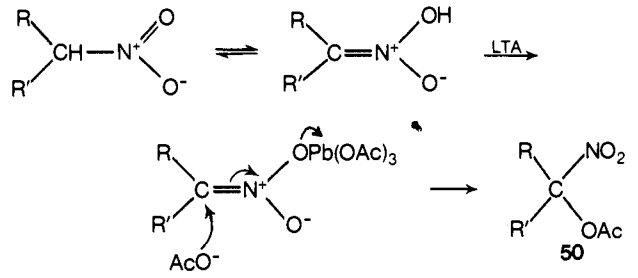
SCHEME V



suggested.[82] Esr signals from solutions of *N*-benzylidene-*tert*-butylamine *N*-oxide (**48**) and LTA in benzene have been interpreted in terms of a trapping of free acetoxyl radicals by the *N*-oxide.[77] However, addition of acetate ion to species **49** followed by homolysis would also ac-

(76) A. R. Forrester and S. P. Hepburn, *J. Chem. Soc. C*, 701 (1971).
(77) E. G. Jansen and B. Blackburn, *J. Amer. Chem. Soc.*, **91**, 4481 (1969).
(78) C. Lagercrantz, *J. Phys. Chem.*, **75**, 3466 (1971).
(79) A. Ohta and E. Ochai, *Chem. Pharm. Bull.*, **10**, 1260 (1962); *Chem. Abstr.*, **59**, 3888b (1963).
(80) A. Ohta, *Chem. Pharm. Bull.*, 11, 1586 (1963); *Chem. Abstr.*, **60**, 10646e (1964).
(81) N. J. A. Gutteridge and F. J. McGillan, *J. Chem. Soc. C*, 641 (1970).
(82) S. Tamagaki and S. Oae, *Bull. Chem. Soc. Jap.*, **43**, 1573 (1970).

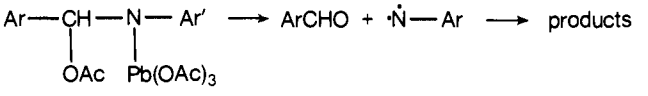
count for the data, and similar spectra were obtained from solutions of compound **48** in benzene–acetic acid containing LTA and in acetic acid containing potassium acetate.[76] A mechanism involving intermolecular acetate ion attack has also been suggested for the LTA oxidation of nitroalkanes to *gem*-acetoxy–nitro compounds[83] (**50**). A systematic mechanistic study of the reaction with azomethine *N*-oxide type systems seems desirable.



50

2. Schiff Bases

Schiff bases have received little attention and only recently the first mechanistic data for LTA oxidation of the HC=N– moiety of Schiff bases (benzylidene anilines) were reported.[84] The reaction was enhanced by electron-donating substituents and slowed by electron-withdrawing substituents in the benzylidene ring. The main products were the parent aromatic aldehyde, a substituted azobenzene, and small quantities of the parent amine. The suggested mechanism[84] involves an electrophilic attack by Pb(IV) on the nitrogen, followed presumably by acetate attack at the methine carbon to yield the intermediate **51** which fragments to the aldehyde and a nitrene.[84] Evidence for the nitrene included comparative oxidations of the corresponding aromatic amines where amino cation radicals[85] or amino radicals[86] are involved and the formation of quantities of bicumyl in cumene solution.



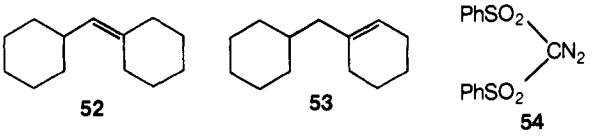
51

In the absence of further mechanistic data brief comments on mechanism will be made, where appropriate, in section III.

III. Synthetic Reactions

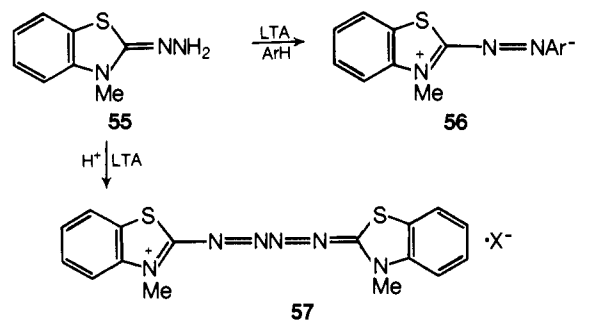
A. Unsubstituted Hydrazones

LTA oxidation of unsubstituted hydrazones containing electron-withdrawing groups at the methine carbon yields substituted diazoalkane products. A number of examples have been cited in section II.A. In general, the reaction with normal unsubstituted hydrazones is useful for replacing carbonyl groups by acetoxy groups or for introducing double bonds. Thus oxidation of 3β-hydroxylanostan-7-one hydrazone with LTA gave, after acetylation, 3β-acetoxylanost-7-ene and 3β,7α-diacetoxylanostane as the major product.[8,87] Oxidation of 3β-hydroxylanost-24-en-7-one hydrazone gave, as major product, 3β-hydroxy-7α-acetoxylanost-24-ene along with 3β-hydroxylanosta-7,24-diene.[8,87] Similarly, oxidation of 17β-acetoxy-5α-androstan-3-one hydrazone gave a 1:2 mixture of olefin and ester.[17a] Dicyclohexyl ketone hydrazone gave methyl dicyclohexyl acetate (43%), parent ketone (2%), and the olefins **52** and **53**.[8] Bis(phenylsulfonyl)diazomethane (**54**)



52 **53** **54**

was obtained by LTA oxidation of the corresponding hydrazone.[88] LTA oxidation of the hydrazone **55** in the presence of a coupling reagent yields dyes of type[89] **56**. In the absence of the coupling agent pentazadienes of type **57** are formed by an interesting reaction involving three molecules of the substrate.[90-93] In general, the azo coupling reaction occurs for the eneamine hydrazones, >N(C=C)$_n$C=NNH$_2$ (n = 0, 1, etc.). The reaction is comparable to the oxidative coupling of *p*-phenylenediamines for which LTA may also be used.[93] Oxidation of benzaldehyde hydrazone with a one molar quantity of LTA yielded mainly benzaldazine.[9] With two molar quantities of LTA, a mixture of the azine and benzaldehyde diacetate was obtained.[9] The nature and yields of the products depended on the conditions employed, particularly the quantity of LTA used and the presence of acid or base.[9] Other unsubstituted hydrazones which have been treated with LTA are in Table I. The purpose of this and the other tables is not to provide a catalog of all the compounds which have been oxidized with LTA but rather to provide a record of the general types of azomethines whose reactions with LTA have been reported.



55 **56** **57**

B. Monosubstituted Aldehyde Hydrazones

1. Acetoxylation

LTA oxidation of aldehyde hydrazones in acetic acid or dichloromethane yields *N*-acyl-*N'*-acetylhydrazines[32,94] (**58**). A range of the compounds **58**, where R is a substituted phenyl group and R' = *p*-NO$_2$Ph,[32,94] *p*-MePhSO$_2$,[94,95] and a number of heterocyclic ring systems, has been reported (Table I). Compounds **58**, which arise from a 1,4 acetyl migration in an unstable hydrazonyl acetate (**15**) (Scheme II), were originally considered to have this

(83) J. J. Riehl and Fr. Lamy, *Chem. Commun.*, 406 (1969).
(84) B. Rindone, E. Santaniello, and C. Scolastico, *Tetrahedron Lett.*, 19 (1972).
(85) F. A. Neugebauer and S. Bamberger, *Angew. Chem., Int. Ed. Engl.*, **10**, 71 (1971).
(86) K. H. Pausacker and J. G. Scroggie, *J. Chem. Soc.*, 4003 (1954).
(87) D. H. R. Barton, P. L. Batten, and J. F. McGhie, *Chem. Commun.*, 450 (1969).
(88) J. Kiekmann, *J. Org. Chem.*, **28**, 2933 (1963).
(89) S. Hunig and K. H. Fritsch, *Justus Liebigs Ann. Chem.*, **609**, 143, 172 (1957).
(90) S. Hunig and H. Quast, *Justus Liebigs Ann. Chem.*, 711, 139 (1968).
(91) S. Hunig, H. Balli, E. Breither, F. Bruhne, H. Geigher, E. Grigat, F. Mueller, and H. Quast, *Angew. Chem., Int. Ed. Engl.*, 1, 640 (1962).
(92) S. Hunig, H. Balli, and H. Quast, *Angew. Chem., Int. Ed. Engl.*, 1, 47 (1962).
(93) S. Hunig, *J. Chem. Educ.*, **46**, 734 (1969).
(94) F. L. Scott and R. N. Butler, *J. Chem. Soc. C*, 1202 (1966).
(95) A. Bhati, *J. Chem. Soc. C*, 1020 (1965).

TABLE I. Hydrazone Types Treated with LTA

A. Unsubstituted Hydrazones, $R'R''C{=}NNH_2$

R′	R″	Ref
CN	CN	13
CF_3, C_2F_5	CF_3, C_2F_5	11, 12
CN	COOMe	15
p-XPh	Ac	15
Ph	Ph	8, 9, 16
p-XPh	Me	9
Ph	H	9
o-XPh	H	9
Cyclohexyl	Cyclohexyl	8
CN	CF_3	14
$PhSO_2$	$PhSO_2$	88
3β-Hydroxylanostan-7-one hydrazone		8
17β-Acetoxy-5α-androstan-3-one hydrazone		17a
Cyclohexanone hydrazone		17b
N-Methylbenzothiazolone hydrazone (**55**)		89–93
N-Methylpyrid-4-one hydrazone		89–93

B. Monsubstituted Aldehyde Hydrazones, $R'CH{=}NNR''$ (Acetoxylation)[a]

R′	R″	Ref
p-XPh	1-Methyl-1*H*-tetrazol-5-yl	94
	p-NO_2Ph	32, 94
	p-SO_2PhMe	94, 95
	2-Methyl-2*H*-tetrazol-5-yl	100
	5-Phenyl-1,3,4-oxadiazol-2-yl	99
	Benzothiazol-2-yl	48
	3-Phenyl-1,2,4-triazol-5-yl	28, 29
PhCH=CH	*p*-NO_2Ph	32
	Me	25
Et	*p*-NO_2Ph	32
Ph	Ph	32, 35
2-Pyridyl	Ph	32

C. Monosubstituted Ketone Hydrazones, $R'R''C{=}NNHR'''$

R′	R″	R‴	Ref
Me	Me	*p*-XPh	24
Me	Me	$PhCH_2CHR$	24
Ph	Ph	Alkyl, aryl	24
p-NO_2Ph	*p*-NO_2Ph	*m*- and *p*-XPh	27
Ph	Ph	*p*-XPh	27, 44
PhCH=CH	Ph	Ph	42
Me	Me	*o*,*p*-$(NO_2)_2C_6H_3$	44
	$-(CH_2)_5-$	Alkyl, aryl	24, 44, 97
Ph	*m*- and *p*-XPh	Ph	133
Me	*m*- and *p*-MeOPh	*p*-XPh	132
Ph	CO_2Et	Ph	134
Ph	2-, 3-, 4-Pyridyl	*p*-NO_2Ph	134
Ph, Me	2-Thiophene	*p*-XPh	134

[a] For others, see Table II, Oxidative Cyclization.

C. Continued

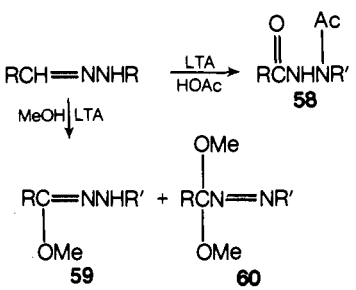
R′	R″	R‴	Ref
Ph	*m*-NO_2Ph	*p*-XPh	135
Me	Me	*o*-BrPh	136
PhCO	Ph	Ph	139
PhCHOH	Ph	*p*-NO_2Ph	139
Ph	Ph	CH_2Ph	139
Ph	Ph, Me	*p*-$MePhSO_2$–	139, 140
Me, Ph	2-Pyridyl	Ph	170
Me	2-Quinolinyl	Ph	170
Me	$-(CH_2)_nX$ (X = OH, COOH, CONHR)	Ph	179
Ac, –COOEt	N=NAr	H, alkyl, aryl	177, 178
Alkyl, aryl	N=NAr	H, alkyl, aryl	171–176
Isophorone monomethylhydrazone			25
3-Methyl-2-cyclopenten-1-one monomethylhydrazone			25
2-Cyclohexen-1-one monomethylhydrazone			25
Dehydroepiandrosterone acetate phenylhydrazone			141

D. 2-Pyrazolines (**93**), Cyclic Hydrazones

R	R′	R″	R‴	Ref
H	Ph, Me	H, alkyl	Me, Et, Ph	145a
H	H	Et	H	148
H	$-(CH_2)_3-$ (to 4-C atom)	Me	Me	146
H	Me	Ph	H	145b
p-XPh	Ph, Me	Ph	H	42
Ph	PhCH=CH	Ph	H	42
Ph	PhN=N	H	H	149
p-PhN=NPh	Me	H	H	149
p-XPh	Ph, Et	CN	H	31, 32

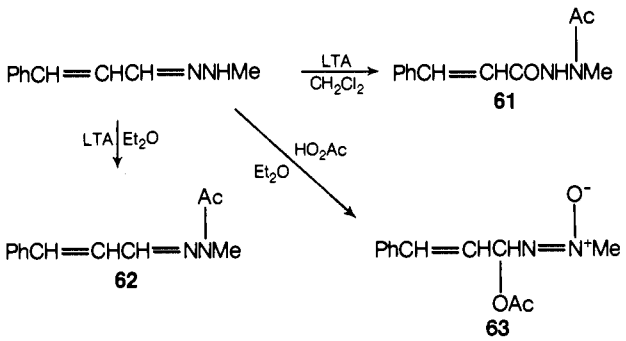
E. Ketone Carbonylhydrazones, $R'R''C{=}NNHCOR'''$

R′	R″	R‴	Ref
Me, Ph	Me, Ph	$N{=}CR_2$	180, 181
Me	Me	HNPhX(*p*)	182
p-XPh	*p*-XPh	HNPh	182
Ph	Ph	NEt_2	185
Ph	Ph	*p*-XPh	139, 193
	$-(CH_2)_5-$	Ph	191–193
Me	Ph	Ph	191–193
Alkyl	Alkyl	Alkyl	197
Aryl	Aryl	Aryl	197
Ph	Ph	OEt	196
Estrone-3-methyl ether monoacetylhydrazone			195
Androstan-17β-ol-3-one acetate monoacetylhydrazone			195
Acetone thiocarbohydrazone			181

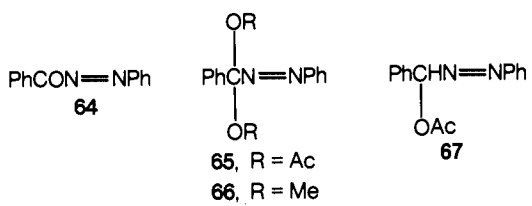


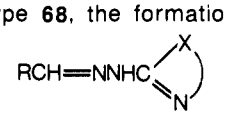
hydrazonyl acetate structure.[95,96] Cinnamaldehyde monomethylhydrazone yields the expected diacylhydrazine (**61**) on treatment with LTA in dichloromethane,[25] but with diethyl ether as solvent a direct acetylation of the hydrazone yields compound[25] **62**. The influence of solvent is further demonstrated by the formation of hydrazonyl methyl ethers (**59**) and azodimethyl ethers (**60**) in methanol,[32] the latter compounds arising from further ox-

(96) A. Bhati, R. A. W. Johnstone, and B. J. Millard, *J. Chem. Soc. C*, 358 (1966).



idation of the former. Diacylhydrazines of the general type **58** have also been obtained from the oxidation of monosubstituted aldehyde hydrazones with peracetic acid in dichloromethane[97] and benzoyl peroxide in benzene.[40] Benzaldehyde phenylhydrazone, when treated with LTA under nitrogen (to avoid autoxidation), yielded a mixture of benzoylazobenzene (**64**), the azodiacetate[32] **65**, and the azoacetate **67**. Oxidation with lead tetrabenzoate gave analogous products. With methanol as solvent high yields of the azodimethyl ether **66** were obtained.[32] Diacetates, dibenzoates, and diethers arise from secondary oxidations of the monoderivatives. They can also be obtained by treating diacylhydrazines of type **58** separately with LTA.[98a] The azoacetate **67** formed in the oxidation of benzaldehyde phenylhydrazone is exceptional since azoacetates are characteristic products from ketone hydrazones. However, the azoacetate *N*-oxide **63** has also been reported from the oxidation of cinnamaldehyde hydrazone with peracetic acid in diethyl ether.[25] A range of aliphatic azoacetates comparable to **67**, hitherto rare compounds, have recently been prepared by treating aliphatic alkoxydiazenium salts with hydroxide ion followed by acetylation.[98b] With heterocyclic hydrazones of general type **68**, the formation of the products





58 may compete with an oxidative cyclization[4] (see below). Generally, when X is an oxygen[99] or sulfur[48] atom, acetoxylation is the dominant process. When X is a nitrogen atom, both processes compete and the balance of the competition depends on the nature of the heterocyclic ring. Thus, for example, with a 1-substituted tetrazole ring[94] the ratio of acetoxylation to cyclization was ca. 2:1, whereas with a 2-substituted tetrazole ring acetoxylation dominated,[100] and with a 1,2,4-triazole ring[28,29] the cyclization was almost completely dominant. The diacylhydrazines (**58**) are less versatile than the azoacetates as intermediates in synthesis. An easy deacetylation in some cases affords a relatively simple method of converting the parent hydrazone to its hydrazide.[101]

(97) B. T. Gillis and K. F. Schimmel, *J. Org. Chem.*, **32**, 2865 (1967).

(98) (a) W. A. F. Gladstone, *J. Chem. Soc. C*, 1571 (1969); (b) G. Buttner and S. Hunig, *Chem. Ber.*, **104**, 1088, 1104 (1971).

(99) R. N. Butler, T. M. Lambe, and F. L. Scott, *J. Chem. Soc. C*, 269 (1972).

(100) R. N. Butler and F. L. Scott, *J. Chem. Soc. C*, 1711 (1968).

(101) R. N. Butler and F. L. Scott, *J. Chem. Soc. C*, 1319 (1966).

2. Oxidative Cyclization. Heterocyclic Systems

Aldehyde hydrazones with a potential cyclization site are readily dehydrogenated and cyclized by LTA. This reaction has been widely used in heterocyclic synthesis.[102-117] Table II, which summarizes the variety of heterocyclic systems which have been prepared by this method, illustrates its generality. The reaction always leads primarily to fused triazolo heterocycles, and cyclizations, which would lead to mesoionic compounds, for example, at S or O in no. **14** and **15** (Table II), are not observed. Fused heterocycles with bridgehead unsaturation, which could arise by cyclization at a site deeper in the heterocyclic substituent, are also not observed. In general, when alternative sites are available, cyclization occurs at the most nucleophilic nitrogen, for example, reaction no. 2, 5c, 7, **11**, 19b (Table II). However, an exception is noted in reaction no. 19a (Table II) where cyclization occurs away from the nitrogen atom nearest the electron-donating methyl group. Steric repulsion by the methyl group has been invoked to explain this[116] as well as the cyclization pattern in no. 19b (Table II). The difference in the nucleophilic character of the **1** and **4** positions of the triazole ring in reaction no. **11** (Table II) is probably quite small. Cyclization occurs exclusively at the **1** position, however.[28,29,111,112] In some cases, for example, reactions 2 and 6 (Table II), isomerization of the primary cyclization products may occur under the reaction conditions.[103,107,108] These isomerizations, which may arise from the action of acid, base, or heat on the products, are common with such heterocyclic systems.[107,116,118-125] Oxidative cyclizations of the type indicated in Table II are also effected with halogens[126] and some other oxidizing agents. With halogens, halogenation of aromatic rings may compete with the cyclization process, thereby creat-

(102) M. Jelenc, J. Kobe, B. Stanovnik, and M. Tisler, *Monatsh. Chem.*, 97, 1713 (1966).

(103) J. Daunis, R. Jacquier, and P. Viallefont, *Bull. Soc. Chim. Fr.*, 2492 (1969).

(104) A. Pollak and M. Tisler, *Tetrahedron*, **22**, 2073 (1966).

(105) J. D. Bower and F. P. Doyle, *J. Chem. Soc.*, 727 (1957).

(106) K. Shirakawa, *J. Pharm. Soc. Jap.*, **80**, 956 (1960).

(107) R. G. W. Spickett and S. H. B. Wright, *J. Chem. Soc. C*, 498 (1967); British Patent 1,070,243 (1967); *Chem. Abstr.*, 67, 100157h (1967).

(108) A. H. Beckett, R. G. W. Spickett, and S. H. B. Wright, *Tetrahedron*, **24**, 2839 (1968).

(109) C. F. Allen, G. A. Reynolds, J. F. Tinker, and L. A. Williams, *J. Org. Chem.*, **25**, 361 (1960).

(110) B. Stanovnik and M. Tisler, *Tetrahedron*, **23**, 387 (1967).

(111) H. Gehlen and F. Lemme, *Justus Liebigs Ann. Chem.*, **703**, 116 (1967).

(112) H. Gehlen and G. Robisch, *Justus Liebigs Ann. Chem.*, **660**, 148 (1962).

(113) H. Berger, K. Stach, and W. Voemel (C. F. Boehringer and G.m.b.H. Soehne), South African Patent 6706255 (1968); *Chem. Abstr.*, **70**, 57869q (1969).

(114) C. F. Boehringer and G.m.b.H. Soehne, British Patent 1130909 (1968); *Chem. Abstr.*, **70**, 28926a (1969).

(115) A. Pollak, B. Stanovnik, and M. Tisler, *J. Heterocycl. Chem.*, **5**, 513 (1968).

(116) J. Kobe, B. Stanovnik, and M. Tisler, *Tetrahedron*, **26**, 3359 (1970).

(117) B. Stanovnik, M. Tisler, M. Ceglar, and V. Bah, *J. Org. Chem.*, **35**, 1138 (1970).

(118) J. A. Bee and F. L. Rose, *J. Chem. Soc. C*, 2031 (1966).

(119) S. E. Mallet and F. L. Rose, *J. Chem. Soc. C*, 2038 (1966).

(120) A. Kreutzberger, *Chem. Ber.*, **99**, 2237 (1966).

(121) L. A. Williams, *J. Chem. Soc.*, 1829 (1960).

(122) G. W. Miller and F. L. Rose, *J. Chem. Soc. C*, 3357 (1965).

(123) G. W. Miller and F. L. Rose, *J. Chem. Soc. C*, 5642 (1963).

(124) C. F. H. Allen, H. R. Beilfuss, D. M. Burness, G. A. Reynolds, J. F. Tinker, and J. A. Van Allen, *J. Org. Chem.*, **24**, 787 (1959).

(125) C. Temple, C. L. Kussner, and J. A. Montgomery, *J. Org. Chem.*, **30**, 3601 (1965).

(126) R. N. Butler and F. L. Scott, *Chem. Ind. (London)*, 1216 (1970).

TABLE II. Types of Monosubstituted Aldehyde Hydrazones Cyclized with LTA

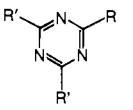
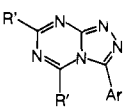
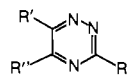
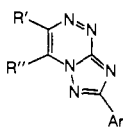
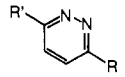
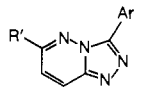
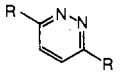
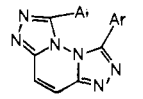
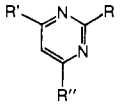
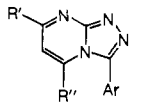
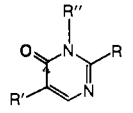
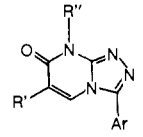
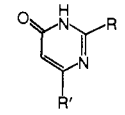
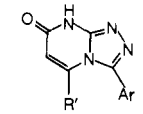
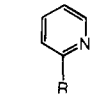
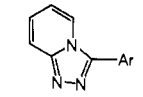
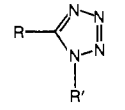
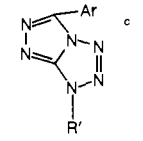
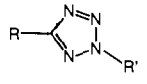
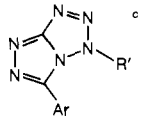
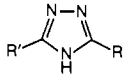
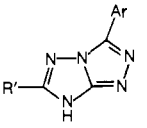
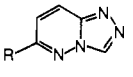
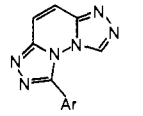
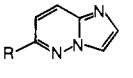
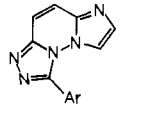
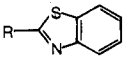
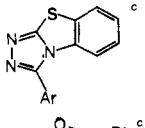
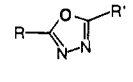
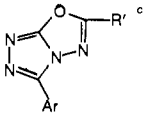
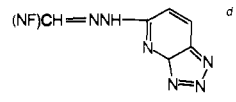
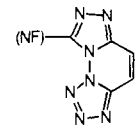
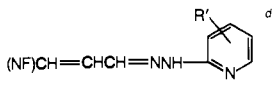
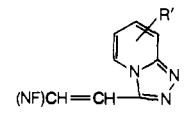
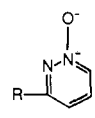
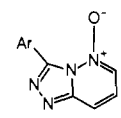
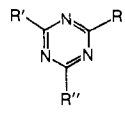
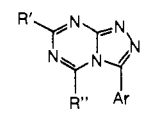
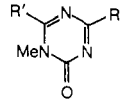
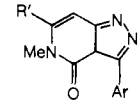
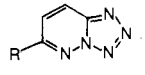
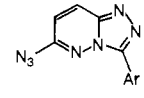
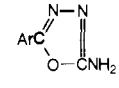
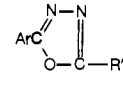
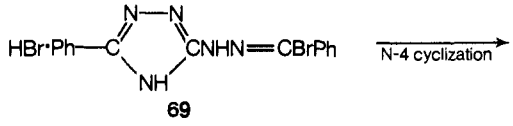
Reaction no.	Hydrazone[a] (R = -NHN=CHC$_6$H$_4$X)	R′	R″	Product[b]	Ref
1		Morpholine	...		102
2		Me	OH		103
3		Cl	...		104
4		...	...		104
5		(a) Me (b) H (c) Me	Me H OH		105 106 105
6		COOEt	$PhCH_2$		107, 108
7		Me	...		109
8		...	...		105
9		Me	...	 [c]	94
10		Me	...	 [c]	100
11		Ph	...		28, 29, 111, 112
12		...	...		104
13		...	...		110
14		...	...	 [c]	48
15		Ph	...	 [c]	99

TABLE II *(Continued)*

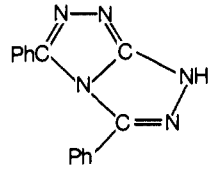
Reaction no.	Hydrazone[a] (R = -NHN=CHC$_6$H$_4$X)	R′	R″	Product[b]	Ref
16		...	...		113
17		...	...		114
18		...	...		115
19		(a) Me (b) Me	H MeO		116
20		Me	...		116
21		...	...		117
22		...	...		51
23		Ph, NPh$_2$	...		32

[a] R = -NHN=CHC$_6$H$_4$X. [b] Ar = C$_6$H$_4$X. [c] Minor product, acetoxylation being the major reaction. For the other reactions acetoxylation has not been reported though it is probably present since yields of cyclized product are often not greater than 80%. [d] (NF) = 5-nitrofur-2-yl.

ing a limitation. In some cases it is also necessary to isolate hydrazonyl halide intermediates.[126] However, these intermediates can prove useful in cases where acetoxylation blocks the LTA cyclization reaction since their reactions are more easily controlled than those of the LTA–hydrazone systems where the process is, for practical purposes, a one-step reaction.[48,99,127] Thus, for example, in reactions 9, 10, 14, and 15 (Table II), the major pathway is acetoxylation, and only low yields of the cyclized products are obtained with LTA. With bromine as reagent the cyclized products are readily obtained *via* hydrazonyl bromides.[126,127] In some cases oxidative cyclization with bromine and LTA may yield different products. Thus, for example, if bromine is used in reaction **11** (Table II), a hydrazonyl bromide hydrobromide (**69**) is formed, and cyclization occurs at the triazole 4-N site.[128]



69



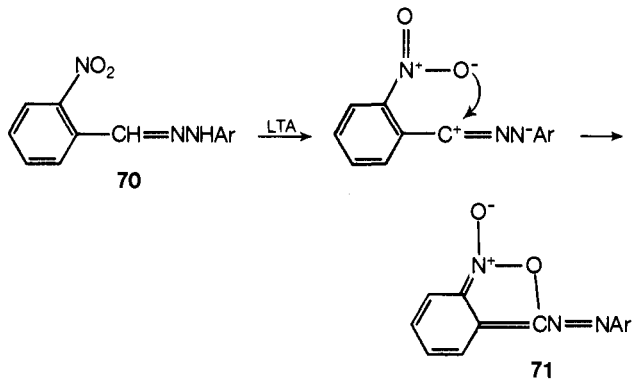
Cyclization of aldehyde carbonylhydrazones and semicarbazones to oxadiazoles is also readily effected with LTA, reactions 22 and 23 (Table II). Oxidative cyclization of *o*-nitrobenzaldehyde hydrazones (**70**) to 3-arylazoanthranil **1**-oxides (**71**)[128a] has also been achieved.[32] Another important route to a wide range of heterocyclic systems *via* LTA oxidation of aldehyde hydrazones is provided by the 1,3-dipolar cycloaddition reactions of the nitrilimine intermediates involved.[32-35] The chemistry of the 1,3-cycloaddition reactions of nitrilimines, which has been thor-

(127) R. N. Butler, P. O'Sullivan, and F. L. Scott, *J. Chem. Soc. C*, 1519 (1972).

(128) A. F. O'Mahony, Ph.D. Thesis, National University, Ireland, 1970.

(128a) Note Added in Proof. Recently the previously accepted structure of compound 71 has been questioned and an alternative six-membered azimine ring structure proposed; *cf.* R. C. Kerber, *J. Org. Chem.*, 37, 1587 (1972).

oughly reviewed,[129-131] is outside the scope of this present article. It suffices to point out that the LTA–hydrazone reaction provides an entrance to this wide area of synthesis.[129-131]

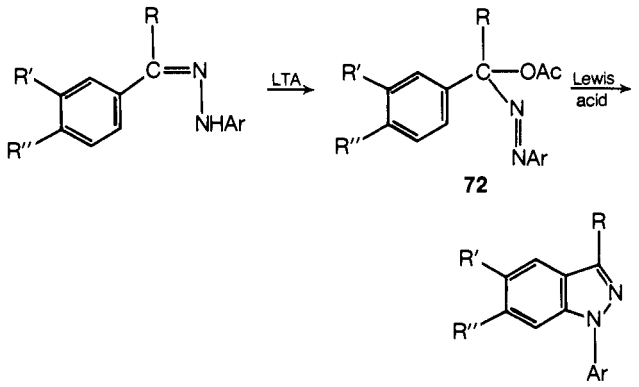


70 71

C. Monosubstituted Ketone Hydrazones

1. Acetoxylation and Reactions of Azoacetates

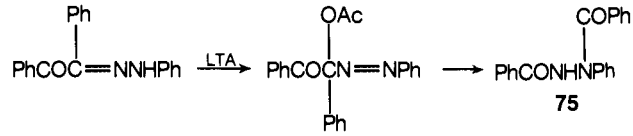
In general, LTA oxidation of ketone hydrazones yields azoacetates,[24] e.g., **72**. A wide range of such materials has been prepared[24] (Table I.C). The azoacetates are useful intermediates for further synthesis. On treatment with Lewis acids, azoacetates of aromatic ketone arylhydrazones are cyclized to 3-alkyl-1-arylindazoles[132] (**73**)



72

73, R = alkyl
74, R = aryl

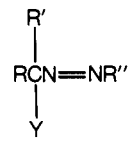
and 1,3-diarylindazoles[133] (**74**). This process has been developed to provide new routes to 1-phenylindazoles, pyridylindazoles, and thieno[3,2-c]pyrazoles.[134] When treated with base such azoacetates may yield the parent ketone, the parent arylhydrazone, or an indazole.[135] Cyclization to the indazole is limited, however, to systems where the arylazo moiety contains electron-withdrawing substituents.[135] When treated with alcoholic sodium ethoxide, azoacetates of ketone arylhydrazones fragmented yielding substituted benzenes and benzyne intermediates which reacted with the solvent.[136-138] Treatment of the azoacetates with sulfuric acid also yielded substituted benzenes along with ketonic products.[136-138] The behavior of azoacetates derived from benzil and benzoin arylhydrazones on treatment with Lewis acids depended on the nature of the aryl moiety.[139] For example, the azoacetate of benzil monophenylhydrazone yielded *N,N'*-dibenzoylphenylhydrazine (**75**) while that of the



75

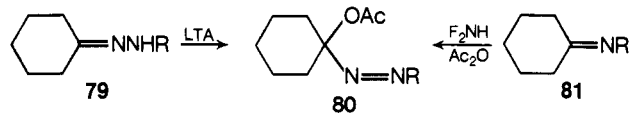
mono-*p*-nitrophenylhydrazone yielded *N*-acetyl-*N'*-benzoyl-*p*-nitrophenylhydrazine (**58**, R = Ph; R' = *p*-NO_2Ph), a compound more characteristic of the oxidation of aldehyde hydrazones.[139] Treatment of benzophenone benzylhydrazone with LTA caused evolution of nitrogen yielding 1,1,2-triphenylethyl acetate from decomposition of the intermediate azoacetate.[139] Evolution of nitrogen also occurred when ketone toluene-*p*-sulfonylhydrazones were treated with LTA. The parent ketone was regenerated with acetic acid as solvent,[140] and ketone dimethyl ketals were formed in a solvent mixture of methanol and dichloromethane.[139]

When alcoholic solvents are used for the LTA oxidation, mixtures of azoacetates **76** and azo ethers **77** are obtained.[27,141] With lead(IV) diacetate difluoride as oxidizing agent mixtures of azoacetates **76** and azofluorides **78** are formed.[44] Generally, the azoacetates are the preferred products, and compounds of type **77** and **78** are formed in low yields.



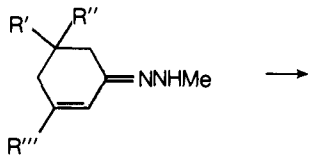
76, Y = OAc
77, Y = OR
78, Y = F

Despite the decomposition encountered with benzophenone benzylhydrazone,[139] azoacetates have been obtained from LTA oxidations of other aliphatic and alicyclic ketone hydrazones.[24,25,97] Cyclohexanone alkylhydrazones (**79**) yielded the azoacetates[24,97] **80**. Such azoacetates have also been obtained by treating cyclohexanone imines (**81**) with difluoramine in acetic anhydride.[142] While isophorone monomethylhydrazone (**82**) yielded an 8:1 mixture of the azoacetates **83** and **84** on treatment with LTA in dichloromethane, or with peracetic acid in diethyl ether,[25] the hydrazone **85** yielded only the C-1 acetoxylated product[25] **86**. Mixtures of 1- and 3-acetoxylated products were also obtained from the α,β-unsaturated system, 3-methyl-2-cyclopenten-1-one monomethylhydrazone.[25] The erratic nature of the reaction of LTA with α,β-unsaturated hydrazone systems is further exemplified by chalcone phenylhydrazone[42] (**87**)

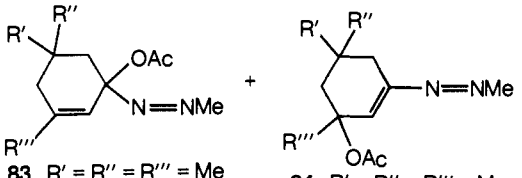


79 80 81

(129) R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, **2**, 565, 633 (1963).
(130) R. A. Firestone, *J. Org. Chem.*, **33**, 2285 (1968).
(131) R. Huisgen, *J. Org. Chem.*, **33**, 2291 (1968).
(132) W. A. F. Gladstone and R. O. C. Norman, *J. Chem. Soc.*, 5177 (1965).
(133) W. A. F. Gladstone and R. O. C. Norman, *J. Chem. Soc.*, 3048 (1965).
(134) W. A. F. Gladstone and R. O. C. Norman, *J. Chem. Soc. C*, 1527 (1966).
(135) W. A. F. Gladstone, M. J. Harrison, and R. O. C. Norman, *J. Chem. Soc. C*, 1781 (1966).
(136) R. W. Hoffmann, *Chem. Ber.*, **97**, 2763 (1964).
(137) R. W. Hoffmann, *Chem. Ber.*, **98**, 222 (1965).
(138) R. W. Hoffmann and G. Guhn, *Chem. Ber.*, **100**, 1474 (1967).
(139) W. A. F. Gladstone and R. O. C. Norman, *J. Chem. Soc. C*, 1531 (1966).
(140) A. Bhati, *Chem. Commun.*, 476 (1965).
(141) J. Buckingham and R. D. Guthrie, *J. Chem. Soc. C*, 1445 (1968).
(142) W. H. Graham, *J. Amer. Chem. Soc.*, 88, 4677 (1966).



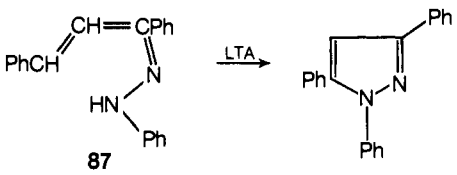
82, R′ = R″ = R‴ = Me
85, R′ = R″ = R‴ = H



83, R′ = R″ = R‴ = Me
86, R′ = R″ = R‴ = H

84, R′ = R″ = R‴ = Me

which underwent a direct oxidative cyclization to 1,3,5-triphenylpyrazole as against the possible formation of mixtures of azoacetates. A similar cyclization of chalcone phenylhydrazone occurs on oxidation with manganese



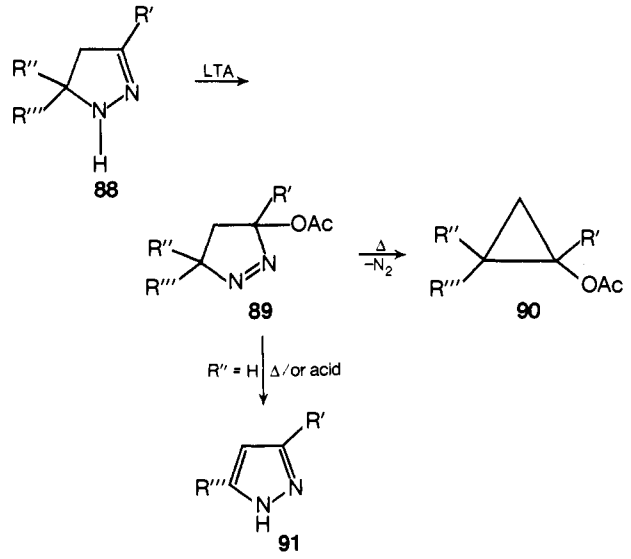
87

dioxide.[143] The formation of 3-acetoxylated products, e.g., **84**, with α,β-unsaturated hydrazones may involve an intermolecular acetate ion attack on an aza-allylic cation. Such a species may readily arise in the ionic mechanism by loss of HOAc and $Pb(OAc)_2$ from the cation **12** in Scheme II. A free radical mechanism has also been suggested.[25]

Osazones and monosubstituted hydrazones of α-diketones undergo oxidative dehydrogenation when treated with a range of oxidizing agents which include LTA, though this reagent has received little attention for such work.[144a] The products are generally 1,2-bisazoethylenes[144b] or substituted 1,2,3-triazoles depending on the nature of the hydrazone N substituent. A recent assessment of earlier structural assignments for the products has shown that with α-diketobisacylhydrazones *O*-acylimidic acid derivatives of 1-amino-1,2,3-triazoles are formed rather than bisazoethylenes.[144c]

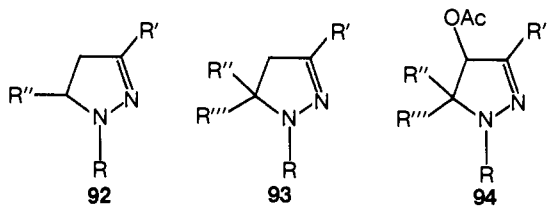
2. 2-Pyrazolines and Cyclic Hydrazone Systems

LTA oxidation of substituted 1-*H*-2-pyrazolines (**88**) leads to the 3-acetoxy-2-pyrazolines (**89**), the cyclic analogs of the azoacetates.[145] Pyrolysis of compounds **89** yields the cyclopropanes[145,146] **90**, this reaction being favored when neither of the substituents at the 5 position is a H atom. When one of these substituents is a H atom, pyrazole (**91**) formation by elimination of acetic acid is favored.[145b,147,148] 1,3,5-Trisubstituted-2-pyrazolines (**92**) are readily aromatized to the corresponding pyra-



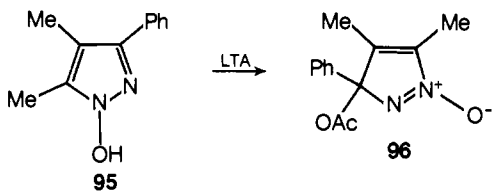
88 **89** **90** **91**

zoles by LTA under mild conditions.[41,42,149] With 1,3-monosubstituted 5-disubstituted 2-pyrazolines (**93**) aromatization cannot occur and the 4-acetoxy derivative **94** is formed.[41,42] When a Lewis acid was added to the product mixture containing compound **94** (R′ = R″ =



92 **93** **94**

R‴ = Me; R = Ph), a pinacol-type of rearrangement occurred yielding 3,4,5-trimethyl-1-phenylpyrazole.[42] Different mechanisms involving initial Pb(IV) attack at either the 3-C atom[41] or the 1-N atom[42] of the pyrazoline ring have been proposed for these oxidations. Oxidation of pyrazolines to pyrazoles has been attempted with other oxidizing agents,[150-157] with varying degrees of success. For pyrazolines lacking functional groups susceptible to LTA attack at low temperatures, the LTA method promises to be more suitable than others because of the solubility of the reagent in organic solvents and the mild conditions of the reaction. Pyrazoline types, which have been oxidized with LTA, are summarized in Table I.D. Recent-

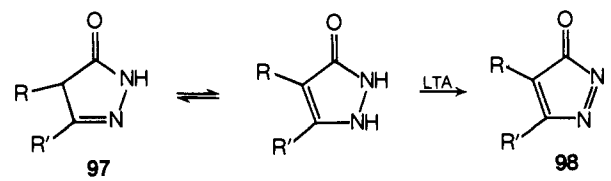


95 **96**

(143) I. Bhatnagar and M. V. George, *Tetrahedron*, **24**, 1293 (1968).
(144) (a) H. El Khadem, *Advan. Carbohyd. Chem.*, **20**, 139 (1965); (b) J. G. Erickson, P. F. Wiley, and V. P. Wystrach, "The Chemistry of Heterocyclic Compounds," Vol. 10, Interscience, New York, N. Y., 1956, Chapter III; (c) H. Bauer, A. J. Boulton, W. Fedeli, A. R. Katritzky, A. Majid-Hamid, F. Mazza, and A. Vaciago, *J. Chem. Soc., Perkin Trans. 2*, 662 (1972).
(145) (a) J. P. Freeman, *J. Org. Chem.*, **28**, 885 (1963); (b) *ibid.*, **29**, 1379 (1964).
(146) B. R. Davis and P. D. Woodgate, *J. Chem. Soc. C*, 2006 (1966).
(147) J. P. Freeman and J. H. Plonka, *J. Amer. Chem. Soc.*, **88**, 3662 (1966).
(148) R. Kuhn and H. Henkel, *Justus Liebigs Ann. Chem.*, **549**, 279 (1941).
(149) G. F. Duffin and J. D. Kendall, *J. Chem. Soc.*, 408 (1954).
(150) K. Von Auwers and P. Heimke, *Justus Liebigs Ann. Chem.*, **458**, 186 (1927).
(151) I. Bhatnagar and M. V. George, *Tetrahedron*, **24**, 1293 (1968).
(152) L. I. Smith and K. L. Howard, *J. Amer. Chem. Soc.*, **65**, 159 (1943).
(153) F. Strauss, C. Muffat, and W. Heitz, *Ber.*, **51**, 1457 (1918).
(154) R. P. Dodwadmath and T. S. Wheeler, *Proc. Indian Acad. Sci., Sect. A*, **2**, 438 (1935).
(155) P. Bouchet, J. Elguero, and R. Jacquier, *Tetrahedron Lett.*, 3317 (1964).
(156) J. Elguero and R. Jacquier, *Bull. Soc. Chim. Fr.*, 610 (1966); 769 (1965).
(157) J. Elguero, R. Jacquier, G. Tarrago, and H. C. N. Tien Duc, *Bull. Soc. Chim. Fr.*, 293 (1966).

ly, it has been reported[158] that the hydroxypyrazole **95** is oxidized by LTA to 3-acetoxy-3-phenyl - 4,5-dimethylpyrazolenine 1-oxide (**96**), but the nature of the reaction is obscure.

LTA oxidation of substituted 2-pyrazolin-5-ones (**97**), cyclic analogs of ketone carbonylhydrazones, yields azodienophiles **98** as intermediates which furnish Diels–Alder adducts when the oxidation is carried out in the presence of dienes.[159-161] Recently, 1-pyrazolin-3-one, the 4,5-dihydro derivative of **98** (R = R′ = H), has been isolated as a crystalline solid at low temperatures from the LTA oxidation of the corresponding pyrazolidin-3-one.[162] Generally, however, azadienophiles of type **98** are unstable intermediates which are generated *in situ*.

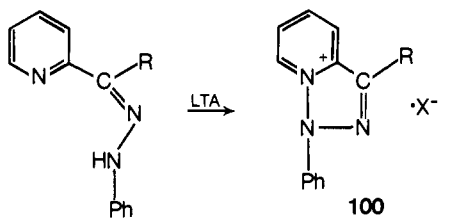


97 **98**

Such intermediates have been prepared by the reaction of LTA with 4-phenylurazole,[163] 1,2-dihydro-3,6-pyridazinedione,[164] 3-indazolinone,[165] 4,4-dialkylpyrazolidin-3,5-diones,[166] phthalhydrazide,[167,168] 5-substituted-*s*-triazolin-3-ones,[169a] and substituted oxadiazinones.[169b]

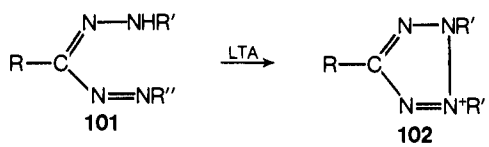
3. Oxidative Cyclization. Carbonylhydrazones and Semicarbazones

Phenylhydrazone derivatives of 2-acylpyridines (**99**) are cyclized to 8-azaindazolium salts (**100**) on treatment



99 (*syn*) **100**

with LTA.[134,170] The reaction, which is reversed on reduction of the cyclic product, works only for syn isomers.[170] With aldehyde derivatives **99** (R = H) cyclization is not observed[32,170] possibly because the anti form is preferred. A somewhat analogous reaction is the oxi-

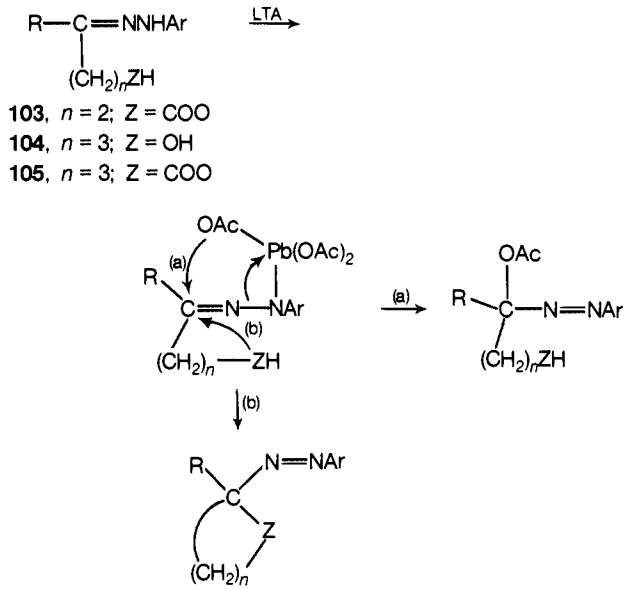


101 **102**

dative cyclization of formazans (**101**) to tetrazolium salts (**102**) for which LTA has proved a useful reagent.[171-178] When R in **101** is an acyl or carbethoxy group, it is replaced by H during the oxidation.[177,178]

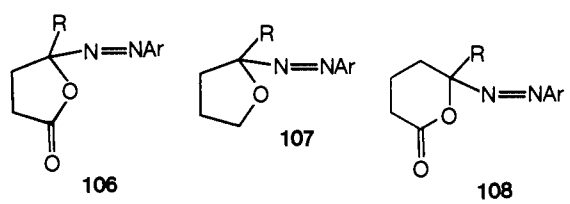
Oxidative cyclization and azoacetate formation are competitive processes in the LTA oxidation of ketone hydrazones containing a suitable cyclization site in the ketone substituents at the fourth or fifth atom from the methine carbon (Scheme VI).[179] In general, the cycliza-

SCHEME VI



103, *n* = 2; Z = COO
104, *n* = 3; Z = OH
105, *n* = 3; Z = COO

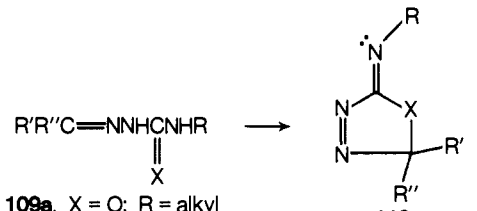
tion is the major reaction and only low yields of the azoacetates are formed.[179] Thus the hydrazones **103**, **104**, and **105** yielded the cyclized products **106**, **107**, and **108**, respectively. When the moiety Z was an olefin



106 **107** **108**

(CH=CH), cyclization did not occur, suggesting that a nucleophilic attack by Z (Scheme VI) rather than a carbonium attack on Z is involved.[179] LTA oxidation of substituted ketone semicarbazones or thiosemicarbazones of type **109** results in cyclization at the O or S atom yielding 2-imino-Δ^2-1,3,4-oxa- and -thiadiazolines (**110**). These are thought to have the anti (azo) configuration.[180-182] With the unsymmetrical carbohydrazones **109b** and **109c** cyclization occurs preferentially to the methine carbon

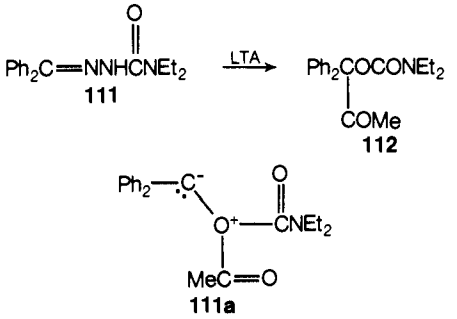
(158) J. P. Freeman and J. J. Gannon, *J. Org. Chem.*, **34**, 194 (1969).
(159) B. T. Gillis and R. Weinkam, *J. Org. Chem.*, **32**, 3321 (1967).
(160) C. W. Rees and M. Yelland, *Chem. Commun.*, 377 (1969).
(161) B. T. Gillis and J. C. Valentour, *J. Heterocycl. Chem.*, **7**, 1131 (1970).
(162) W. Nagata and S. Kamata, *J. Chem. Soc. C*, 540 (1970).
(163) B. T. Gillis and J. D. Hagarty, *J. Org. Chem.*, **32**, 330 (1967).
(164) R. A. Clement, *J. Org. Chem.*, **27**, 1115 (1962).
(165) E. F. Ullman and E. A. Bartkus, *Chem. Ind. (London)*, 93 (1962).
(166) H. Stetter and P. Woernle, *Justus Liebigs Ann. Chem.*, **724**, 150 (1969).
(167) R. A. Clement, *J. Org. Chem.*, **25**, 1724 (1960).
(168) O. L. Chapman and S. J. Dominianni, *J. Org. Chem.*, **31**, 3862 (1966).
(169) (a) B. T. Gillis and J. G. Dain, *J. Org. Chem.*, **36**, 518 (1971); (b) M. Rosenblum, A. Longroy, M. Neuveu, and C. Steel, *J. Amer. Chem. Soc.*, **87**, 5716 (1965).
(170) R. Kuhn and W. Munzing, *Chem. Ber.*, **85**, 29 (1952).
(171) R. Kuhn and D. Jerchel, *Chem. Ber.*, **74B**, 941 (1941).
(172) F. L. Scott, D. A. O'Sullivan, and J. Reilly, *J. Amer. Chem. Soc.*, **75**, 5309 (1953).
(173) J. N. Ashley, B. M. Davis, A. W. Nineham, and R. Slack, *J. Chem. Soc.*, 3881 (1953).
(174) D. Jerchel and F. Fischer, *Justus Liebigs Ann. Chem.*, **563**, 200, 208 (1949).
(175) D. Jerchel, *Chem. Ber.*, **75B**, 75 (1942).
(176) Yu. A. Sedov and I. Ya. Postovskii, *Zh. Org. Khim.*, **5**, 781 (1969); *Chem. Abstr.*, 71, 22074v (1969).
(177) B. Hirsch, *Justus Liebigs Ann. Chem.*, **648**, 151 (1961).
(178) B. Hirsch, *Justus Liebigs Ann. Chem.*, **637**, 189 (1960).
(179) G. G. Gubelt and J. Warkin, *Can. J. Chem.*, **47**, 3983 (1969).
(180) J. Warkentin and P. R. West, *Tetrahedron Lett.*, 5815 (1966).
(181) P. R. West and J. Warkentin, *J. Org. Chem.*, **33**, 2089 (1968).
(182) A. M. Cameron, P. R. West, and J. Warkentin, *J. Org. Chem.*, **34**, 3230 (1969).



109a, X = O; R = alkyl
b, X = O; R = N=CR$_2$
c, X = S; R = N=CR$_2$

110

bearing aliphatic rather than aromatic substituents. An intramolecular displacement mechanism similar to that in Scheme VI has been inferred.[7] Thermolysis[183] and hydrolysis reactions[184] of the products **110** have been reported, the latter providing a useful route to the corresponding oxadiazolin-2-ones. The 4,4-disubstituted semicarbazone **111** was not cyclized by LTA.[185] With this compound an *in situ* loss of nitrogen occurred yielding the carbamate[185] **112**. This interesting reaction is consid-

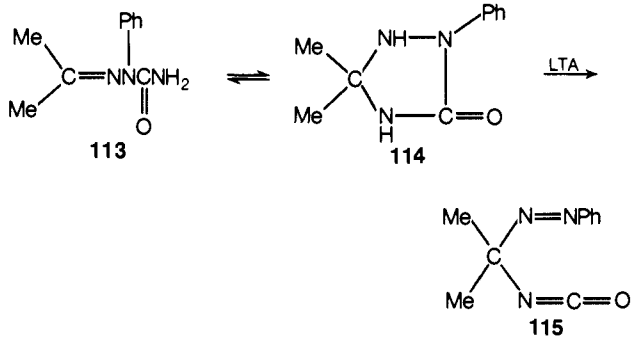


111

112

111a

ered to involve a 1,2-shift in the zwitterion **111a**, itself formed by elimination of nitrogen from an intermediate azoacetate.[185] LTA oxidation[186,187] of the 2-substituted semicarbazone **113** yielded the isocyanate **115**. This may arise from the cyclic form **114** of the semicarbazone,[188]



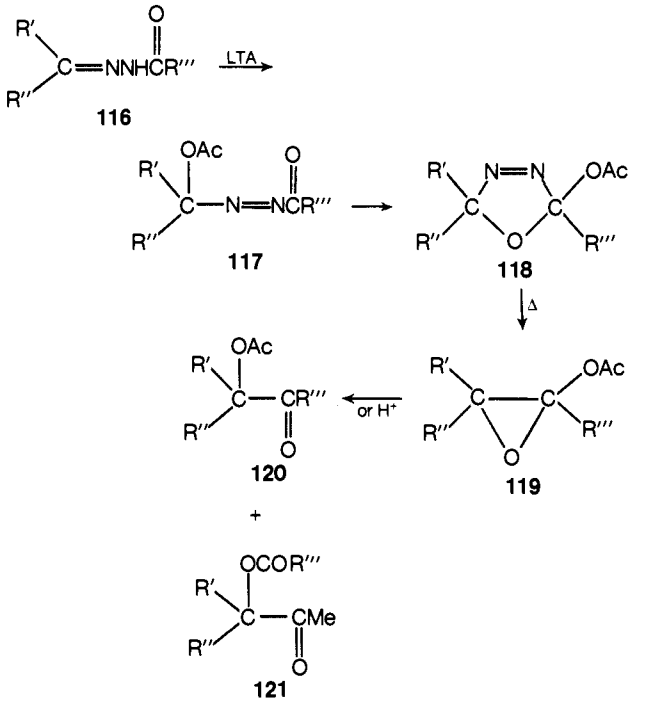
113

114

115

or possibly from a direct nucleophilic attack at a Pb(IV) activated methine. Similar products are obtained with iodine[189] or chromyl acetate[187] as oxidizing agent. The isocyanates **115** are cyclized to 1,2,4-triazolones on heating.[190]

Ketone carbonylhydrazones of type **116**, where the substituent R''' is not bonded by an N atom to the carbonyl group, yield azoacetates **117** on treatment with LTA.[191-197] Azoacetates **117** are highly reactive, the most stable types being those with alkyl substituents.[191,195,197] Azoacetates **117** with aromatic substituents may be isolated at low temperatures[191-193] (−40 to −70°). On heating to ca. −20° cyclization to Δ^3-1,3,4-oxadiazolines occurs.[191-193] Between ca. room temperature and 50° nitrogen evolution occurs yielding epoxide[139,191-193] **119**. Further heating or treatment with acid yields α-ketoacetates **120** and the esters[191-197] **121**. Hoffmann and



116

117

118

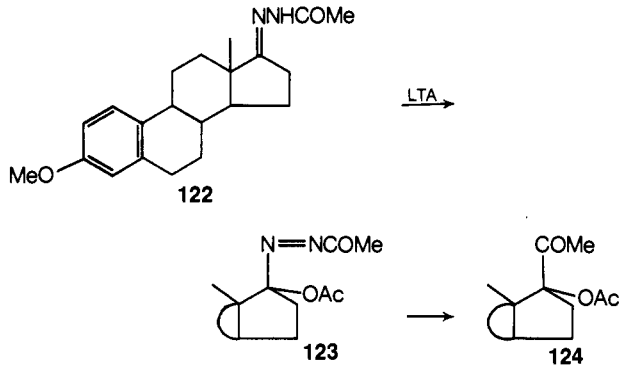
120

119

121

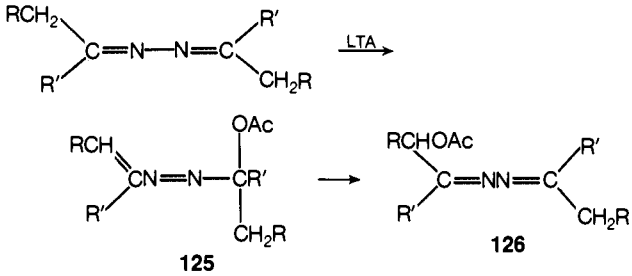
Luthardt[191-193] suggested an ionic mechanism for the formation of the compounds **118** involving fission of acetate ion from the azoacetate **117** followed by attack on the resulting carbonium ion by the carbonyl oxygen with subsequent attack by acetate ion at the carbonyl carbon. This contrasts with the intramolecular mechanism inferred for the cyclization of semicarbazone-type systems,[7] although it is not clear whether the cyclization occurs prior to or subsequent to azoacetate formation with these latter compounds. LTA oxidation of the carbethoxyhydrazones **116** (R' = R'' = Ph; R''' = OEt) yielded a complex mixture of products which included benzophenone, the expected azoacetate (28%), and acetyldiphenylmethyl ethyl carbonate.[196] The *N*-acetylhydrazone of estrone-3-methyl ether (**122**) yielded a stable azoacetate (**123**) which, when heated, under reflux in xylene, gave the diacetyl derivative[195] **124**. Other carbonylhydrazones which have been oxidized with LTA are in Table I.E.

(183) P. R. West and J. Warkentin, *J. Org. Chem.*, **34**, 3233 (1969).
(184) S. L. Lee, G. B. Gubelt, A. M. Cameron, and J. Warkentin, *Chem. Commun.*, 1074 (1970).
(185) D. C. Iffland and T. M. Davies, *J. Amer. Chem. Soc.*, **85**, 2182 (1963).
(186) J. Schantl, *Monatsh. Chem.*, **100**, 1479 (1969).
(187) H. Schildknecht and G. Hatzmann, *Angew. Chem., Int. Ed. Engl.*, 7, 293 (1968).
(188) H. Schildknecht and G. Hatzmann, *Justus Liebigs Ann. Chem.*, 724, 226 (1969).
(189) D. J. Blackstock and D. A. R. Happer, *Chem. Commun.*, **63** (1968).
(190) H. Schildknecht and G. Hatzmann, *Angew. Chem., Int. Ed. Engl.*, 8, 456 (1969).
(191) R. W. Hoffmann and H. J. Luthardt, *Tetrahedron Lett.*, 411 (1966).
(192) R. W. Hoffmann and H. J. Luthardt, *Tetrahedron Lett.*, 3501 (1967).
(193) R. W. Hoffmann and H. J. Luthardt, *Chem. Ber.*, **101**, 3851 (1968).
(194) R. W. Hoffmann and H. J. Luthardt, *Chem. Ber.*, **101**, 3861 (1968).
(195) C. G. Pitt, *J. Org. Chem.*, **30**, 3242 (1965).
(196) N. Rabjohn and M. C. Chaco, *J. Org. Chem.*, **30**, 3227 (1965).
(197) D. C. Iffland and L. M. Weisenberger, paper presented at the 154th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1967.

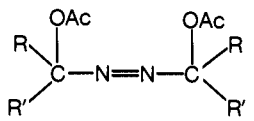


D. N,N-Disubstituted Hydrazones and Azines

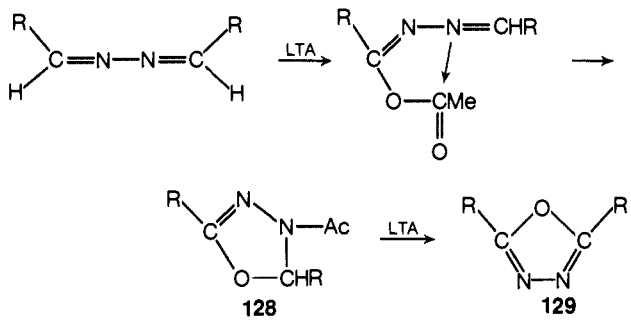
LTA oxidation of N,N-disubstituted hydrazones of aldehydes[49] and ketones,[50] in which one of the N substituents is aliphatic, results in an initial dealkylation to a monosubstituted hydrazone which reacts normally with the remaining LTA.[49,50] These reactions have been discussed in section II.A.3. Similar reactions were observed with such reagents as benzoyl peroxide in dichloromethane and manganese dioxide in chloroform acetic acid mixtures.[50] With peracetic acid cleavage of disubstituted hydrazones occurred giving carbonyl compounds and tetrazenes arising from dimerization of the hydrazine functions.[198] LTA oxidation of aliphatic ketazines yielded



α,β-unsaturated azoacetates[199] (**125**) which rearranged on heating to α-acetoxyazines (**126**). Ketazines which lack acidic hydrogens on the α-C atoms yielded the



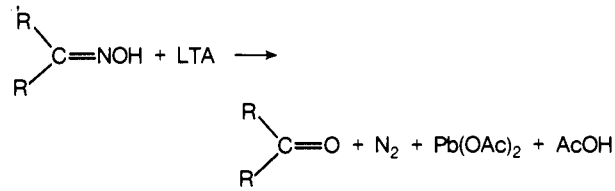
diacetoxyazo compounds[26] **127**. Aromatic ketazines failed to react with LTA. Aromatic and aliphatic aldazines yielded 1,3,4-oxadiazolines (**128**) as shown.[199] Further



reaction with, or use of excess LTA, converted the materials **128** to 1,3,4-oxadiazoles (**129**). Some nitrogen analogs of hydrazones (-N=NN) including substituted triazenes[200] and tetrazenes[201] have been treated with LTA. The reactions involve fragmentation of the nitrogen chain and are not formally comparable with the hydrazone reaction.

E. Aldoximes

The reaction of LTA with oximes is sensitive to a number of factors (section II.B) not least of which is temperature. While interesting reactions are observed at temperatures not higher than room temperature, when the reaction was carried out at 70° in a number of solvents, a wide range of oximes including aromatic and aliphatic aldoximes and ketoximes fragmented to the parent carbonyl compound and nitrogen as follows.[202]



At −78° *syn*-aldoximes yield nitrile oxides (**36**) in high yields.[55,56] The nitrile oxides have considerable synthetic value by virtue of their 1,3-dipolar addition reactions. Recently, the mechanism of these 1,3-addition reactions with phenylacetylenes,[203,204] thiobenzophenones,[205] aqueous acid,[206] and *N*-sulfinylanilines[207] and self-dimerization of nitrile oxides[208] has been investigated, the debate revolving about the involvement of a two-step or a concerted process.[129-131] The synthetic value of the 1,3-dipolar addition reactions has been reviewed.[209] Recent new reactions include addition of free radicals[210] and cyclic imidates and amidines.[211] Since addition of acetic acid leads to acetylhydroxamates, the 1,3-dipolar coupling reaction with nitrile oxides, derived by LTA oxidation of oximes, is best carried out *in situ* in the presence of sufficient triethylamine to neutralize the acetic acid generated in the reaction. The mild conditions (−78°) allow for the conversion of aromatic and aliphatic aldoximes with functional groups, which would not normally permit the use of standard preparative methods, to nitrile oxides. Limitations are the stereochemical requirement of a *syn*-aldoxime and the reactivity of LTA toward functional groups with labile hydrogen atoms.

The main products from the oxidation of aliphatic *anti*-aldoximes and *syn*-aldoximes at room temperature were the nitrosoacetate dimers (**33**) along with acetic anhydride and acetic acid.[53,55,212] Compounds **130**, **131**, and

(198) L. Horner and H. Fernekess, *Chem. Ber.*, **94**, 712 (1961).
(199) B. T. Gillis and M. P. La Montague, *J. Org. Chem.*, **32**, 3318 (1967).
(200) C. M. Camaggi, M. Tiecco, and A. Tundo, *J. Chem. Soc. B*, 680 (1968).
(201) G. Koga and J.-P. Anselme, *J. Amer. Chem. Soc.*, 91, 4323 (1969).
(202) Y. Yukawa, M. Sakai, and S. Suzuki, *Bull. Chem. Soc. Jap.*, **39**, 2266 (1966).
(203) A. Battaglia, A. Dondoni, and A. Mangini, *J. Chem. Soc. B*, 554 (1971).
(204) P. Beltrame, C. Veglio, and M. Simonetta, *J. Chem. Soc. B*, 867 (1967).
(205) A. Battaglia, A. Dondoni, C. Maccagnani, and G. Mazzanti, *J. Chem. Soc. B*, 2096 (1971).
(206) J. T. Edward and P. H. Tremaine, *Can. J. Chem.*, **49**, 3489 (1971).
(207) P. Beltrame and C. Vintani, *J. Chem. Soc. B*, 873 (1970).
(208) G. Barbaro, A. Battaglia, and A. Dondoni, *J. Chem. Soc. B*, 588 (1970).
(209) C. Grundmann and P. Grunanger, "The Nitrile Oxides," Springer-Verlag, New York, N. Y., 1971.
(210) T. Caronna and A. Quilico, *Tetrahedron Lett.*, 3633 (1970).
(211) K.-H. Magosh and R. Feinauer, *Angew. Chem.*, **83**, 882 (1971).
(212) H. Kropf, *Angew. Chem., Int. Ed. Engl.*, **4**, 983 (1965).

TABLE III. Oxime Types Treated with LTA

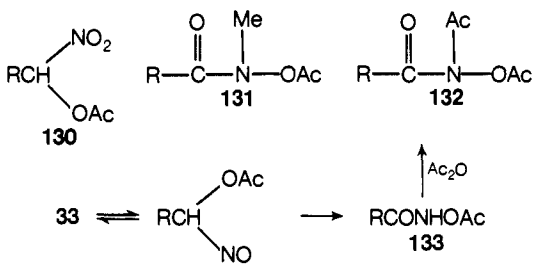
A. Aldoximes, RCH=NOH

R	Ref
p-XPh	54–56, 202, 213
PhCH=CH	54, 202, 213
PhCH=C(alkyl)	202
Me	56
Me_3C	55, 56
n-Hexyl	55, 56
$Me(CH_2)_n$- (*n* = 4–10)	53, 202, 212
$PhCH_2$	53, 212
2-Thiophene	54
2-Furan	54, 213
16-Nor-*O*-methylpodocarp-4-β-yl	55, 56
Abietinaldoxime	56
Mesityl	55, 56

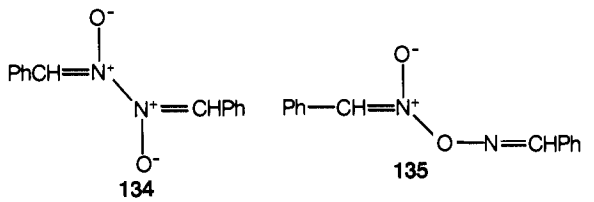
B. Ketoximes, RR'C=NOH

R	R'	Ref
$-CR_2(CH_2)_3CR_2-$		56, 57
Ph	PhC=NOH	54, 220
Me	$Me(CH_2)_n$-	53, 72, 202, 212
$-(CH_2)_n-$		53, 72, 202, 212, 216
Me	*p*-XPh	73, 202
Ph	Ph	202, 213, 219
Ph	NHPh	218
Me	Me_3C	212
Me	$PhCH_2$	53, 212
Me	$-CH_2CH_2COOH$	179
Ph	PhCO	213, 219
Bicyclic oximes		74
Cholestanone oxime		202
Phenanthraquinone dioxime		54
Camphor oxime		57, 202
Fluorenone oxime		219
Xanthone oxime		219
Indanone oxime		219
Pregna-5,16-dien-3β-acetoxy-20-one oxime		221

132 were also detected spectroscopically.[55] Compounds **132** probably arose from an acetylation of the acetyl hydroxamates (**133**), the analogs of the acetoxylation products (**58**) of aldehyde hydrazones. Compounds such as **133** could arise by rearrangement of the monomeric form of the nitrosoacetate dimers (**33**).



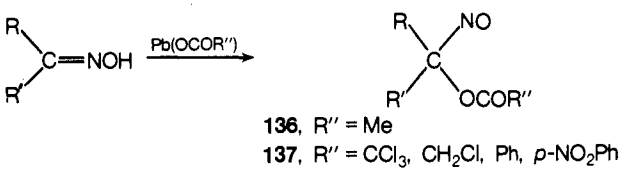
The oxidation of aromatic aldoximes with LTA at 0–5° yielded compounds which have been assigned both of the structures **34** and **35** in ca. 50% yields as well as parent carbonyl compounds.[54,55,213] At −78° *anti*-benzaldoxime also yielded the product **134**/**135** in 65% yield.[55] Compounds of type **34**/**35** have been obtained from the oxidation of aromatic aldoximes at room temperature with other oxidizing agents[214] and by treating phenyldiazomethane with nitric oxide.[215] Arguments in favor of structure[55,214,215] **34** and structure[54,213] **35** have been presented. Types of oximes which have been oxidized with LTA are recorded in Table III.



F. Ketoximes

1. Aliphatic and Alicyclic Ketoximes

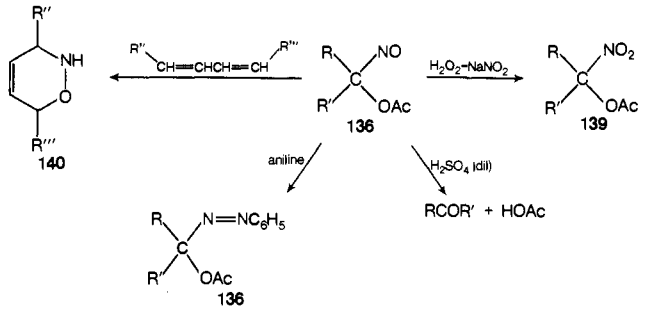
gem-Nitrosoacetates **136** are formed by LTA oxidation of aliphatic and alicyclic ketoximes.[53,72,212,216] The reaction is general for lead(IV) salts of the type Pb(O-



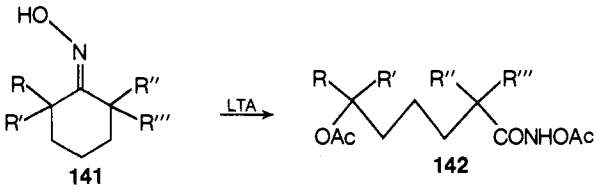
136, R'' = Me
137, R'' = CCl_3, CH_2Cl, Ph, *p*-NO_2Ph

(213) H. Kropf, *Angew. Chem., Int. Ed. Engl.*, 4, 1091 (1965).
(214) L. Horner, L. Hockenberger, and W. Kirmse, *Chem. Ber.*, 94, 290 (1961).
(215) O. L. Chapman and D. C. Heckert, *Chem. Commun.*, 242 (1966).
(216) D. C. Iffland and G. X. Criner, *Chem. Ind. (London)*, 176 (1956).

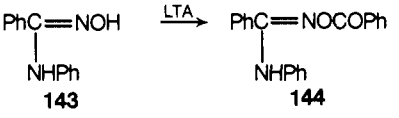
$COR)_4$, and a range of the nitrosoacylate compounds **137** has been reported.[53] Treatment of the *gem*-nitrosoacetates **136** with aniline yielded the azoacetates[212] **138**. On treatment of the compounds **136** with dilute acid the parent ketone was regenerated.[212] This process has also been achieved by oxidation of oximes with Ce(IV) salts[217] and by carrying out the LTA reaction at high temperatures.[202] The *gem*-nitrosoacetates are generally unstable deep blue oils. When they were treated with hydrogen peroxide and sodium nitrate, the stable colorless nitro derivatives **139** were formed.[212] On treatment of the nitrosoacetates **136** with 1,4-disubstituted butadienes the 1,2-oxazines **140** were formed.[212]



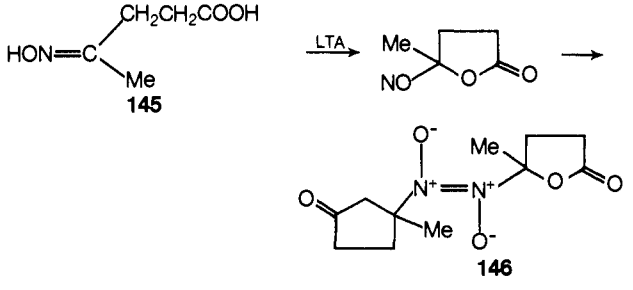
LTA oxidation of sterically hindered ketoximes resulted in a C–C bond fission in preference to nitrosoacetate formation.[56,57] Thus with a range of 2,2,6,6-tetrasubstituted cyclohexanone oximes (**141**) the products were acetyl hydroxamates (**142**) arising from addition of acetic acid to a nitrile oxide intermediate.[56,57] The acetyl hydroxamates were readily cleaved to hydroxamic acids. The carbon–carbon cleavage reaction was more dominant in trifluoroacetic acid than in acetic acid and was enhanced by increased steric hindrance around the methine carbon atom.[56,57]



The oxime of benzanilide (**143**) yielded the *O*-benzoyl derivative **144** on treatment with LTA or a number of

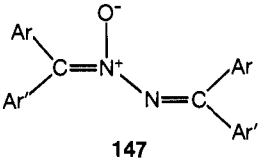


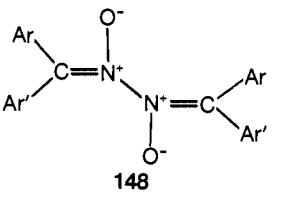
other oxidizing agents.[218] The reaction is thought to involve 1,2-diphenyl-2-nitrosoazomethine, arising from dehydrogenation of the oxime, as an intermediate which reacts with an unchanged molecule of starting material.[218] Oxidative cyclization of the oxime of levulinic acid (**145**) to the γ-nitroso-γ-valerolactone dimer (**146**) occurs on oxidation with LTA in a reaction similar to the oxidative cyclization of the corresponding phenylhydrazone.[179]

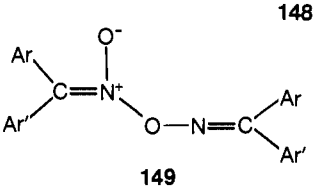


2. *Aromatic and α,β-Unsaturated Ketoximes*

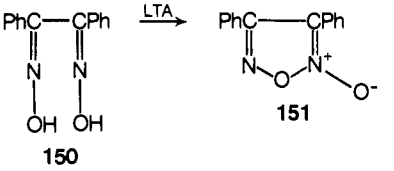
LTA oxidation of aromatic ketoximes does not proceed *via* a single pathway. In addition to the primary oxidation a number of secondary reactions involving oxygen and nitrogen dioxide take place,[219] particularly with acetic acid as solvent. In solvents such as ether, tetrahydrofuran, and dichloromethane the primary oxidation process is dominant[213,219] and the main products are the parent carbonyl compound, azine monoxides (**147**), and azine bis-*N*-oxides (**148**), which have the same structural ambiguity as the compounds **134**/**135**, and hence have also been assigned structure[213] **149**. The parent carbonyl

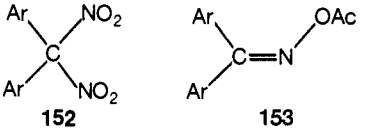


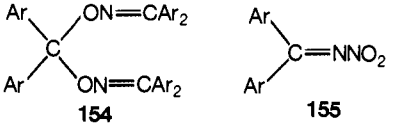




compound is considered to arise from decomposition of an intermediate *gem*-nitrosoacetate.[213,219] The dimeric products have been considered to arise by combinations of iminoxy radicals[219] and by trapping of an iminoxy cation, $Ar_2C{=}NO^+$, by the parent oxime.[213] Aromatic dioximes behave similarly and yield furoxan products,[54,213,220] *e.g.*, benzil α- or β-dioxime (**150**) yields diphenylfuroxan[220] (**151**). The reaction in acetic acid was characterized by the appearance of nitrous gases[213] and a mixture of the products **152**–**155** was obtained from complicated secondary reactions.[219] A similar mixture of products was obtained in acetic acid under an atmosphere of nitrogen while the reaction in other solvents was insensitive to molecular oxygen.[219] LTA oxidation of substituted acetophenone oximes in dichloromethane yielded *gem*-







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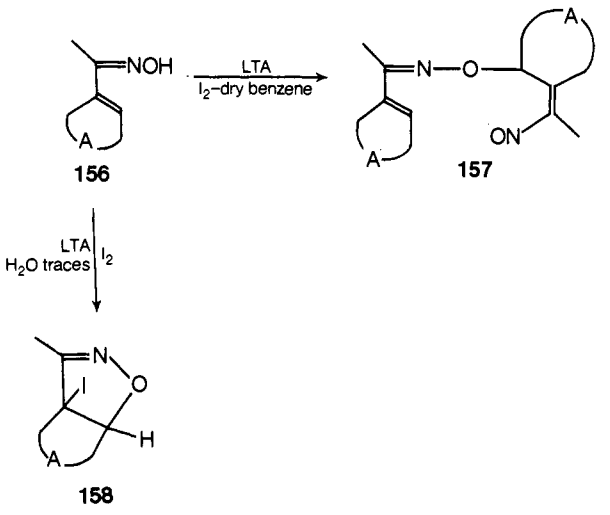
nitrosoacetates as unstable blue oils which decomposed readily on heating to give the parent acetophenone, acetic acid, and nitrous fumes.[73] LTA oxidation of α,β-unsaturated steroidal oximes (**156**) in dry benzene containing iodine yielded the dimers[221] **157**. In the presence of water the addition products **158** were formed.[221] Other



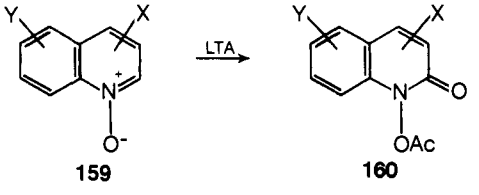
A = steroid residue

ketoximes which have been treated with LTA and give reactions similar to those described are in Table III.

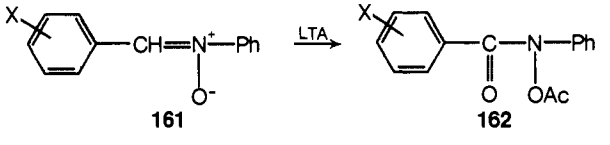
G. General Azomethines

1. Azomethine N-Oxides (Nitrones)

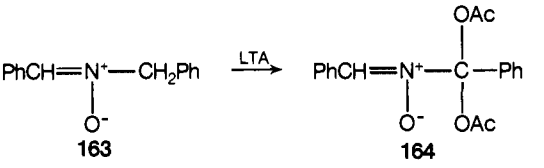
The reaction of LTA with azomethines other than hydrazones and oximes has been little exploited. The general reaction with azomethine *N*-oxides has been described in section II.C.1. Substituted quinoline *N*-oxides (**159**) on treatment with LTA in benzene yielded the *N*-acetoxycarbostyrils[79,80,222] (**160**). Hydrolysis of products



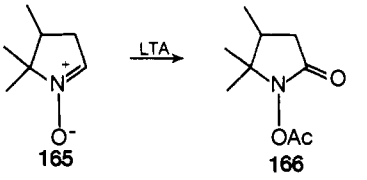
160 *in situ* with dilute acid gave the corresponding hydroxamic acids. Yields in the LTA oxidation were lower with acetic acid as solvent.[79,80] The reaction, which was enhanced by electron-donating substituents, was reported to fail for 4-nitroquinoline 1-oxide[79] but was subsequently proved to be successful with this compound also, giving 30% of the quinoline hydroxamic acid.[222] LTA oxidation of the *N*-arylidene-*N*-phenyl *N*-oxides (**161**)



gave quantitative yields of the *N*-acetoxy-*N*-aroylanilines[82] (**162**). An *O*-acetyl *N*-oxide structure was also assigned to the product of this reaction[223] but, in view of the facile 1,4-acetyl migrations which are common in such systems, structure **162** is probably correct. With the corresponding *N*-benzyl derivative **163** the product was

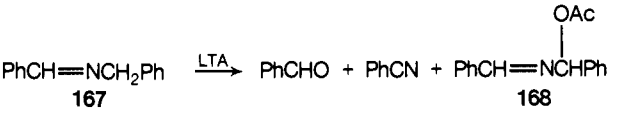


the diacetate[223] **164**. LTA oxidation of 4,5,5-trimethyl-1-pyrroline 1-oxide (**165**) gave the 1-acetoxy-2-pyrrolidone[81] (**166**).

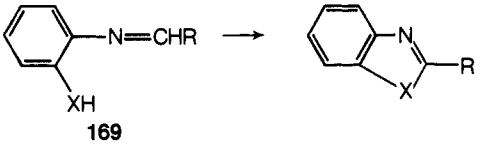


2. Schiff Bases

LTA oxidation of aromatic Schiff bases results in cleavage of the >CH=N- moiety to the parent aldehyde and a nitrene intermediate,[84] section II.C.2. With an *N*-alkyl Schiff base,[224] *N*-benzylidenebenzylamine (**167**), the reaction was somewhat different, the products being benzaldehyde, benzonitrile, and the acetoxybenzylamine (**168**) which compares with the product **164** also ob-



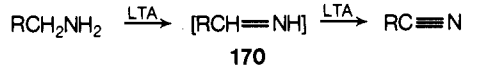
tained from an *N*-benzyl system. LTA oxidation of Schiff bases containing labile ortho substituents in the *N*-aryl ring, *e.g.*, **169**, involves an oxidative cyclization to benziminazoles and benzoxazoles.[225-227] The reaction is synthetically useful and gives better yields than the Skraup synthesis of benziminazoles.



X = NH, O

3. Imines

LTA oxidation of imines **170** usually involves a dehydrogenation to a nitrile or an oxidative cyclization. Imines of type **170** are usually formed in the LTA oxidation of primary amines and oxidized *in situ* to nitriles.[224,228-230]



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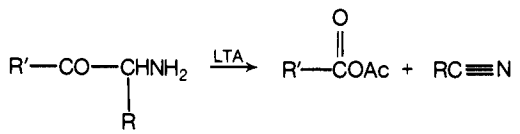
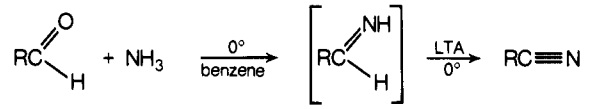
With α-amino ketones[229] (**171**) or α-amino alcohols[1,230] cleavage of the molecule between the carbonyl and carbinamine function occurs yielding acid derivatives from the carbonyl or alcoholic moiety of the molecule and nitriles from the carbinamine moiety. Reviews which include LTA oxidations of amines have been published.[1,6]



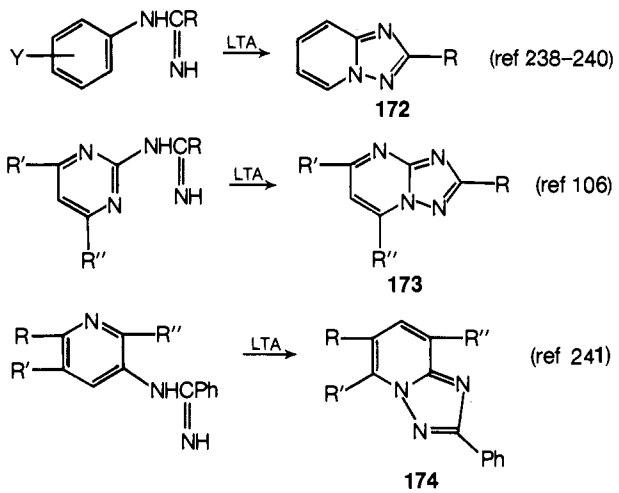
171

Imines of type **170** may be easily prepared from the reactions of aldehydes with ammonia but have received little attention because of their high reactivity. Such unsubstituted imines have recently[231] been stabilized by complexing with cobalt. High yields of nitriles were obtained on oxidation of the cobalt complexes.[231] An easy and important conversion of aldehydes to nitriles by LTA oxidation of intermediate imines *in situ* has also been developed as follows.[232,233]



Nitriles have also been obtained from the LTA oxidation of substituted *o*-phenylenediamines,[234] 2-aminobenzotriazoles,[235,236] and 3,5-disubstituted-4-amino-1,3,4-triazoles.[237]

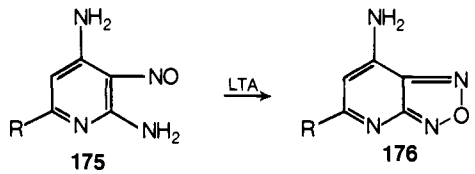
LTA has proved a useful reagent for the oxidative cyclization of amidines but has not been used widely in this context. The triazolopyridines[238-240] (**172**), triazolopyrimidines[106] (**173**), and triazolopyrazines[241] (**174**) have been obtained from LTA oxidation of the corresponding amidines. Although a free radical mechanism has been suggested,[238] systematic mechanistic data are not available and the dimeric products to be expected from such a mechanism have not been isolated. Other reactions with synthetic promise are the recently reported cyclization of 2-substituted 4,6-diamino-5-nitrosopyrimidines (**175**) to the furazanopyrimidines[242] (**176**) and a ring expansion of pyrrolopyrimidines to pyrimidopyrimidines,[243] both effected by LTA oxidations.



172 (ref 238–240)

173 (ref 106)

174 (ref 241)



175 **176**

Pyrolysis of lead tetraacylate salts $Pb(OCOR)_4$ has been used to provide radicals (R·) for homolytic substitution in heterocycles containing C=N moieties including pyridine,[244,245-248] quinoline,[245,246] isoquinoline,[245,246] and substituted isoxazoles.[249] Since these reactions do not involve an interaction between the Pb(IV) salt and the C=N moiety, their consideration is not included in this review.

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