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# OXIDATIVE REARRANGEMENT OF α-METHOXYSTYRENE DERIVATIVES WITH THALLIUM(III) SALTS: SYNTHESIS OF 2-ARYL ALKANOIC ACIDS

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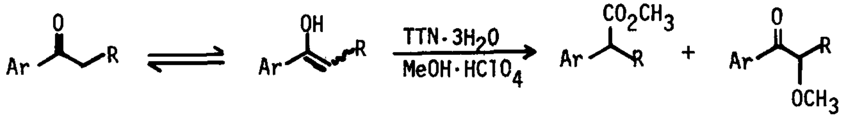
In 1971, the oxidative rearrangement of acetophenones to methyl phenyl acetates with thallium(III) nitrate ($TTN \cdot 3H_2O$) in methanol-perchloric acid was reported.[1] The oxidation of propiophenone was much less selective under the described conditions and gave rise to substantial amounts of α-oxidation product (III).[2]

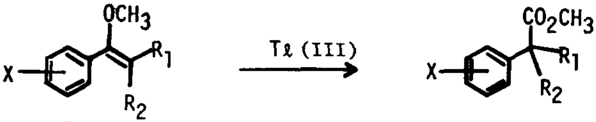


I II III

| | | | |
|---|---|---|---|
| I | | II | III |
| a) R = H, Ar = phenyl | 84% | (94:6 ) | |
| b) R = $CH_3$, Ar = phenyl | 45% | (58:42) | |
| c) R = $CH_3$, Ar = p-isobutylphenyl | - | (51:49) | |

More recently, however, the use of TTN in trimethylorthoformate (TMOF)-methanol[3,4] or "anhydrous TTN" ($TTN \cdot 3CH_3OH$) on a solid support[4,5] have been reported to allow high conversion of I (R = alkyl) to II with the virtual exclusion of III. The results of the former study suggested that in TMOF the reaction might proceed *via in situ* formation and oxidation of the methyl enol ether derivative of the ketone.[6]

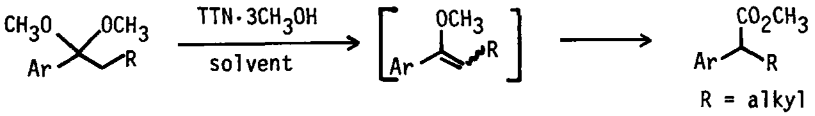
We would like to report some of our findings which substantiate the intermediacy of enol ethers in these transformations. Furthermore, we have found that, unlike the parent ketones, enol ether derivatives of many alkyl aryl ketones are oxidized very selectively to 2-aryl alkanoates by a number of simple hydrated thallium(III) salts, as well as by anhydrous salts, in the absence of TMOF or a solid support.



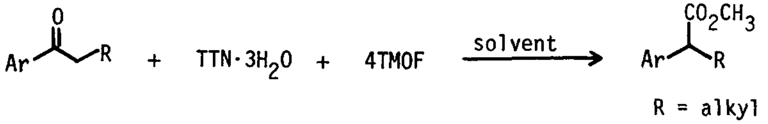
IV V

While ketone Ic reacted with TTN·$3CH_3OH$ (in the absence of a solid support) under a variety of conditions to give mixtures of IIc and IIIc, the related methyl enol ether (IVa, $R_1$=$CH_3$, $R_2$=H, X = p-isobutyl) was found to undergo an extremely facile reaction to give IIc as essentially the only product (less than 2% IIIc was detected). The reaction was exothermic, being complete within minutes at 0°, and could be carried out in a variety of solvents (methanol, tetrahydrofuran, hexane, etc.). Under the same mild conditions, the parent ketone was completely unreactive. The observed selectivity was not unique to TTN·$3CH_3OH$. Other thallium(III) salts, such as the sulfate and the acetate, showed similar high selectivity under anhydrous conditions.[7]

That enol ethers are easily formed from precursors under mild conditions was evident. Under anhydrous conditions, *in situ* generation from the corresponding ketal was found to occur readily at <60° with TTN or thallium(III) sulfate in a variety of solvents (methanol, benzene, hexane, etc.).

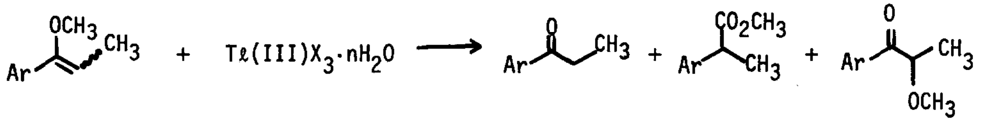


Furthermore, alkyl aryl ketones were found to be rapidly ketalized by reagents such as TMOF in the presence of thallium(III) salts under anhydrous conditions.[8] A "direct" conversion of the parent ketone to a 2-aryl alkanoate is thus readily accomplished by reacting the ketone and a hydrated thallium(III) salt with sufficient TMOF to insure dehydration of the salt and ketalization of the ketone; e.g.,[9]



While an excess of TMOF is not detrimental, it is not necessary to bring about the desired transformation.[10] These results indicate that the selective oxidation of simple alkyl aryl ketones which is observed with TTN in methanol-TMOF[3] is undoubtedly the result of formation and reaction of the methyl enol ether derivative.[11]

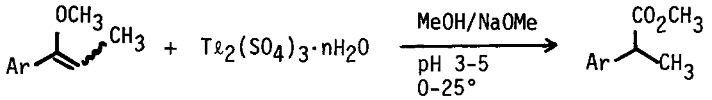
Although the use of anhydrous conditions proved convenient for the direct conversion of alkyl aryl ketones to 2-aryl alkanoates, such conditions are not required for the oxidation of enol ethers with high selectivity. Hydrated TTN (TTN·$3H_2O$) was found to undergo facile reaction in a variety of solvents (MeOH, THF, hexane-THF) to give the desired 2-aryl alkanoates. Other hydrated thallium(III) salts also proved effective, even under aqueous conditions (see Table I). Although hydrolysis was a problem in some cases, particularly when stoichiometric amounts of reactants were used, it is significant that oxidation occurred selectively to give IIc with all the simple thallium(III) salts examined.



Ar = p-isobutylphenyl Ic IIc IIIc

| Salt | Conditions | Ratio I/II/III | | |
|---|---|---|---|---|
| TTN·3$H_2O$ | 1.1 eq.,MeOH,70% aq. $HClO_4$ ,0°,5 min. | 24 | 72 | $\sim$1 |
| | 1.1 eq.,MeOH,rt.,5 min. | 7 | 92 | <1 |
| $T\ell_2(SO_4)_3\cdot nH_2O$ | 1.1 eq.,MeOH,0° ,5 min. | 42 | 56 | <1 |
| | 1.7 eq.,MeOH,0° ,5 min. | 11 | 89 | <1 |
| $T\ell(ClO_4)_3\cdot nH_2O$ | 1.1 eq.,MeOH,0° ,5 min. | 16 | 78 | <1 |
| $T\ell(OAc)_3\cdot 1\ 1/2\ H_2O$ | 1.1 eq.,80% aq.,HOAc,25°,30 min. | 25 | 72 | <1 |
| | 2.0 eq.,80% aq.,HOAc,25°,30 min. | 8 | 89 | <1 |

Somewhat surprisingly, it was found that the undesired hydrolysis could be controlled in some cases by carrying out the oxidation under less acidic conditions. While most simple thallium(III) salts, including TTN·3$H_2O$, have been reported to be unstable in solution above pH 2,[4] a fairly stable thallium(III) species was obtained from hydrated thallium(III) sulfate in methanol/sodium methoxide at an apparent pH of 3-5 which smoothly oxidized enol ether (IVc) to the desired 2-aryl alkanoate:[12]



Under such conditions ∿1.1 equivalent of hydrated thallium(III) sulfate could be used with only minor hydrolysis of the enol ether (< 10%) being observed.

The oxidative rearrangement of α-methoxystyrene derivatives with thallium(III) ion has been found to be a fairly general transformation which occurs under a wide variety of conditions. The intermediacy of enol ether derivatives would appear to be a major controlling factor in the facile conversion of alkyl aryl ketones to 2-aryl alkanoates with TTN and numerous other thallium (III) salts. The factors responsible for the striking differences in products obtained from the ketone and the enol ether derivative are currently under study.

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## Notes and References

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6. In reference 3, the intermediacy of α-methoxystyrene (from TTN-catalyzed loss of methanol from acetophenone dimethyl ketal) in the oxidation of acetophenone with two equivalents of TTN in 1:1 TMOF-MeOH to α-methoxyphenylacetate was indicated.
7. The "anhydrous salts" were obtained by treatment of the hydrated salt with the theoretical amount of trimethylorthoformate: $T\ell(X)_3\cdot nH_2O + nTMOF \rightarrow T\ell(X)_3\cdot nCH_3OH + nHCO_2CH_3 + nCH_3OH$. Thallium(III) sulfate in methanol or benzene was similar to TTN in reactivity (II/III > 98/2); thallium(III) acetate (2 eq) in methanol (50°, 1 hr) gave II/III > 98/2.

8. That TTN can catalyze the ketalization of some carbonyl compounds in TMOF has been pointed out.[3] We found alkyl aryl ketones were quantitatively converted to their ketals even with only stoichiometric quantities of TMOF.

9. When the solvent is 1:1 TMOF-MeOH, the conditions are presumably the same as those used in reference 3. A variety of solvents can be used with methanol being convenient. The following example is typical: To a solution of 1.9 gm (10 mmol) p-isobutylpropiophenone and 5.3 gm (50 mmol) trimethylorthoformate in 25 ml abs. methanol was added 5.4 gm (12 mmol) $TTN \cdot 3H_2O$. The resulting solution was stirred at 55° for 1.5 hrs. On cooling the precipitated $T\ell NO_3$ was removed by filtration and the filtrate was concentrated *in vacuo*. The resulting product was taken up in hexane, and the solution was washed with dilute aq acid. Removal of the solvent after drying over $Na_2SO_4$ gave essentially pure methyl 2-(p-isobutylphenyl) propionate. Basic hydrolysis followed by a standard isolation gave 2.0 gm (97% based on p-isobutylpropiophenone) crude 2-(p-isobutylphenyl) propionic acid. Recrystallization from hexane gave 1.8 gm (87%)pure acid, m.p. 73-75°. In a similar manner, propiophenone, butyrophenone, hexanophenone, isobutyrophenone, p-chloropropiophenone, and p-methoxypropiophenone were oxidized to give the corresponding 2-aryl alkanoic acids in > 85% yields. As would be expected, acetophenone derivatives yield substantial amounts of α-methoxyphenylacetates under anhydrous conditions (see reference 3).

10. In reference 3, it was indicated that the use of TMOF as co-solvent plays an important role in determining the products formed on oxidation of some carbonyl compounds with TTN by lowering the dielectric constant of the reaction medium, thus favoring SN2 as opposed to SN1 reactions of the methoxythallated intermediates. Our results do not substantiate any such solvent effect in the oxidative rearrangement of alkyl aryl ketones.

11. We would also like to suggest that the selectivity observed with "anhydrous TTN" on a solid support may be due to the formation and selective reaction of the same enol ether intermediate. The major function of the support would thus be to facilitate ketalization and enol ether formation. In this regard, E.C.Taylor has informed us that the support of choice, K-10 (on acidic montmorillonite clay), is a very effective catalyst for the ketalization of carbonyl compounds in TMOF. We thank Professor Taylor for a preprint of a forthcoming communication on this subject.

12. Procedure: To an efficiently stirred mixture of 56 mmol hydrated thallium(III) sulfate and 120 ml abs. MeOH at 0°C. was added dropwise a solution of 20% methanolic sodium hydroxide until an apparent pH of ∿4 (SCE) was obtained. Crude p-isobutylpropiophenone methyl enol ether (prepared from 50 mmol of isobutylpropiophenone) was then added and the mixture was allowed to warm to room temperature. The apparent pH was maintained between 3 and 5 by the gradual addition of 20% methanolic sodium hydroxide solution until the reaction was essentially complete (∿3 hrs.). Sodium bisulfite (20 mmol) was then added and the apparent pH was adjusted to < 1 with 20% methanolic $H_2SO_4$. The solvent was removed *in vacuo* and 150 ml 1N aq $H_2SO_4$ was added. The resulting mixture was extracted with hexane and the extracts were washed with 1N aq $H_2SO_4$ before drying over $Na_2SO_4$. Concentration of the solution *in vacuo* gave crude methyl 2-(p-isobutylphenyl)propionate. Basic hydrolysis followed by isolation of the acidic products gave an 80% yield of crude 2-(p-isobutylphenyl)propionic acid. Recrystallization from hexane gave the pure acid, m.p. 73-75° in 66% yield (based on p-isobutylpropiophenone).