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Hypervalent Iodine Oxidation of Aryl Methyl Ketones: A Convenient Route to Methyl α-Methoxyarylacetates

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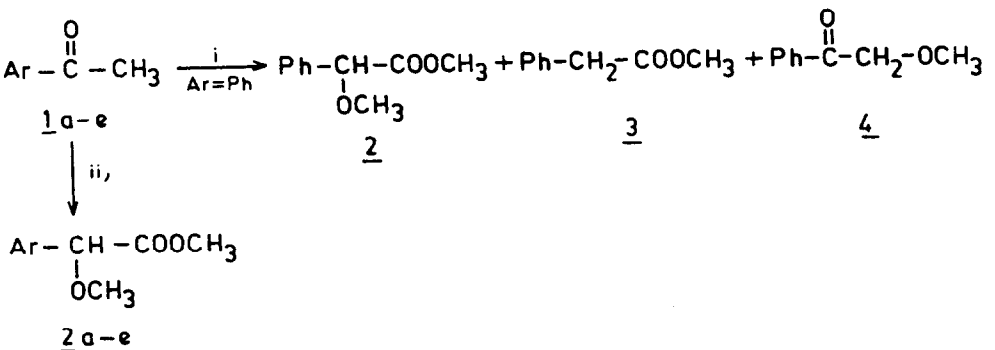
Summary: Hypervalent iodine oxidation of aryl methyl ketones using two equivalents of iodosobenzene diacetate leads to 1,2-aryl migration followed by solvohyperiodination to yield the corresponding methyl α-methoxyarylacetates.

Hypervalent iodine oxidation of aryl alkyl ketones via 1,2-aryl migration using hypervalent iodine reagents[1-3] is a valuable route to α-arylalkanoic acids possessing anti-inflammatory activity[4]. Thus, aryl methyl ketones on treatment with [hydroxy(tosyloxy)iodo]benzene/iodosobenzene BF_3-Et_2O/iodosobenzene diacetate-(IBD)-H_2SO_4 afforded methyl arylacetates along with small amount of corresponding α-methoxy ketones in methanol and a complex mixture of products in trimethyl orthoformate(TMOF) while higher analogues of aryl methyl ketones yielded corresponding methyl α-arylalkanoates on treatment with IBD in TMOF. In continuation of earlier work on the oxidation of ketonic compounds in TMOF using hypervalent iodine reagents[5], here I report the oxidation of aryl methyl ketones(1) using IBD in TMOF and the results are summarised in Scheme I.



i, IBD (1 equivalent), conc.H_2SO_4 in TMOF;
ii, IBD (2 equivalents), conc.H_2SO_4 in TMOF.

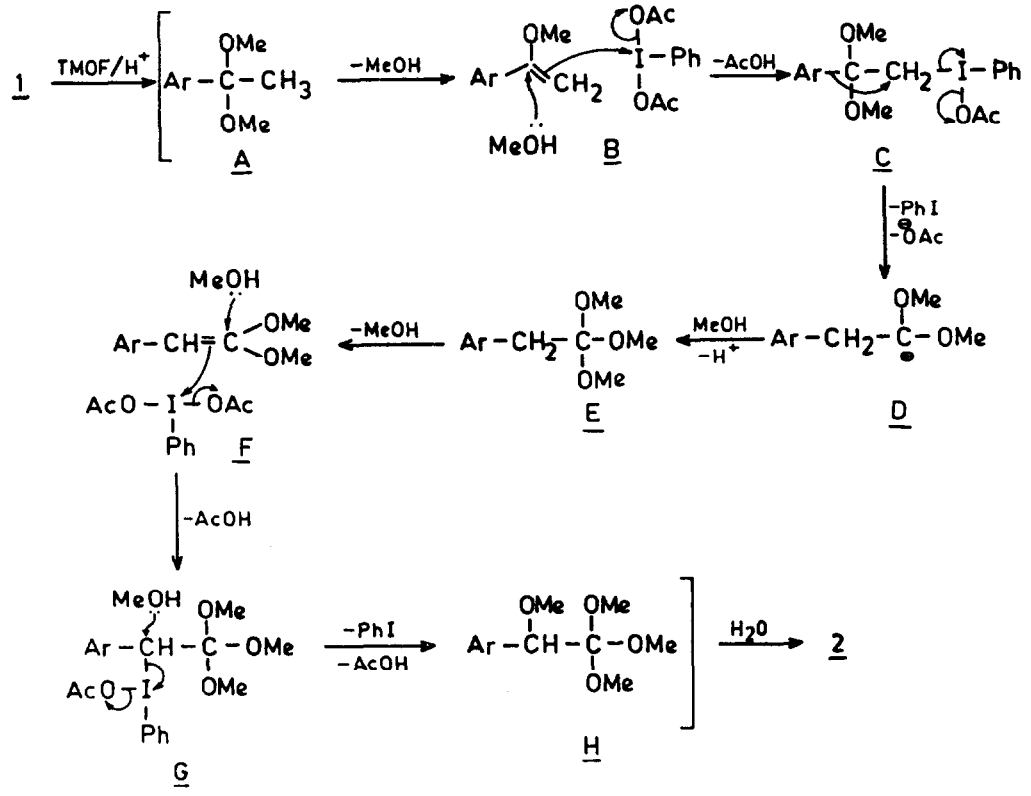
Scheme I

Thus, treatment of acetophenone(1a) with one equivalent of IBD in TMOF in presence of conc.H_2SO_4 afforded a mixture of methyl α-methoxyphenyl-acetate(2a), methyl phenylacetate(3) and α-methoxyacetophenone(4) along with

small amount of starting ketone(1a) as identified by ^{1}H-NMR and t.l.c. of the reaction mixture by comparison with authentic samples. Further, treatment of 1a with two equivalents of IBD in TMOF yielded only methyl α-methoxyphenyl acetate(2a) in good yield[6]. All known compounds were identified by their IR and ^{1}H-NMR spectral data by comparison with literature values.

The above transformation shows that one mole of IBD is utilised in the oxidative 1,2-aryl migration to afford methyl phenylacetate(3) as described earlier[1,2] and the second mole is used in the methoxyhyperiodination to yield the product 2. Hence, 3 should yield 2 upon treatment with IBD in TMOF and the case has not been found to be true as 3 is recovered unchanged under the reaction conditions which excludes the possibility of 3 as intermediate in the above transformation.

A plausible mechanism for the above transformation is depicted in Scheme II



Scheme II

It is clear from the above proposed mechanism that α-methoxystyrene(B) [from loss of methanol from acetophenones dimethylketals(A)] and trimethyl orthoester of arylacetic acid(E) are both intermediates in this transformation which, therefore, involves two successive methoxyhyperiodination. The first involves α-methoxystyrene (B) as substrate involving 1,2-aryl migration and the second utilises arylketene dimethylketals(F) [from loss of methanol from trimethyl orthoester of arylacetic acid(E)] as substrate and terminates into the products 2 with reductive displacement of iodobenzene with methanol from the hypervalent iodine adduct G. The utilisation of arylketene dimethylketal as substrate in the second methoxyhyperiodination is further supported by the fact that diphenylketene is transformed into the α-methoxydiphenylacetic acid on treatment with iodosobenzene followed by methanolysis as described earlier[7].

The present method represents a convenient, single step synthesis of 2 from easily available acetophenones and is of general applicability. The earlier known procedures for the synthesis of 2 utilises either arylacetic acids or their esters[8] or the silyl enol ethers of arylacetates[9] as starting materials and the present method also replaces the highly toxic thallium(III) nitrate[10] for this transformation.

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5. Oxidation of chalcones to esters using IBD in TMOF [O.V.Singh, C.P.Garg and R.P.Kapoor, Synthesis, submitted (1990)].

6. A mixture of IBD (0.022 mol), acetophenones (0.01 mol) and H_2SO_4 (0.25ml) in TMOF (30 ml) was stirred overnight. Most of the solvent was removed under reduced pressure and the residue was treated with saturated solution

of $NaHCO_3$. Extraction with CH_2Cl_2 (3x50 ml), drying ($MgSO_4$) followed by concentration in vacuo and the mixture was purified by column chromatography on silicagel using benzene-pet.ether (4:1) to yield 2 as an oil; 2a, Ar = C_6H_5 (82%); 2b, Ar = 4-$CH_3OC_6H_4$ (86%); 2c, Ar =4-$CH_3C_6H_4$ (84%); 2d, Ar = 4-ClC_6H_4 (80%); 2e, Ar = 4-BrC_6H_4 (84%).

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