APPLICATIONS OF THALLIUM(III) NITRATE (TTN) TO ORGANIC SYNTHESIS

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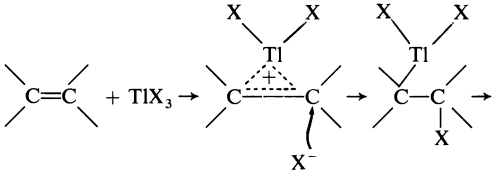
ABSTRACT

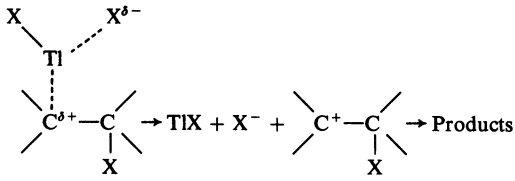
The scope and utility of thallium(III) nitrate (TTN) as an oxidant in organic synthesis is reviewed. Reactions which are described are the oxidations and oxidative rearrangements of olefins, acetylenes, ketones and compounds containing carbon–nitrogen double bonds. The effects of solvent on TTN oxidations are discussed, and the use of TTN/trimethyl orthoformate for the oxidative rearrangement of α,β-unsaturated carbonyl compounds is outlined. Preliminary investigations into TTN/support systems are described and their application to the oxidative rearrangement of alkyl aryl ketones is illustrated.

INTRODUCTION

Thallium and its derivatives exhibit some unusual and some unique properties, and these have been systematically exploited and applied to organic synthesis during the last few years[1]. Thallium differs from the other Group IIIB metals (B, Al, Ga, In) in that stable derivatives are known of both the + 1 and the + 3 valence states: inorganic thallium compounds are generally more stable in the + 1 valence state, while covalent organothallium compounds are stable only in the +3 valence state. Perhaps the most interesting and useful aspect of thallium chemistry, however, is the ease with which transitions occur between the two oxidation levels, and especially the great facility with which thallium(III) undergoes reduction to thallium(I). It is with this particular thermodynamically favourable valence change that I shall be concerned during the following discussion, and my objective is to illustrate some of the synthetically useful transformations which are based upon it.

Inorganic thallium(III) salts are Lewis acids and can react as typical electrophiles with unsaturated organic substrates such as olefins:





The organothallium compounds thus formed in the addition reaction are, however, unstable and highly reactive intermediates which undergo rapid decomposition via C—Tl bond heterolysis to give a thallium(I) salt, TlX, and carbonium ions or carbonium ion-like species, the ultimate fate of which depends upon the nature of X, the structure of the organic substrate and the reaction conditions, especially the solvent. Of these various parameters, however, the nature of X is perhaps the most important. For example, thallium(III) chloride is largely covalent and poorly electrophilic; it does not therefore react at all readily with olefins and is a poor oxidant. Thallium-(III) nitrate (TTN), on the other hand, is highly ionic and powerfully electrophilic, and reacts almost instantaneously with a wide range of olefins.

TTN is the subject of the present dicussion and the reagent with which we have worked for some years. It is the reagent of choice for oxidation of many organic functional groups, not only because it is highly electrophilic, but because:

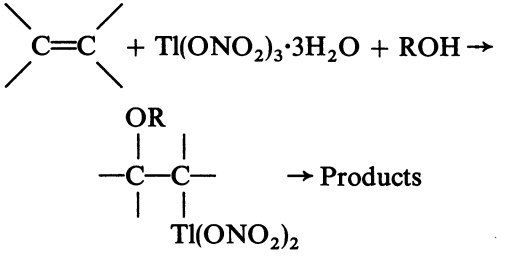
(1) It can be prepared easily and rapidly in almost quantitative yield simply by dissolving thallium(III) oxide in nitric acid:

$$Tl_2O_3 + 6\,HNO_3 \rightarrow 2\,Tl(ONO_2)_3{\cdot}3H_2O$$

(2) It is a stable, crystalline solid which can be stored in sealed bottles for many months without any appreciable decomposition.

(3) It is freely soluble in a wide range of inorganic and organic solvents, whereas its reduction product formed during reaction, thallium(I) nitrate, is insoluble in almost all common solvents and thus precipitates from solution.

(4) The nitrate ion is poorly nucleophilic. Consequently, if reactions are carried out in nucleophilic solvents such as water, alcohols or acids, it is the solvent, and not the nitrate ion, which is incorporated into the organic molecule:



In the following discussion I shall review the reactions of TTN with non-aromatic, unsaturated substrates, specifically olefins, ketones, acetylenes and compounds containing carbon–nitrogen double bonds, and describe

some of the synthetic transformations that have been discovered thus far. I shall then show how the choice of solvent can have a profound effect, not only on the rate, but also on the overall course of reaction and illustrate the type of changes possible by reference to the TTN/trimethyl orthoformate system. Finally, I shall mention some recent work on the use of TTN on supports such as florisil.

OXIDATIONS OF OLEFINS

A solution of TTN in methanol is a convenient reagent for the direct oxidative rearrangement of many olefins to aldehydes and ketones[2]. Most reactions are complete within a few minutes at room temperature, and isolation of pure products in high yield is a simple process. Thus, oxidation of cyclohexene gives initially cyclopentanecarboxaldehyde dimethyl acetal, from which the free aldehyde may readily be obtained in excellent yield by normal acid hydrolysis. The mechanism of this transformation is outlined in *Figure 1*: that is, initial trans oxythallation of the double bond by methanol and TTN followed by heterolysis of the C—Tl bond and simultaneous ring contraction. Acetic acid and various dilute mineral acids can be used equally

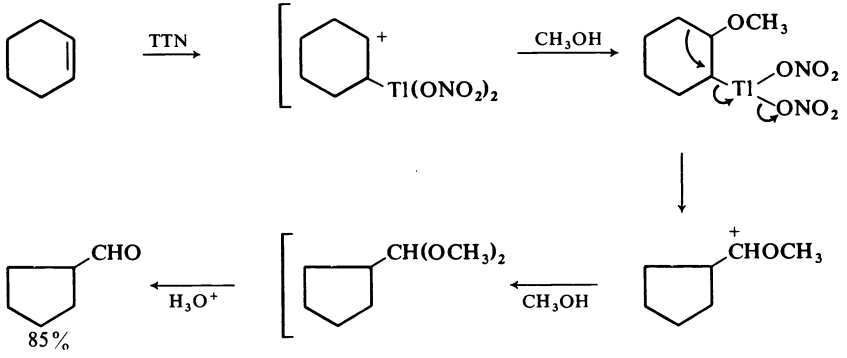


Figure 1

effectively as solvents in these oxidations, and yields of rearranged products are almost quantitiative when an activated aromatic ring is the migrating group (*Figure 2*).

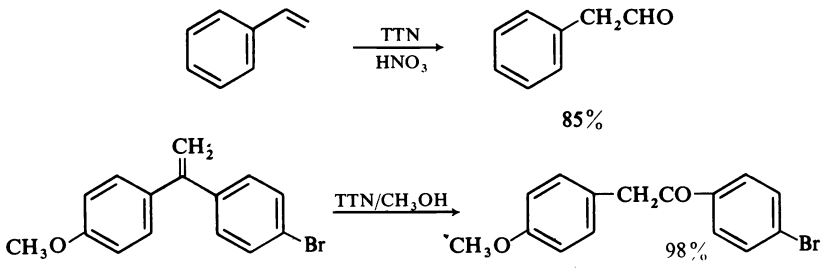


Figure 2

The oxidative rearrangement of a wide range of olefins by TTN has now been studied in some detail, and no serious limitations with respect to other functional groups have been reported. Three examples from the recent literature are shown in *Figure 3*, the oxidative rearrangement of elemol to 4-acetoxybulnesol constituting a particularly elegant demonstration of the

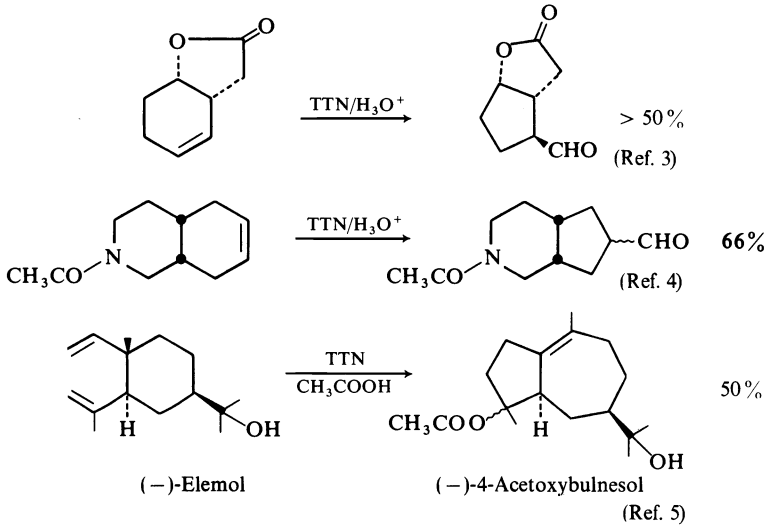


Figure 3

utility of TTN for the preparation of otherwise difficultly accessible compounds from materials which are readily available.

Carbonyl compounds which enolize under acidic conditions are also readily oxidized by TTN. Thus, treatment of aryl methyl ketones with TTN in methanol results in smooth oxidative rearrangement and formation of the corresponding methyl arylacetates in excellent yield[6]:

$$ArCOCH_3 + TTN/CH_3OH \rightarrow \underset{35\text{–}91\,\%}{ArCH_2COOCH_3} + TlONO_2$$

and the mechanism of this reaction is outlined in *Figure 4*. Kenner, Smith and

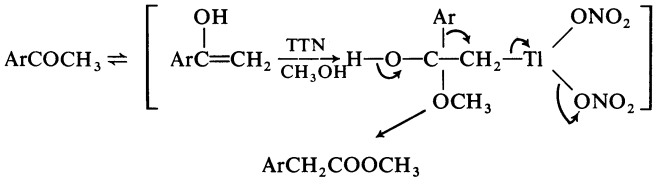


Figure 4

Unsworth have recently utilized this reaction for the preparation of a key pyrrole intermediate in the synthesis of porphobilinogen (*Figure 5*)[7].

Oxidation of cyclohexanones by TTN in acetic acid similarly proceeds

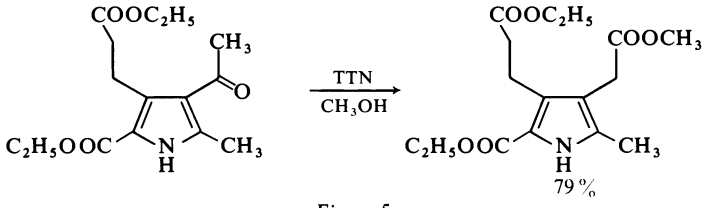


Figure 5

via initial enolization; the products formed, however, depend on the isolation procedure employed[8]. If oxidation is allowed to proceed until all of the TTN is consumed and the reaction mixture then treated with dilute base, acyloins are obtained in high yield. If, on the other hand, the acidic reaction medium is gently heated for a few minutes, the corresponding cyclopentanecarboxylic acids are obtained (*Figure 6*). This latter transformation has been

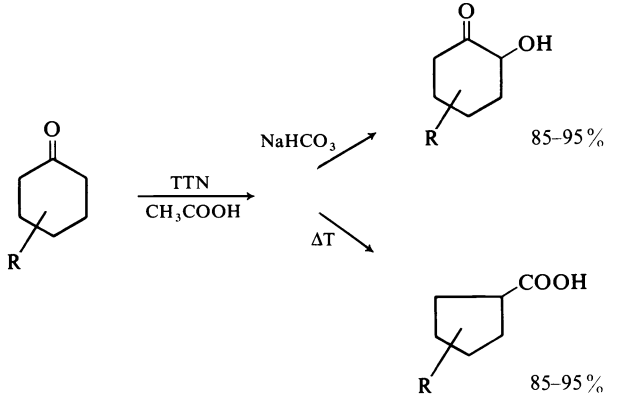


Figure 6

used by Romeo and Ortar for the preparation of 2-α-carboxy-A-norsteroids (*Figure 7*)[9]. There is no definitive evidence on the mechanisms of these trans-

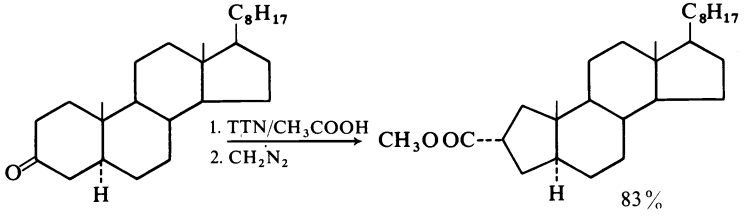


Figure 7

formations; the reaction sequence that has been proposed (*Figure 8*) is enolization, hydroxythallation and subsequent intramolecular nucleophilic displacement of the thallium substituent to give the intermediate (I), from which the final products are derived.

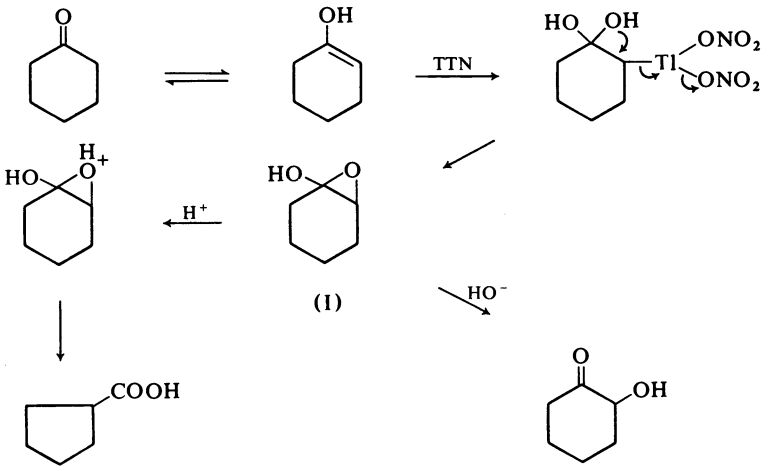


Figure 8

Finally, within this context, treatment of chalcones with three equivalents of TTN in aqueous acid results in smooth conversion into the corresponding benzils[10]:

$$ArCH{=}CHCOAr' + 3\ TTN/H_3O^+ \rightarrow ArCOCOAr'$$
$$44\text{–}70\%$$

Three distinct oxidation steps are involved, one carbon atom is lost and the over-all mechanism is outlined in *Figure 9*. Oxidative rearrangement

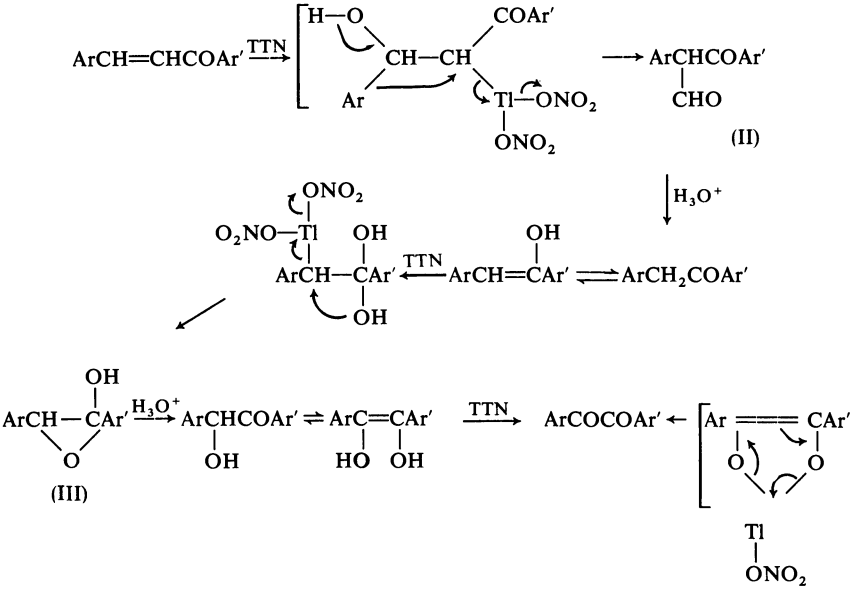


Figure 9

of the chalcone gives the β-aldehydo ketone (II), which, under the acidic reaction conditions, undergoes retro-Claisen condensation and gives the corresponding deoxybenzoin. Acid-catalysed enolization of this latter intermediate followed by hydroxythallation and intramolecular displacement of the thallium substituent leads to the α-hydroxyepoxide (III), hydrolysis of which gives a benzoin. Oxidation of the benzoin via the ene–diol tautomer then gives the benzil.

OXIDATIONS OF ACETYLENES

Thallium(III) is isoelectronic with mercury(II) and might therefore be expected to catalyse the hydration of acetylenes. We have examined the reactions of diarylacetylenes, alkylarylacetylenes, dialkylacetylenes and monoalkylacetylenes with TTN under various conditions and found that, while smooth oxidation is observed with each type of acetylene, hydration of the C≡C bond does *not* take place[11]. Thus, oxidation of diarylacetylenes requires two equivalents of TTN, and benzils are obtained in good yield:

$$ArC{\equiv}CAr' + 2\ TTN/H_3O^+ \rightarrow \underset{45\text{–}97\%}{ArCOCOAr'}$$

Hydroxythallation of the C≡C bond leads to the enolic intermediate (IV) (*Figure 10*); displacement of the thallium substituent from the correspond-

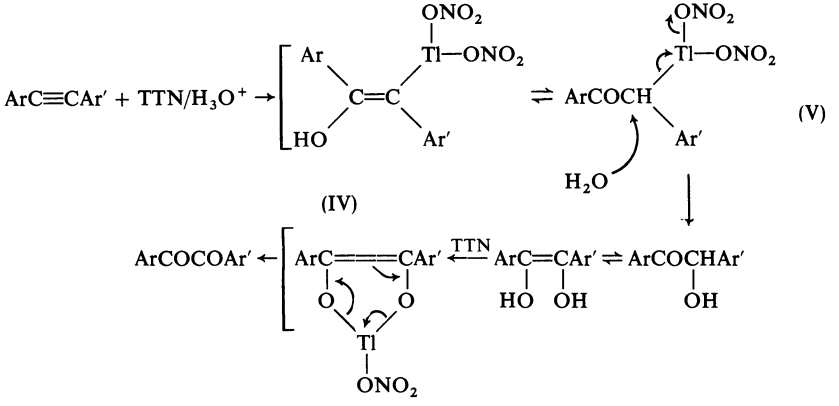


Figure 10

ing keto tautomer (V) probably proceeds via an S_N2 type of reaction rather than by initial heterolysis of the carbon–thallium bond, as this latter process would necessitate the generation of positive charge on a carbon atom adjacent to an already electropositive centre. Displacement of the thallium substituent results in formation of a benzoin, which is oxidized to the corres-

ponding benzil by the second equivalent of TTN in exactly the same way as was described above (see *Figure 9*).

A similar type of reaction is observed with dialkylacetylenes; that is, hydroxythallation, ketonization of the initially formed enolic organothallium intermediate, and S_N2 type displacement of the thallium substituent (*Figure 11*).

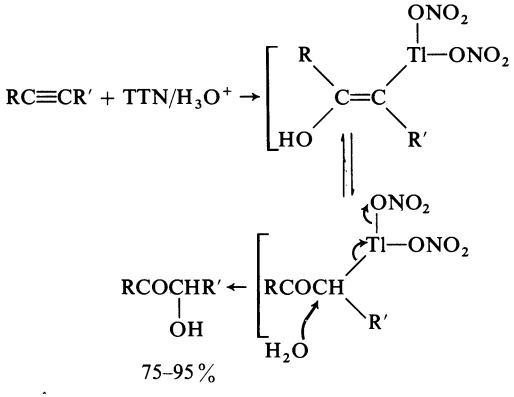


Figure 11

Unlike benzoins, however, simple dialkyl acyloins show little tendency to enolize under acidic conditions, and hence the oxidation can easily be stopped at the acyloin stage. It is, however, more difficult to control the reactions of monoalkylacetylenes with TTN and the intervention of a second, rapid oxidation step results in overall cleavage of the C≡C bond and formation of carboxylic acids (*Figure 12*). Thus, the α-hydroxy ketone

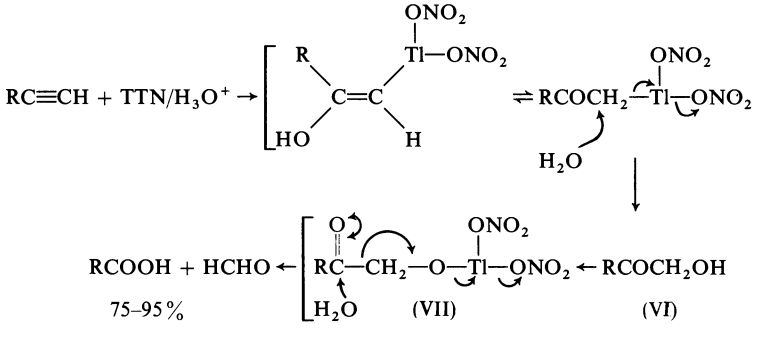


Figure 12

(VI) which is formed by a similar sequence of reactions to those outlined in *Figures 10* and *11* undergoes ligand exchange with TTN to generate the mixed salt (VII), fragmentation of which leads to the observed products.

The reactions of alkylarylacetylenes with TTN are quite different from those of the other types of acetylenes. Oxidation with TTN in aqueous acid

gives a complex mixture of products, but when methanol is employed as solvent, smooth oxidative rearrangement occurs, and methyl α-alkylarylacetates are formed in excellent yield:

$$ArC{\equiv}CR + TTN/CH_3OH \rightarrow \underset{78\text{–}98\%}{ArCH(R)COOCH_3}$$

In this case, the intermediate oxythallation adduct cannot ketonize, and displacement of the thallium substituent proceeds with concomitant 1,2-aryl migration (*Figure 13*).

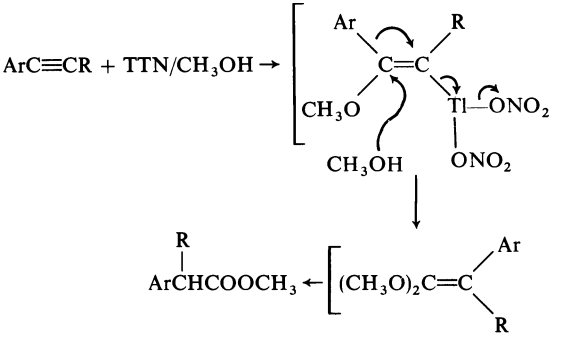


Figure 13

OXIDATIONS OF COMPOUNDS CONTAINING C=N BONDS

The reactions of compounds containing C=N bonds with electrophiles are seldom straightforward and simple addition reactions, for example, are not common. Relatively little research has been reported in this area so far with respect to TTN; the following examples, however, indicate the potential utility of TTN as an oxidant for substrates which contain C=N bonds.

Treatment of oximes with TTN in methanol results in virtually instantaneous deoximation and formation of the parent carbonyl compounds in

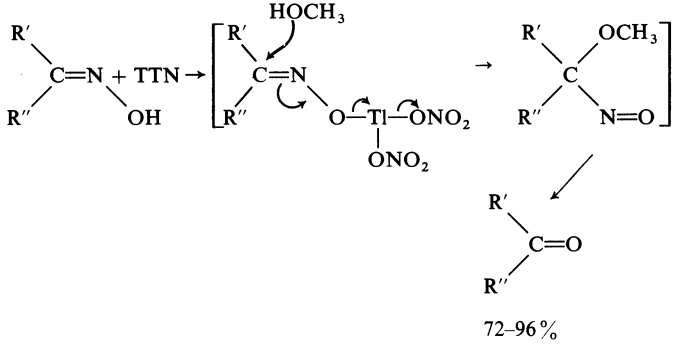


Figure 14

very high yield, probably via the transesterification reaction shown in *Figure 14*[12]. Semicarbazone and phenylhydrazone derivatives react analogously.

Incorporation of the C=N bond into a ring system leads to a totally different type of reaction. Thus, 5-pyrazolones—which are readily prepared in quantitative yield from hydrazine and β-keto esters—are converted into the methyl esters of α,β-acetylenic acids on treatment with TTN in methanol (*Figure 15*)[13]. This reaction is believed to involve thallation (i.e. substitution)

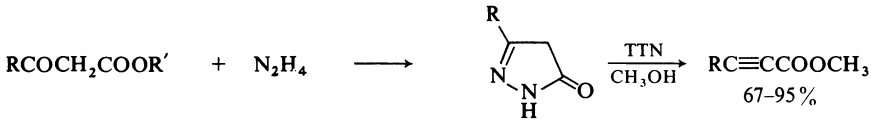


Figure 15

of the pyrazolone ring by TTN to give the intermediate organothallium derivative (VIII) as shown in *Figure 16*. Oxidation of the hydrazino group

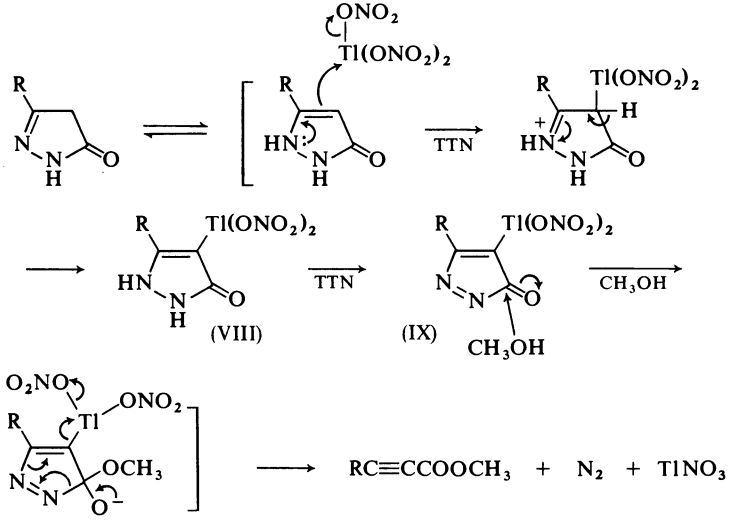


Figure 16

in (VIII) by a second equivalent of TTN gives the diazacyclopentadienone (IX), which undergoes complete fragmentation as shown to yield the observed products.

β-Keto esters which are alkylated at the α-position are converted under the same conditions—treatment with hydrazine followed by addition of TTN and methanol—into the corresponding allenic esters (*Figure 17*)[14]. Formation of the allene is due to the fact that there is no longer a hydrogen atom at the 4-position of the pyrazolone in the intermediate thallation

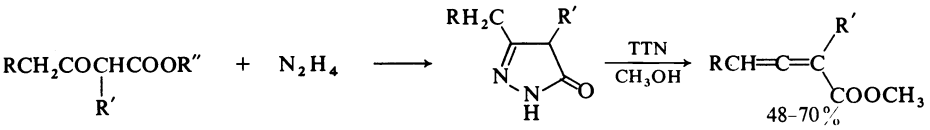


Figure 17

product (X), and, hence, deprotonation occurs from the 3-substituent (*Figure 18*). One particularly useful application of this reaction is to the

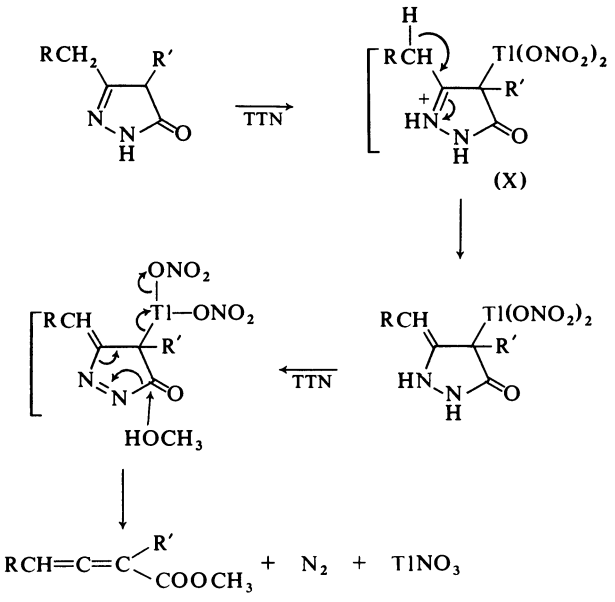


Figure 18

synthesis of carbocyclic allenic esters, as illustrated in *Figure 19*[15].

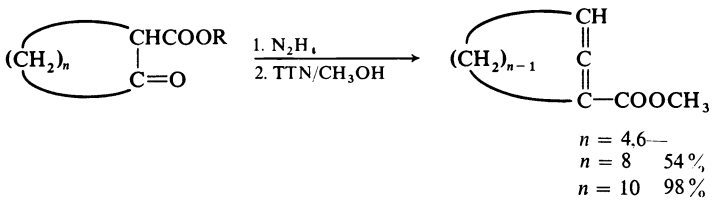


Figure 19

OXIDATIONS BY TTN IN TRIMETHYL ORTHOFORMATE

As mentioned earlier, choice of solvent can have a profound effect on TTN oxidations. This can be illustrated with reference to trimethyl orthoformate, which is not a commonly used solvent in preparative organic chemistry. Its application to TTN oxidations originated in the studies carried

out on the oxidation of chalcones. As outlined in *Figure 9*, the initial product of oxidative rearrangement of chalcones is the β-aldehydo ketone (II), which undergoes rapid retro-Claisen condensation to give a deoxybenzoin. Compounds of the type (II), which are not readily accessible by other means, are potentially useful intermediates for the synthesis of many carbocyclic and heterocyclic systems, and hence the reaction conditions for the chalcone rearrangement were varied in attempts to prevent the retro-Claisen reaction from occurring. No completely satisfactory method could be found, but use of TTN in methanol containing boron trifluoride did lead to the corresponding acetals in acceptable yields in certain cases:

$$ArCH{=}CHCOAr' + TTN/CH_3OH/BF_3 \rightarrow \underset{\underset{\underset{25\text{–}80\%}{|}}{CH(OCH_3)_2}}{ArCHCOAr'}$$

and this general technique has been applied by Nógrádi to the synthesis of a variety of isoflavanoids (*Figure 20*)[16].

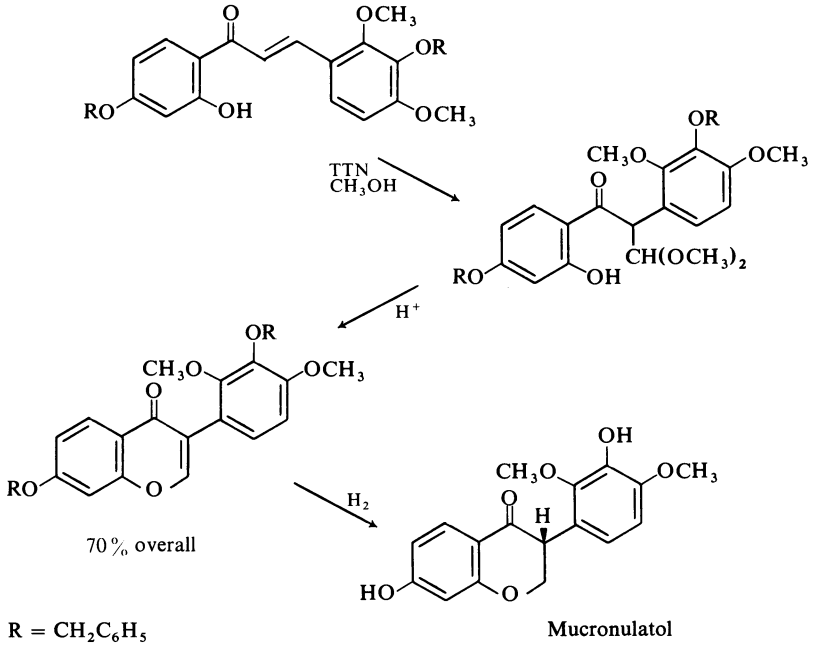


Figure 20

Compared with other TTN oxidations, however, isolation of pure products from these reactions is tedious. The water of crystallization in TTN reacts with the solvent system and with the acetals, and complex mixtures of products are usually obtained. Attempts to avoid these complications due to water were concentrated on efforts to obtain anhydrous TTN; various classical methods for the removal of water of crystallization were examined,

but none of them proved successful. Hence, trimethyl orthoformate was employed:

$$Tl(ONO_2)_3 \cdot 3\,H_2O + 3\,HC(OCH_3)_3 \rightarrow Tl(ONO_2)_3 + 6\,CH_3OH + 3\,HCOOCH_3$$

TTN dissolves readily in trimethyl orthoformate; the resultant, stable solutions contain TTN, methanol—which is the desired nucleophile for most reactions—and methyl formate, which does not interfere with any of the reactions and which can, if required, readily be removed by evaporation under reduced pressure.

Oxidations with TTN/trimethyl orthoformate are very much faster than oxidations with TTN/methanol. Moreover, TTN in trimethyl orthoformate is an excellent medium for the conversion of aldehydes and ketones into the corresponding dimethyl acetals and ketals. Consequently, while there is little practical advantage in utilizing the trimethyl orthoformate system for oxidation of simple olefins which react satisfactorily with TTN/methanol, it is an ideal reagent for the oxidation of α,β-unsaturated carbonyl compounds, with which TTN in methanol reacts slowly and inefficiently.

Thus, chalcones are smoothly converted into the corresponding β-aldehydo ketone dimethyl acetals in excellent yield[17]:

$$ArCH{=}CHCOAr' + TTN/HC(OCH_3)_3 \rightarrow ArCH\begin{matrix}COAr' \\ \\ CH(OCH_3)_2\end{matrix}$$

58–98%

and the mechanism of this transformation is outlined in *Figure 21*. Ketaliza-

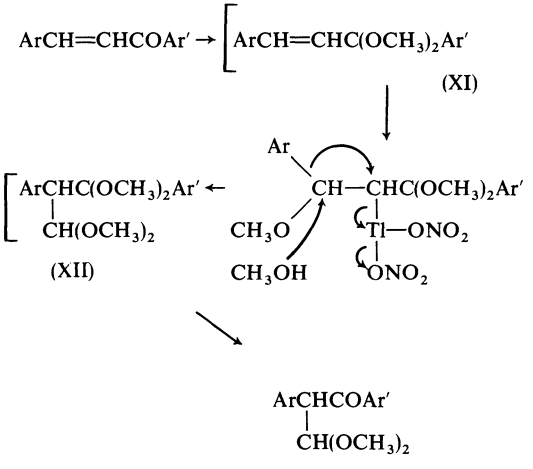
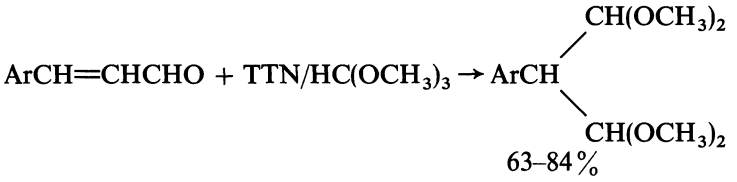


Figure 21

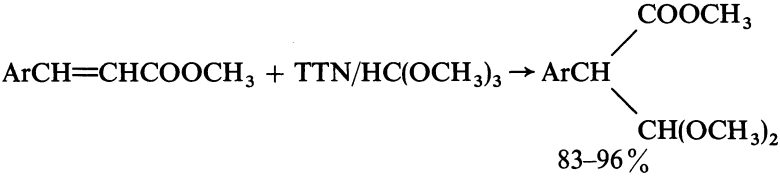
tion of the chalcone by trimethyl orthoformate gives (XI), the double bond of which is considerably more nucleophilic than that of the parent chalcone.

Hence, oxidative rearrangement of the olefinic double bond takes place rapidly to give the acetal–ketal (XII); preferential hydrolysis of the ketal group during the isolation procedure gives the observed product.

Analogous reactions occur with other types of α,β-unsaturated carbonyl compounds. Thus, cinnamaldehydes undergo smooth oxidative rearrangement to give phenylmalonaldehyde bis-dimethyl acetals[18]:



while cinnamic esters are converted into the corresponding β-aldehydo ester dimethyl acetals[17]:



Not all of the TTN/trimethyl orthoformate reactions follow the expected course, however. Thus, while aryl methyl ketones are converted into methyl arylacetates on treatment with TTN in acidic methanol, oxidation with TTN/trimethyl[18] orthoformate gives methyl α-methoxyarylacetates in excellent yield (*Figure 22*). Moreover, it can easily be shown that methyl

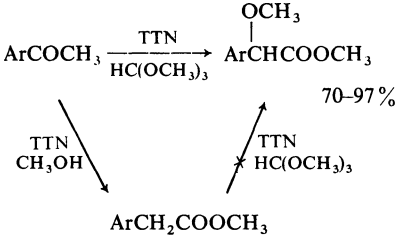


Figure 22

arylacetates are not formed as intermediates in the trimethyl orthoformate reaction, as they are inert to the reagent under the same reaction conditions. The mechanism outlined in *Figure 23* has been proposed for this reaction; that is, ketalization of the methyl ketone followed by elimination of methanol and formation of a methoxystyrene. Oxidative rearrangement of this latter intermediate by TTN gives the *ortho* ester (XIII), which can lose methanol to yield the dimethoxystyrene (XIV). Oxythallation of (XIV) followed by S_N2 displacement of the thallium substituent by methanol yields the α-methoxy *ortho* ester (XV), from which the observed final product is formed on hydrolytic work-up of the reaction mixture.

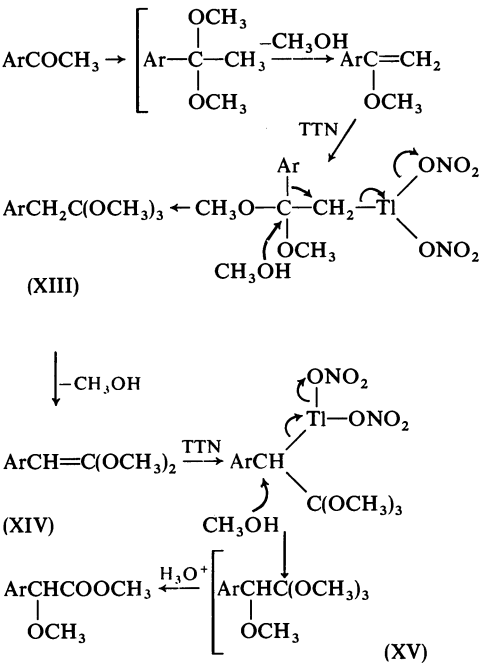


Figure 23

OXIDATIONS BY TTN/SUPPORT SYSTEMS

There has been considerable interest during the last few years in polymer-bound reagents and in reagents adsorbed on various supporting materials. We have recently begun to investigate the possibility of utilizing TTN/support systems for some of the oxidations described above, and initial results confirm that, at least for certain reactions, use of such systems offers distinct advantages over the use of TTN in methanol solution. Reactions are generally much cleaner and often faster, and isolation of pure products uncontaminated by inorganic salts is extremely simple.

The essential features of these reactions can be illustrated with reference to the oxidative rearrangement of alkyl aryl ketones to methyl arylacetates. Using acetophenone as standard substrate, the relative activity and efficiency of various TTN/support systems have been examined and the results are summarized in *Table 1*[19]. From these data it can be seen that TTN/florisil is the reagent of choice for this transformation.

These reactions are experimentally very simple. The reagent is prepared by mixing florisil, TTN, methanol and trimethyl orthoformate (the latter reagent to remove the water of crystallization from TTN); oxidation is effected by adding the supported reagent to a solution of acetophenone in carbon tetrachloride and stirring the mixture at room temperature; and isolation of the product consists merely in filtration to remove the inorganic salt/support and evaporation of the filtrate. In this way, acetophenone can

Table 1. Oxidative rearrangement of acetophenone by TTN/support

Support	$TTN/C_6H_5COCH_3$	Time, h	% Reaction	$\frac{C_6H_5CH_2COOCH_3}{C_6H_5COCH_2OCH_3}$
Celite	2	1	100	100/0
	1.5	1	95	96/4
Alumina (neutral)	2	0.5	100	95/5
	1.2	0.5	100	95/5
	1.2	0.25	85	95/5
Alumina (basic)	1.2	0.25	100	92/8
Charcoal	1.2	0.5	~ 10	—
Florisil	1.2	0.5	100	100/0
	1.2	0.25	98	100/0

be smoothly and rapidly converted into methyl phenylacetate in virtually quantitative yield. Moreover, the TTN/florisil system is apparently much more reactive than the TTN/methanol reagent, as can be seen from the conversions in *Figure 24*[19]. Consequently, it is confidently anticipated that

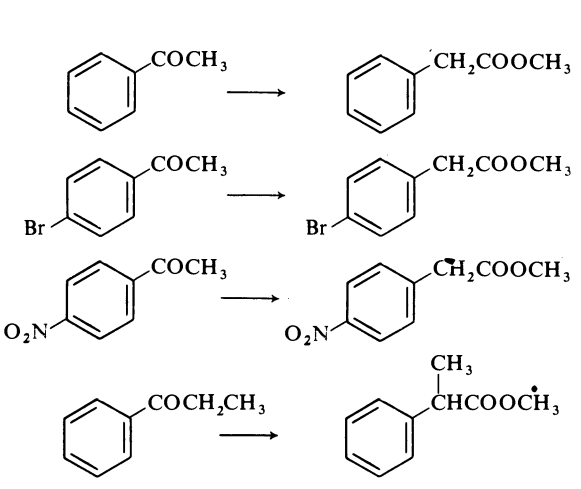


Figure 24

further research into the use of TTN/support systems will enhance considerably the scope of TTN as an oxidant for organic substrates.

SUMMARY

The applications of TTN to organic synthesis that are discussed above illustrate the utility and versatility of this remarkable reagent. The outstand-

ing features of the reactions described are their manipulative simplicity and the formation of pure products in high yield under mild conditions.

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