Thallium in Organic Synthesis. XXXIV. Oxidations of Acetylenes with Thallium(III) Nitrate (TTN)[1-3]

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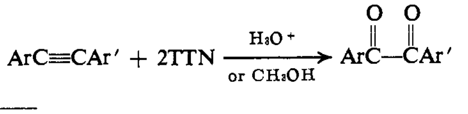
Received July 18, 1972

Abstract: The reactions of a variety of acetylenes with thallium(III) nitrate (TTN) have been examined, and the nature of the products has been found to depend on the solvent employed and the structure of the acetylene. Diarylacetylenes are converted into benzils in high yields on treatment with TTN in either aqueous acidic glyme or in methanol; dialkylacetylenes give acyloins in aqueous media and α-methoxy ketones in methanol; monoalkylacetylenes undergo degradation to carboxylic acids containing one carbon atom less than the starting material; and alkylarylacetylenes undergo smooth oxidative rearrangement in methanol solution to give methyl α-alkylarylacetates. All of the reactions proceed in high yield, and the specificity in oxidation is explained in terms of the mechanisms of the various reactions. Hydration of the C≡C bond does not occur to a significant extent.

One of the classic reactions in the chemistry of acetylenes is mercury(II) salt catalyzed hydration of the C≡C bond. This important process has been the subject of detailed investigation,[5] but there are few reports on the reactions of acetylenes with other electrophilic metal salts.[6] In particular, the reactions of C≡C bonds with lead(IV) and thallium(III) salts, which are isoelectronic with mercury(II), remain virtually uninvestigated. The first reports on the oxidation of acetylenes with lead(IV) acetate were published in 1961; Jadot and Neuray showed that C≡C bonds reacted much more slowly than C=C bonds with lead(IV) acetate in acetic acid, and that complex mixtures of products were obtained.[7] Subsequent investigations confirmed these initial findings and indicated that the nature and relative proportions of the products formed were probably dependent on the reaction conditions.[8]

There is only one report in the literature on the oxidation of acetylenes with thallium(III) salts. Uemura and his coworkers studied the hydration of acetylenes with a variety of thallium(III) salts and claimed that phenylacetylene could be converted into acetophenone in yields as high as 84%, using thallium(III) chloride or acetate in acetic acid at temperatures ranging from 60 to 110°.[9] This claim, however, appears to us to be highly suspect for two main reasons. Firstly, the reaction conditions employed by the Japanese workers are incompatible with the known properties of the thallium salts used. Thallium(III) chloride is known to be thermally unstable with respect to thallium(I) chloride and chlorine at temperatures in excess of 40°,[10] while thallium(III) acetate has been shown to oxidize hot acetic acid rapidly and quantitatively to give thallium(I) acetoxyacetate.[11] Secondly, hydration of phenylacetylene is known to occur particularly easily and may even be effected by superheated steam.[12] With strong acids, hydration takes place readily at room temperature.[13] Consequently, it is doubtful if the inorganic salts participated to any significant extent in the hydration reaction, and it appears that Uemura and his colleagues were merely studying the acid-catalyzed hydration of phenylacetylene.[14]

In view of the marked differences in the reactions of olefins with mercury(II) and thallium(III) salts, and in particular thallium(III) nitrate,[15] we have examined the oxidation reactions which occur when acetylenes are treated with this reagent. We have found that these reactions show a striking dependence on the structure of the acetylene and on the solvent system employed. Four major structural types of acetylenes were studied, namely, diarylacetylenes, dialkylacetylenes, monoalkylacetylenes, and alkylarylacetylenes. Two standard solvent systems were used, namely aqueous glyme acidified with a little perchloric acid, and methanol. The results of our investigations are summarized in eq 1–4.



$$ArC\equiv CAr' + 2TTN \xrightarrow[\text{or } CH_3OH]{H_3O^+} ArC(=O)-C(=O)Ar' \quad (1)$$

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[1] Part XXXIII: A. McKillop, B. P. Swann, and E. C. Taylor, *J. Amer. Chem. Soc.*, in press.

[2] We gratefully acknowledge partial financial support of this work by Eli Lilly and Co., Indianapolis, Ind.

[3] Preliminary communication: A. McKillop, O. H. Oldenziel, B. P. Swann, E. C. Taylor, and R. L. Robey, *J. Amer. Chem. Soc.*, **93**, 7331 (1971).

[4] (a) University of East Anglia, Norwich, Norfolk, England; (b) Princeton University, Princeton, N. J.

[5] L. G. Makarova and A. N. Nesmeyanov, "Methods of Elemento-Organic Chemistry," Vol. 4, "The Organic Compounds of Mercury," North-Holland Publishing Co., Amsterdam, 1967, pp 203–211.

[6] H. Gopal and A. J. Gordon, *Tetrahedron Lett.*, 2941 (1971).

[7] J. Jadot and M. Neuray, *Bull. Soc. Roy. Sci. Liege*, 30, 34, 52 (1961).

[8] (a) S. Moon and W. J. Campbell, *Chem. Commun.*, 470 (1966); (b) R. O. C. Norman and C. B. Thomas, *J. Chem. Soc. B*, 771 (1967).

[9] S. Uemura, R. Kitoh, K. Fujita, and K. Ichikawa, *Bull. Chem. Soc. Jap.*, 40, 1499 (1967).

[10] N. V. Sidgwick, "The Chemical Elements and Their Compounds," Oxford University Press, London, 1950, p 470.

[11] E. C. Taylor, H. W. Altland, G. McGillivray, and A. McKillop, *Tetrahedron Lett.*, 5285 (1970).

[12] A. Desgrez, *Ann. Chim. (Paris)*, 3, 231 (1894).

[13] (a) R. W. Bott, C. Eaborn, and D. R. M. Walton, *J. Chem. Soc.*, 384 (1965); (b) D. S. Noyce and M. D. Schiavelli, *J. Amer. Chem. Soc.*, **90**, 1020, 1023 (1968).

[14] It is noteworthy that phenylacetylene is unaffected by mercury(II) chloride in methanol: G. F. Dvorko and E. A. Shilov, *Ukr. Khim. Zh.*, **28**, 833 (1962); *Chem. Abstr.*, **59**, 1449 (1963).

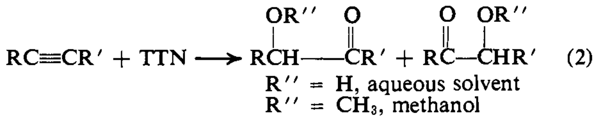
[15] A. McKillop, J. D. Hunt, E. C. Taylor, and F. Kienzle, *Tetrahedron Lett.*, 5275 (1970).

Table I. Oxidation of Diarylacetylenes to Benzils with TTN–H_3O^+

$ArC{\equiv}CAr' \longrightarrow ArCOCOAr'$

Compd no.	Acetylene Ar	Acetylene Ar′	Time, hr	Benzil Yield, %	Benzil Mp, °C	Benzil Lit. mp, °C
14	C_6H_5	C_6H_5	3	85	93–94	94–95[a]
15	C_6H_5	4-$CH_3C_6H_4$	2.5	85	29–30	30–31[b]
16	C_6H_5	4-$CH_3OC_6H_4$	2.5	75	61–62	62–63[a]
17	C_6H_5	2-$NO_2C_6H_4$	4	65	99–100	98–100[c]
18	C_6H_5	4-$NO_2C_6H_4$	6	45	139–141	142[d,e]
19	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	2.5	97	100–102	104–105[f]
20	4-$CH_3C_6H_4$	4-$CH_3OC_6H_4$	2	90	105–106	*g*
21	4-$CH_3C_6H_4$	2-$NO_2C_6H_4$	4	55	96–97	*h*
22	4-$CH_3C_6H_4$	4-$NO_2C_6H_4$	5	60	191–192	*i*
23	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	2.5	88	128–130	133[a]

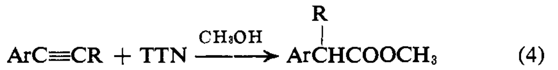
[a] N. J. Leonard, R. T. Rapala, H. L. Herzog, and E. R. Blout, *J. Amer. Chem. Soc.*, **71**, 2997 (1949). [b] H. H. Hatt, A. Pilgrim, and W. J. Hurran, *J. Chem. Soc.*, 93 (1936). [c] P. Ruggli and B. Hegedüs, *Helv. Chim. Acta*, **22**, 147 (1939). [d] F. D. Chattaway and E. A. Coulson, *J. Chem. Soc.*, 1080 (1928). [e] 12% of starting material was recovered. [f] R. Stierlin, *Chem. Ber.*, **22**, 376 (1889). [g] *Anal.* Calcd for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55. Found: C, 75.51; H, 5.23. [h] *Anal.* Calcd for $C_{15}H_{11}NO_4$: C, 66.91; H, 4.11. Found: C, 66.74; H, 4.01. [i] *Anal.* Calcd for $C_{15}H_{11}NO_4$: C, 66.91; H, 4.11. Found: C, 66.70; H, 4.69.



$$RC{\equiv}CR' + TTN \longrightarrow RCH(OR'')\text{—}C({=}O)R' + RC({=}O)\text{—}CH(OR'')R' \quad (2)$$

R″ = H, aqueous solvent
R″ = CH_3, methanol

$$RC{\equiv}CH + 2TTN \xrightarrow{H_3O^+} RCOOH \quad (3)$$



$$ArC{\equiv}CR + TTN \xrightarrow{CH_3OH} ArCH(R)COOCH_3 \quad (4)$$

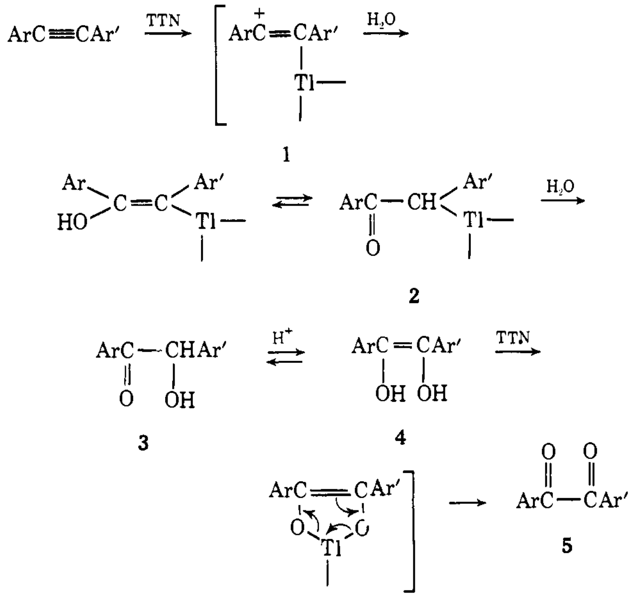
Discussion

Diarylacetylenes (Eq 1). Diphenylacetylene was selected as the standard substrate, and its reactions with a variety of thallium(III) salts were investigated. The salts employed were those of acetic, isobutyric, trifluoroacetic, and nitric acids, and preliminary experiments established that TTN was the most efficient reagent in terms of product yield, rate of reaction, and experimental simplicity. The reaction was found to proceed cleanly and smoothly in a hot aqueous glyme–perchloric acid medium similar to that previously employed in the oxidation of chalcones with TTN.[16] Under these conditions, the only product which could be detected from the reaction of diphenylacetylene with any of the above salts was benzil. With 1 equiv of TTN a 1:1 mixture of benzil and unchanged starting material was obtained, but when 2 equiv of oxidant was used, the acetylene was completely consumed and benzil was obtained in 85% yield.

The generality of this transformation was then investigated by treatment of a variety of diarylacetylenes with TTN under similar conditions. The acetylenes were readily prepared by the Castro–Stephens coupling procedure,[17] and experimental data for the oxidations of these compounds to the corresponding benzils are summarized in Table I. From these data it is evident that the present method constitutes a simple and rapid procedure for the preparation of benzils, and one which is especially useful for the synthesis of unsymmetrical compounds.[18]

A noticeable substituent effect was observed during this study, both in the relative reaction times necessary for oxidation and in the yields of benzils isolated. Thus, reaction proceeded most rapidly, and in highest yield, with diarylacetylenes containing electron-donating substituents in the aromatic ring(s). This result would be expected on the basis of a mechanism in which oxythallation of the C≡C bond was the first step, and we suggest that the overall conversion is best represented by the reactions shown in Scheme I. Then, with respect to nuclear substituents, (a) the direction of oxythallation in an unsymmetrical diarylacetylene is predictable, and (b) vinyl cationic intermediates such as **1** would be stabilized by electron-donating substituents in Ar and destabilized by electron-withdrawing substituents. Conversion of the alkylthallium(III) intermediate **2** into the benzoin **3** is presumably a rapid reaction, as organothallium derivatives of the type $RTlX_2$ are known to be highly unstable to solvolysis.[19] The final oxidation sequence, *viz.* conversion of the benzoin **3** to the benzil **5** *via* the enediol tautomer **4**, has been demonstrated previously with TTN,[16] and more detailed studies on the oxidation of a wide range of benzoins

Scheme I



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[16] A. McKillop, B. P. Swann, and E. C. Taylor, *Tetrahedron Lett.*, 5281 (1970).

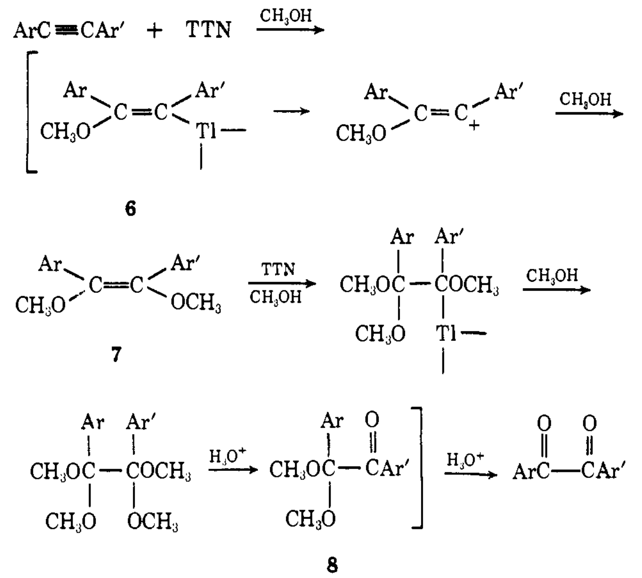
[17] C. E. Castro and R. D. Stephens, *J. Org. Chem.*, **28**, 2163, 3313 (1963).

[18] Efficient oxidation of various acetylenes to 1,2-dicarbonyl compounds with NBS in anhydrous DMSO has recently been described: S. Wolfe, W. R. Pilgrim, T. F. Garrard, and P. Chamberlain, *Can. J. Chem.*, **49**, 1099 (1971).

[19] W. Kitching, *Rev. Pure Appl. Chem.*, **19**, 1 (1969).

to the corresponding benzils with 1 equiv of TTN have shown that, under reaction conditions identical with those used in the acetylene oxidations, the yields of benzils are comparable with or better than those shown in Table I.[20] Surprisingly, a change in solvent from aqueous acid to methanol also led to the formation of benzils in excellent yield. On the basis of this observation and the experiments outlined below, we suggest that the mechanism of oxidation of diarylacetylenes in methanol is different from that in aqueous solution, and is best represented by the reaction sequence outlined in Scheme II. Vinylthallium(III) derivatives similar to the oxythallation adduct **6** have been prepared previously by classical organometallic exchange reactions, and, while they are moderately stable relative to alkylthallium(III) compounds, they are known to decompose by apparently similar pathways.[21] Hence solvolysis of the thallium substituent, possibly *via* a vinyl cation, would give the olefin **7**, conversion of which into benzil merely necessitates a second oxythallation step and subsequent solvolysis of the thallium substituent. Attempts to isolate the vinylthallium derivative **6** were unsuccessful; when oxidation of diphenylacetylene was carried out in anhydrous methanol in the presence of molecular sieves, however, the monoketal of benzil (**8**, Ar = Ar′ = C_6H_5) was isolated in 65% yield together with benzil. The structure of this product was verified by comparison with a genuine sample prepared by ketalization of benzil using silver oxide and methyl iodide.[22] Furthermore, oxidation of *cis*-stilbenediol dimethyl ether[23] (**7**, Ar = Ar′ = C_6H_5) with 1 equiv of TTN in methanol occurred smoothly to give the monoketal **8** (Ar = Ar′ = C_6H_5) in 37% isolated yield (75% by direct glpc examination of the reaction mixture) together with a small amount of benzil.

Scheme II



There is precedent for the formation of intermediates analogous to **7** and **8**. Electrolytic oxidation of diphenylacetylene at a carbon electrode has been shown to be essentially a cationic oxidation process, and, using acetic acid as the solvent, Koehl found that benzoin, benzoin acetate, benzil, and stilbenediol diacetate were among the products formed.[24] Benzoin acetate was shown to be inert to further oxidation under these conditions, and thus Koehl concluded that stilbenediol diacetate served as the precursor to benzil.

Dialkylacetylenes and Terminal Alkylacetylenes (Eq 2 and 3). Dialkylacetylenes reacted exothermically with 1 equiv of TTN in aqueous glyme–perchloric acid to give acyloins and small amounts of the corresponding α-diketones. Isolation of pure products was extremely tedious; such mixtures are known to be separable only with difficulty.[25] High yields of acyloins were obtained with symmetrical acetylenes such as 3-hexyne and 4-octyne (70–90%), but with unsymmetrical acetylenes 1:1 mixtures of the isomeric acyloins were obtained which could not be satisfactorily separated. The mechanism of this conversion is presumably similar to that outlined in Scheme I (leading to **3**). Whereas benzoins are rapidly oxidized to benzils by TTN, however, standard control reactions with acyloins showed that these compounds are oxidized rather slowly to the corresponding α-diketones, presumably because enediol formation is less favorable.

Dialkylacetylenes reacted with TTN in methanol to give α-methoxy ketones; analogous results were obtained even with the poorly electrophilic thallium(III) acetate. Thus, treatment of 3-hexyne with thallium(III) acetate in methanol gave 4-methoxyhexan-3-one in 85% yield. The mechanism of this transformation is not clear at present, but a possible reaction sequence is shown in Scheme III. The main difference between this and the other mechanisms is the apparent necessity for proto-dethallation of the vinylthallium(III) intermediate **9** rather than direct solvolysis of the thallium substituent; similar mechanisms have been postulated for analogous reactions using mercury(II) salts.[26,27]

Terminal alkylacetylenes reacted exothermically with

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[20] A. McKillop, M. E. Ford, B. P. Swann, and E. C. Taylor, to be submitted for publication.

[21] H. Kurosawa and R. Okawara, *Organometal. Chem. Rev., Sect. A*, **6**, 65 (1970).

[22] R. Kuhn and H. Trischmann, *Chem. Ber.*, **94**, 2258 (1961).

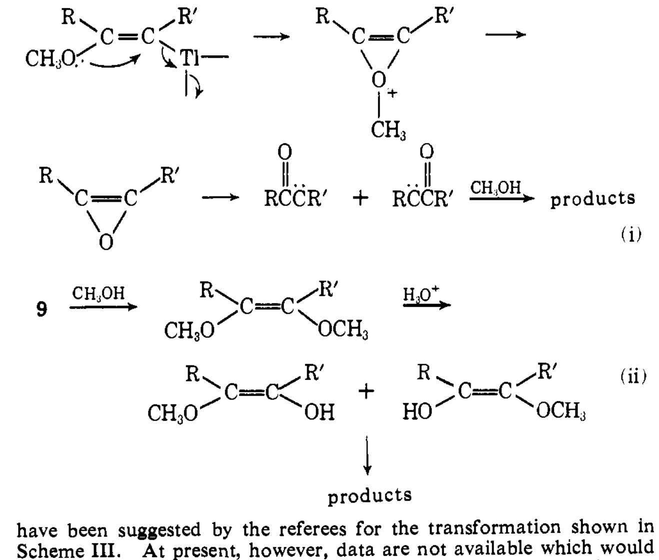
[23] E. O. Fischer, B. Heckl, K. H. Dötz, J. Müller, and H. Werner, *J. Organometal. Chem.*, **16**, P29 (1969).

[24] W. J. Koehl, *J. Org. Chem.*, 32, 614 (1967).

[25] (a) R. Jacquier, *Bull. Soc. Chim. Fr.*, 83 (1950); *Chem. Abstr.*, **45**, 1958 (1951); (b) D. L. Bunbury and M. S. Osyany, *J. Chromatogr.*, **14**, 98 (1964).

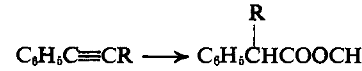
[26] H. Lemaire and H. J. Lucas, *J. Amer. Chem. Soc.*, 77, 939 (1955).

[27] Alternative and equally plausible mechanisms, eq i and ii,



have been suggested by the referees for the transformation shown in Scheme III. At present, however, data are not available which would allow a definitive choice to be made among these various alternatives.

Table II. Oxidation of Alkylarylacetylenes with TTN-CH_3OH

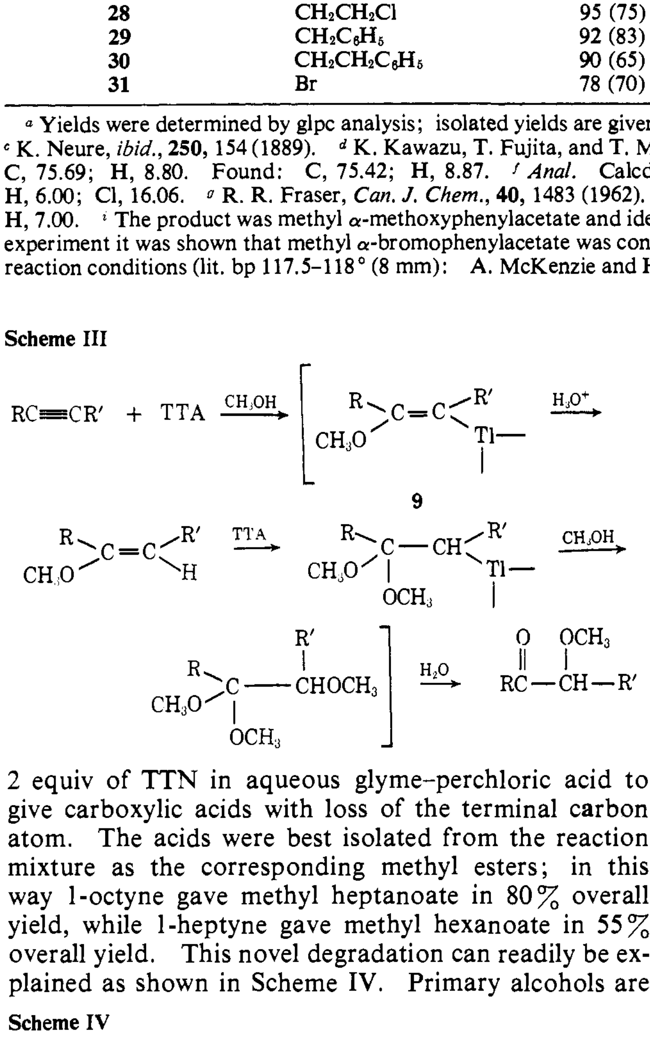


$$C_6H_5C{\equiv}CR \longrightarrow C_6H_5\overset{R}{\overset{|}{C}}HCOOCH_3$$

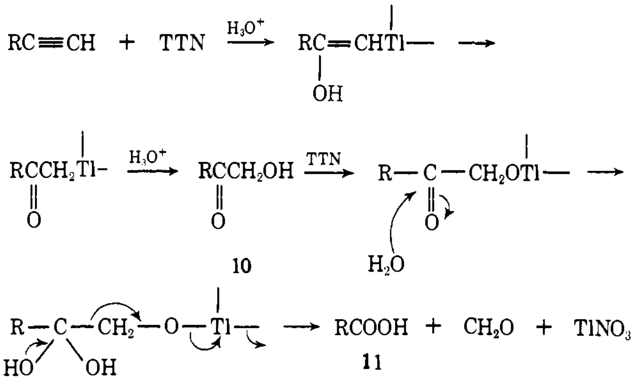
Compd no.	R	Yield, %[a]	Bp, °C (mm)	Lit. bp (mp), °C
24	CH_3	95 (80)	109–113 (20)	221[b]
25	CH_2CH_3	95 (82)	63–67 (0.4)	228[c]
26	$(CH_2)_2CH_3$	97 (83)	75–77 (0.2)	123–125 (17 mm)[d]
27	$(CH_2)_3CH_3$	98 (77)	78–80 (0.5)	*e*
28	CH_2CH_2Cl	95 (75)	94–97 (0.3)	*f*
29	$CH_2C_6H_5$	92 (83)	124–127 (0.1)	(31.5–32.5)[g]
30	$CH_2CH_2C_6H_5$	90 (65)	138–140 (0.3)	*h*
31	Br	78 (70)	78–82 (0.2)	*i*

[a] Yields were determined by glpc analysis; isolated yields are given in parentheses. [b] K. Neure, *Justus Liebigs Ann. Chem.*, **250,** 151 (1889). [c] K. Neure, *ibid.*, **250,** 154 (1889). [d] K. Kawazu, T. Fujita, and T. Mitsui, *J. Amer. Chem. Soc.*, **81,** 932 (1959). [e] *Anal.* Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.42; H, 8.87. [f] *Anal.* Calcd for $C_{11}H_{13}ClO_2$: C, 62.10; H, 6.16; Cl, 16.68. Found: C, 62.19; H, 6.00; Cl, 16.06. [g] R. R. Fraser, *Can. J. Chem.*, **40,** 1483 (1962). [h] *Anal.* Calcd for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13. Found: C, 79.87; H, 7.00. [i] The product was methyl α-methoxyphenylacetate and identity was confirmed by comparison with a genuine sample. In a control experiment it was shown that methyl α-bromophenylacetate was converted quantitatively into methyl α-methoxyphenylacetate under identical reaction conditions (lit. bp 117.5–118° (8 mm): A. McKenzie and H. Wren, *J. Chem. Soc.*, **97,** 484 (1910)).

Scheme III



Scheme IV

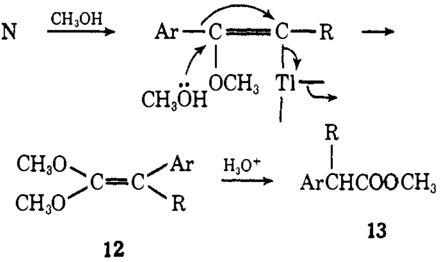


2 equiv of TTN in aqueous glyme–perchloric acid to give carboxylic acids with loss of the terminal carbon atom. The acids were best isolated from the reaction mixture as the corresponding methyl esters; in this way 1-octyne gave methyl heptanoate in 80% overall yield, while 1-heptyne gave methyl hexanoate in 55% overall yield. This novel degradation can readily be explained as shown in Scheme IV. Primary alcohols are known to undergo rapid ligand exchange with thallium(III) salts;[28] the validity of the fragmentation step **10** → **11** was checked independently. Thus, treatment of 1-hydroxyoctan-2-one[29] (**10**, R = C_6H_{13}) with 1 equiv of TTN resulted in smooth reduction of the thallium from thallium(III) to thallium(I) and simultaneous oxidative degradation to **11** (R = C_6H_{13}) in 76% yield.

Alkylarylacetylenes (Eq 4). Treatment of alkylarylacetylenes with 1 equiv of TTN in acidic glyme under the same conditions as were used for the other types of acetylenes resulted in formation of complex mixtures of products. Thus, oxidation of methylphenylacetylene gave a mixture of methyl phenyl diketone, ethyl phenyl ketone, benzyl methyl ketone, and unchanged starting material.[30] When oxidation was carried out in methanol solution, however, smooth oxidative rearrangement occurred to give methyl α-alkylarylacetates in high yield. Data for representative conversions are summarized in Table II.

It has recently been shown[31] that oxidation of acetophenones with TTN results in direct formation of methyl arylacetates, and the present procedure thus extends the general utility of TTN for the preparation of these valuable synthetic intermediates. We believe that the initial steps in this rearrangement (Scheme V) are similar to those postulated for the oxidation of diarylacetylenes with TTN in methanol (see Scheme II). So far all attempts to isolate either a vinylthallium intermediate or a ketene acetal from these reactions have been unsuccessful.[32] In accordance with the

Scheme V



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(28) R. Criegee, L. Kraft, and B. Rank, *Justus Liebigs Ann. Chem.*, **507,** 159 (1933).

(29) E. Pfeil and H. Barth, *ibid.*, **593,** 81 (1955).

(30) Infrared spectral analysis of the mixture also revealed the presence of hydroxy compounds; these were almost certainly the acyloins $C_6H_5CH(OH)COCH_3$ and $C_6H_5COCH(OH)CH_3$, but they could not be detected by glpc (see ref 25b).

(31) A. McKillop, B. P. Swann, and E. C. Taylor, *J. Amer. Chem. Soc.*, **93,** 4919 (1971).

(32) Phenylacetylene has been shown to react with nitrous oxide in ethanol at 300° (500 atm) to give ethyl phenylacetate. Phenylketene was implicated as an intermediate in this rearrangement, since ketenes were actually isolated when alkylacetylenes were subjected to similar reaction conditions in inert solvents: G. D. Buckley and W. J. Levy, *J. Chem. Soc.*, 3016 (1951).

proposed mechanism, however, the rate and yield of reaction showed a marked dependence on the nature of substituents in the aromatic ring. Thus, *p*-nitrophenylacetylene was not oxidized to methyl *p*-nitrophenylacetate by TTN under the standard reaction conditions, while phenylacetylene gave a complex mixture of products of which methyl phenylacetate constituted only 17%. *p*-Methoxyphenylacetylene, on the other hand, reacted exothermically with TTN in methanol to give methyl *p*-methoxyphenylacetate in 61% yield. These results are consistent with the relative migratory aptitudes of the three aromatic groups, with the data available on the corresponding oxidative rearrangements of olefins with TTN,[15] and with the observation that no significant amount of oxidative rearrangement was observed in any of the reactions conducted in aqueous solvents. Under the latter conditions intermediates of the type –COCHTl< are formed, and S_N1-type heterolysis of the C–Tl bond, an almost certain prerequisite for 1,2-alkyl or -aryl migration, would necessitate the generation of carbonium ion character α to an already electron-deficient carbon. Consequently, direct S_N2-type solvolysis of the thallium substituent is preferred to oxidative rearrangement.

In none of the above reactions conducted in aqueous acidic solution was any evidence obtained for the intermediacy of ketones derived by thallium(III)-catalyzed hydration of the triple bond. Independent studies have established that deoxybenzoins are oxidized smoothly to benzils by TTN in aqueous acidic glyme, but the characteristic feature of these latter oxidations is the formation of small but constant amounts (7.5–10% each) of the cleavage products, ArCHO and ArCOOH. No detectable amount of either of these two cleavage products was observed in any of the diarylacetylene oxidations. The ketones derived by hydration of mono- and dialkylacetylenes would have been major products of the TTN oxidation experiments if they had been formed, since independent experiments established that their subsequent oxidation under the reaction conditions employed was extremely slow (relative to the rate of TTN oxidation of the acetylenes). Again, such ketones were not observed as products of the TTN oxidation experiments. From these results it is evident that thallium(III) salts, and in particular TTN, are inefficient catalysts in the hydration of $C\equiv C$ bonds.

There is thus little similarity between the reactions of mercury(II) and thallium(III) salts with acetylenes. This is most probably attributable to the ease with which C–Tl bonds undergo heterolysis to form carbonium ion and possibly vinyl cation intermediates. Heterolysis of the stronger C–Hg bond does not occur spontaneously and, while the mechanism of the mercury(II) salt-catalyzed hydration of acetylenes is not known, there is evidence that the initial oxymercuration adducts decompose by pathways involving initial acid-catalyzed cleavage of the C–Hg bond.[33]

Experimental Section

Melting points were determined on a Kofler hot-stage melting point apparatus and are uncorrected. Where appropriate, identity of compounds was confirmed by comparison of ir spectra, determined by the normal Nujol mull or liquid film techniques on Perkin-Elmer Model 257 and 237 B grating infrared spectrophotometers, and nmr spectra, determined as solutions in carbon tetrachloride using tetramethylsilane as internal standard on Perkin-Elmer R12 and Varian A-60 instruments. Glpc analyses were performed using Perkin-Elmer Models PE 452 and F11 gas chromatographs equipped with 1-m Apiezon L and 50-m PPG columns, respectively, and with an Aerograph A90-P3 instrument equipped with a 30 ft × $^3/_8$ in. column with 30% QF-1 on 45–60 Chromosorb W.

Starting Materials. Compounds **14**, **25**, and **26** were commercially available and were purified prior to use. The following compounds were prepared by literature procedures: **15**,[17,34] **16**,[17] **17**,[17] **18**,[17] **19**,[17,35] **22**,[17,36] **23**,[17,37] **24**,[38] **27**,[39] **28**,[39] **29**,[40] **30**,[41] **31**,[42] 4-methylphenylacetylene,[43] 4-methoxyphenylacetylene,[44] 4-nitrophenylacetylene,[45] and benzil mono(dimethyl)ketal.[22]

General Procedure for the Oxidation of Diarylacetylenes with TTN–Glyme–Perchloric Acid. A solution of 0.01 mol of the diarylacetylene in 20 ml of glyme was added to a solution of 8.9 g (0.02 mol) of TTN in 10 ml of water containing 5 ml of 70% perchloric acid, and the reaction mixture was heated gently under reflux for 2–7 hr (see Table I). After cooling, thallium(I) nitrate was removed by filtration and the filtrate diluted with 100 ml of water. The mixture was extracted with chloroform (2 × 25 ml), the extracts were dried (Na_2SO_4) and concentrated, and the crude product was freed from traces of inorganic thallium salts by passage through a short column of acid-washed alumina (2 × 10 cm) using benzene–chloroform (1:1) as eluent. Evaporation of the eluate gave the crude benzil, which was purified by crystallization or distillation.

Preparation of Benzil Mono(dimethyl)ketal by Oxidation of Diphenylacetylene with TTN–CH_3OH. Diphenylacetylene (7.2 g, 0.04 mol) was added to a solution of 35 g (0.08 mol) of TTN in 250 ml of anhydrous methanol containing molecular sieves, and the dark brown mixture was heated under reflux for 2.5 hr. Removal of thallium(I) nitrate from the cooled reaction mixture by filtration gave a pale yellow solution which was diluted with water and extracted with benzene. The extracts were dried (Na_2SO_4) and evaporated, and the residue was distilled to give 6.4 g (65%) of a pale yellow oil, bp 132–136° (0.03 mm), which, by glpc, was pure benzil mono(dimethyl)ketal. Trituration of the oil with petroleum ether (bp 40–60°) gave the ketal as a colorless solid, mp 60–61° (lit.[22] mp 63–64°) whose ir, nmr, and glpc spectra were identical with those of a genuine sample.[22]

Oxidation of *cis*-Stilbenediol Dimethyl Ether. A mixture of 1 g (0.0042 mol) of the ether and 3 g (0.0067 mol) of TTN in methanol was heated under reflux for 1 hr. After the reaction mixture had cooled, thallium(I) nitrate was removed by filtration and the filtrate diluted with water. Extraction with chloroform followed by drying (Na_2SO_4) and evaporation of the extracts gave a pale yellow liquid from which a colorless solid separated on trituration with petroleum ether (bp 40–60°). Filtration gave 0.40 g (37%) of pure benzil mono(dimethyl)ketal. Glpc examination of the initial crude reaction mixture showed it to consist of benzil mono(dimethyl)ketal and benzil, the former product being present in 75% overall yield from *cis*-stilbenediol dimethyl ether.

General Procedure for the Oxidation of Dialkylacetylenes with TTN–Glyme–Perchloric Acid. TTN (0.011 mol) was added to a stirred solution of 0.011 mol of the alkyne in 25 ml of glyme, 10 ml of water, and 5 ml of 70% perchloric acid. After the initial vigorous reaction had subsided the mixture was stirred at room temperature for 30 min, the thallium(I) nitrate removed by filtration, and the filtrate diluted with 100 ml of water. The crude acyloins, con-

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taminated by small amounts of the corresponding α-diketones, were isolated in the same manner as described above for the benzils.

Oxidation of 3-Hexyne with Thallium(III) Nitrate–CH_3OH–Perchloric Acid. A solution of 0.82 g (0.01 mol) of 3-hexyne in 5 ml of methanol was added to a stirred solution of 8.9 g (0.02 mol) of TTN in 25 ml of methanol and 5 ml of 70% perchloric acid. An exothermic reaction ensued, thallium(I) nitrate precipitated after a few seconds, and the reaction mixture turned pale yellow in color. Stirring was continued for 30 min at room temperature, the thallium(I) nitrate was then removed by filtration, and the filtrate was diluted with water and dichloromethane. The dichloromethane layer was separated, dried (Na_2SO_4), and carefully evaporated at 25° to leave a pale yellow oil. Distillation gave 0.90 g (70%) of slightly impure (purity *ca.* 95%) 4-methoxy-3-hexanone, bp 52–56° (11 mm) (lit.[46] bp 62–63° (40 mm)). The impurities present were shown by glpc, using genuine samples as both internal and external standards, to be 4-hydroxy-3-hexanone and hexane-3,4-dione.

The same conversion could be carried out in 85% yield by using thallium(III) acetate rather than TTN.

General Procedure for the Oxidation of Terminal Alkylacetylenes with TTN-Glyme–Perchloric Acid. The terminal acetylene (0.01 mol) was added to a stirred solution of 0.02 mol of TTN in 25 ml of glyme, 15 ml of water, and 8 ml of 70% perchloric acid and, after the initial vigorous reaction had subsided, the yellow reaction mixture was stirred at room temperature for a further hour. Complete removal of all of the thallium(I) salt was ensured by addition of 15 ml of 2 *N* potassium iodide solution, followed by stirring for a further 20 min. The inorganic salts were removed by filtration, and the filtrate was diluted with water and extracted with benzene. The extracts were dried (Na_2SO_4) and evaporated, and the residual oil was esterified by heating at 50° for 2 hr with 40 ml of methanol containing 5 ml of 70% perchloric acid. The cooled reaction mixture was diluted with water, and extracted with benzene, and the extracts were concentrated and distilled to give the ester. Methyl heptanoate was obtained in 80% overall yield in this way from 1-octyne, and methyl hexanoate in 55% overall yield from 1-heptyne.

Oxidation of 1-Hydroxyoctan-2-one with TTN–CH_3OH. 1-Hydroxyoctan-2-one was prepared by the general procedure of Pfeil and Barth[29] from glycolonitrile (10.0 g, 0.175 mol) and *n*-hexylmagnesium bromide (from 70 g, 0.425 mol, of *n*-hexyl bromide and 10.0 g, 0.42 g-atom, of magnesium turnings). Distillation of the reaction product gave a fraction of bp 57–62° (0.4 mm) weighing 13.6 g (54%), identified as 1-hydroxyoctan-2-one (lit.[47] bp 70–76° (6 mm)).

To a solution of 1.44 g (0.01 mol) of 1-hydroxyoctan-2-one in 30 mol of methanol was added 4.44 g (0.01 mol) of TTN. Thallium(I) nitrate separated rapidly after a few seconds. The reaction mixture was stirred at room temperature for 1 hr and filtered, and the filtrate was diluted with water and extracted with chloroform (2 × 20 ml). The chloroform extracts were chromatographed on a short alumina column (2 × 10 cm), using benzene as eluent, to give 1.10 g (76%) of a sweet-smelling liquid identified as methyl heptanoate by comparison of its glpc retention time with that of an authentic sample. An attempt to trap formaldehyde formed in this reaction by means of reaction with dimedone was unsuccessful, probably owing to complexation of the dimedone with Tl(I) and/or Tl(III).

General Procedure for the Oxidative Rearrangement of Alkylarylacetylenes with TTN–CH_3OH. The alkyne (0.01 mol) was added to a stirred solution of 4.88 g (0.011 mol) of TTN in 25 ml of methanol, and the mixture was heated under reflux for 2 hr. Thallium(I) nitrate was removed from the cooled reaction mixture by filtration, and the filtrate was extracted with ether or chloroform. The extracts were washed with water and 5% aqueous sodium bicarbonate solution and dried (Na_2SO_4). The solution was then filtered through a short column of Florisil (10 g) using chloroform as eluent; evaporation of the eluate gave the methyl α-alkylarylacetate which, in every case, was shown to be pure at this stage by glpc.

Acknowledgment. One of us (B. P. S.) is grateful for the receipt of an S.R.C. Scholarship.

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Use of the Vanadyl(IV) Ion as a New Spectroscopic Probe of Metal Binding to Proteins. Vanadyl Insulin[1a,b]

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Abstract: This study was undertaken to investigate the potential use of vanadyl ion, VO^{2+}, as a physicochemical marker of metal binding sites in proteins. VO^{2+} was substituted for Zn^{2+} in rhombohedral bovine insulin crystals, and the metal binding was characterized by the epr, optical, and infrared spectra of the protein bound VO^{2+}. Two types of binding sites, A and B, were found. The A sites are identical with the two sites in the zinc insulin hexamer in which the metal is bound to three imidazole groups of B10 His residues, and the B sites are the 24 carboxyl groups of the 24 Glu residues per hexamer. The coordination geometry about the VO^{2+} ion in both A and B sites was determined. In general, the binding in VO^{2+} insulin parallels that in Zn^{2+} insulin. This approach to studying metal binding should be applicable to other proteins as well.

Numerous proteins have metal ions as an integral part of their structure and in some cases these ions provide a convenient spectrochemical probe of molecular structure and enzyme kinetics. There are, however, a large number of proteins which require Zn^{2+} or Mg^{2+} ions as structurally or functionally essential constituents, but these ions provide only limited means by which to extract information about their coordination

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(1) (a) Supported by the National Institutes of General Medical Sciences Grant GM 20194-01, the Petroleum Research Fund of the American Chemical Society, National Science Foundation Grants GP11387 and GP28215, and the National Science Foundation Undergraduate Research Participation and College Science Improvement Programs. (b) A preliminary account of this work was presented at the Rocky Mountain Regional Meeting of the American Chemical Society, Fort Collins, Colo., June 30–July 1, 1972. (c) Send correspondence to this author at the Department of Chemistry, University of New Hampshire, Durham, N. H. 03824. (d) Lawrence University. (e) NSF-COSIP participant, 1971. (f) NSF-URP participant, 1971. (g) University of Colorado.