Synthesis of Methyl 2,3-Diaryl-3-methoxypropanoates by Oxidative Rearrangement of Chalcones using Hypervalent Iodine Reagents in Trimethyl Orthoformate

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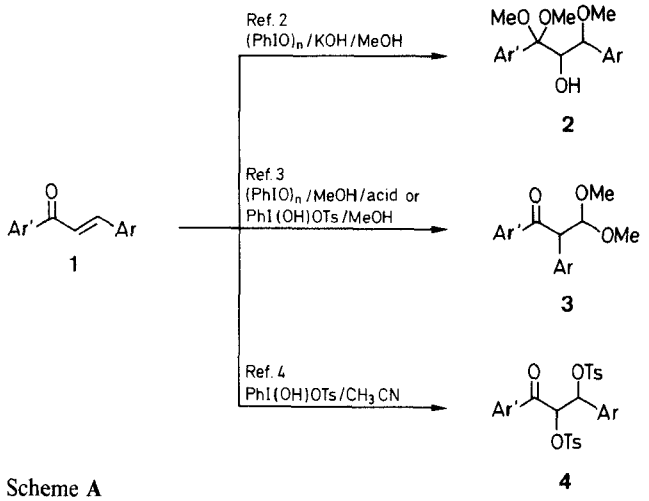
A diastereoselective synthesis of methyl 2,3-diaryl-3-methoxypropanoates **8a–f** by oxidative rearrangement of chalcones **1a–f** using (diacetoxyiodo)benzene and hydroxy(tosyloxy)iodobenzene in trimethyl orthoformate is described.

During the past decade hypervalent iodine has been shown to be a versatile reagent in organic synthesis effecting many useful and unique transformations.[1] A noteworthy feature of the reaction of chalcones with hypervalent iodine reagents is that different products have been obtained under different conditions.[2–4] For instance, oxidation of chalcones **1** with (i) iodosylbenzene/potassium hydroxide in methanol affords 1,3-diaryl-2-hydroxy-1,1,3-trimethoxypropanes **2**,[2] (ii) iodosylbenzene in methanol under acidic conditions and hydroxy(tosyloxy)iodobenzene in methanol gives 3,3-dimethoxy-1,2-diarylpropan-1-ones **3**,[3] and (iii) hydroxy(tosyloxy)iodobenzene in acetonitrile yields 1,3-diaryl-2,3-ditosyloxypropan-1-ones **4**.[4] Out of the conditions described above, the use of hypervalent iodine reagents in acidic methanol leads to oxidative 1,2-migration of the Ar group attached to the olefinic moiety (Scheme **A**).

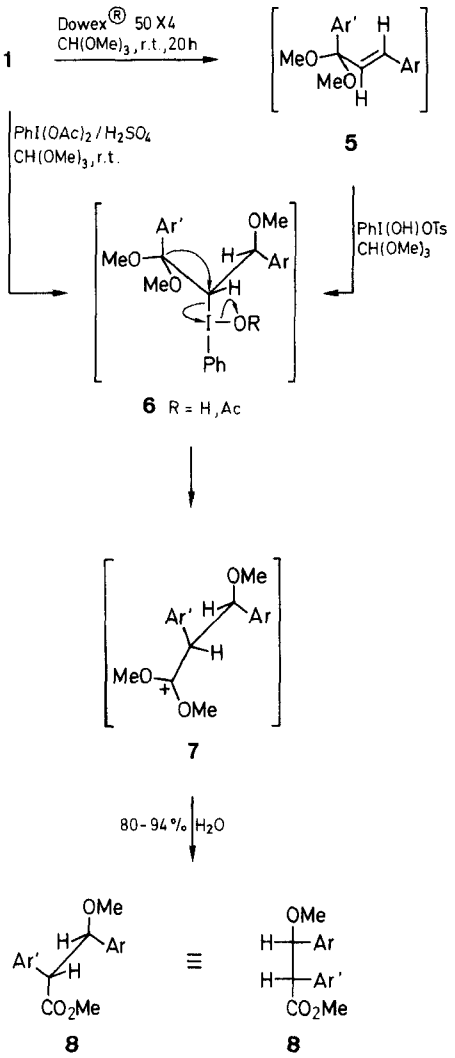


Scheme **A**

During the course of the present investigations we have observed the migration of Ar' group attached to carbonyl moiety rather than Ar group attached to the olefinic moiety, when chalcones **1a–f** are treated with (diacetoxyiodo)benzene/sulfuric acid in trimethyl orthoformate leading to the formation of methyl 2,3-diaryl-3-methoxypropanoates **8a–f** (Table).

Initial scanning of ^{1}H-NMR spectra of the crude products revealed that the reaction mixture does not contain even traces of 3,3-dimethoxy-1,2-diarylpropan-1-ones **3**. On passing this mixture through a silica gel column with benzene as eluent, only a single compound **8** is isolated from all fractions. Keeping in view the stereoeletronic requirements of all the steps involved in the transformation, i.e., **1** → **8** (Scheme **B**), it may be inferred that the present synthesis is diastereoselective yielding **8** in their *erythro* forms.

Exclusive formation of *erythro* isomers **8** can be rationalised in analogy with the earlier reports.[5] An initial acid-catalysed acetalisation of chalcones is responsible for the exclusive formation of **8** presumably because of two reasons. Firstly, acetalisation of carbonyl group makes the double bond more reactive to electrophilic attack of



1–8	Ar'	Ar
a	Ph	Ph
b	Ph	4-ClC$_6$H$_4$
c	4-MeOC$_6$H$_4$	Ph
d	4-MeOC$_6$H$_4$	4-ClC$_6$H$_4$
e	4-MeC$_6$H$_4$	Ph
f	4-MeC$_6$H$_4$	4-ClC$_6$H$_4$

Scheme **B**

Table. Compounds **8** Prepared

Product	Reaction Time (h)	Yield[a] (%)	mp (°C)	Molecular Formula[b] or Lit. mp (°C)	IR (Nujol) $\nu_{C=O}$ (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS) δ, J(Hz)
8a	24	80	93–95	93.5–95.5[5]	1730	3.22 (s, 3H), 3.70 (s, 3H), 3.81 (d, 1H, J = 11), 4.68 (d, 1H, J = 11), 7.08 (s, 10H)
	12	94[c]				
8b	20	92	82–84	81.5–84[5]	1730	3.21 (s, 3H), 3.66–3.84 (m, 4H), 4.75 (d, 1H, J = 11), 6.90–7.24 (m, 9H)
8c	18	88	81–82	80.5–82[5]	1735	3.22 (s, 3H), 3.66–3.86 (m, 7H), 4.76 (d, 1H, J = 11), 6.60–7.21 (m, 9H)
8d	18	94	92–93	91.5–93[5]	1735	3.22 (s, 3H), 3.64–3.78 (m, 7H), 4.64 (d, 1H, J = 11), 6.62–7.20 (m, 8H)
8e	18	90	97–98	97–98.5[5]	1735	2.18 (s, 3H), 3.21 (s, 3H), 3.68–3.84 (m, 4H), 4.66 (d, 1H, J = 11), 6.92–7.16 (m, 9H)
8f	18	90	77–78	$C_{18}H_{19}ClO_3$ (318.8)	1730	2.20 (s, 3H), 3.21 (s, 3H), 3.68–3.82 (m, 4H), 4.66 (d, 1H, J = 11), 6.92–7.22 (m, 8H)

[a] Yields are based on isolated products.
[b] Calc.: C 67.82, H 6.01; found: C 67.54, H 5.93.
[c] Reaction is performed with the preformed dimethyl acetal of chalcone **(5a)** with hydroxy(tosyloxy)iodobenzene.

(diacetoxyiodo)benzene resulting in the formation of the *trans*-adduct **6**. Secondly, the rearrangement of **6** involves intramolecular displacement of iodobenzene by Ar′ rather than Ar group obviously due to enhanced stability of the resulting carbocation **7** by *gem*-dimethoxy groups (Scheme **B**).

Support for this mechanism comes from the fact that chalcone dimethyl acetal **(5a)**, formed *in situ* by treating **1a** with trimethyl orthoformate in the presence of Dowex® 50X4 at room temperature, also affords **8a** in its *erythro* form on reaction with hydroxy(tosyloxy)-iodobenzene. This reaction pathway can not be followed if the reaction of chalcones is carried out with hypervalent iodine reagents in methanol, which excludes the rapid acetal formation[3] (Scheme **A**).

Thus, the reaction of chalcones **1** with (diacetoxyiodo)benzene/sulfuric acid in trimethyl orthoformate constitutes a convenient route for the diastereoselective synthesis of **8**, provided that the migratory aptitudes of the groups Ar′ are moderate to good.[6] Further, this method is better than the thallium(III) nitrate mediated oxidative rearrangement of chalcones in trimethyl orthoformate,[5] since the latter yieldes 1:1 mixture of **3** and **8** whereas the former yields only **8**, in addition to the fact that (diacetoxyiodo)benzene is much less toxic than thallium(III) salts.

Full details of the effect of substrate modification, relative migratory aptitude of the Ar and Ar′ groups and solvent dependency on these oxidative rearrangements will be reported in a future communication.

(Diacetoxyiodo)benzene was purchased from Aldrich Chemical Co.

Methyl *erythro*-2,3-Diphenyl-3-methoxypropanoate (8a); Typical Procedure:
To a stirred solution of chalcone (**1a**; 2.08 g, 10 mmol) in trimethyl orthoformate (30 mL) and conc. H_2SO_4 (1 mL) is added (diacetoxyiodo)benzene (3.6 g, 11 mmol). The mixture is stirred at r.t. for a period of 24 h, quenched with 10% aq $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers are washed with water (100 mL), and dried ($MgSO_4$). The solvent is evaporated at reduced pressure and the residue is purified by column chromatography on silica gel using benzene as eluent to give the pure ester **8a**; yield: 2.20 g (80%); mp 93–95°C (Lit.[5] mp 93.5–95.5°C) (Table).

Methyl *erythro*-2,3-Diphenyl-3-methoxypropanoate (8a) via Chalcone Dimethyl Acetal (5a):
To a stirred solution of chalcone (**1a**; 1.04 g, 5 mmol) in trimethyl orthoformate (20 mL) is added Dowex® 50X4 cation exchange resin (3 g), and the mixture is stirred at r.t. for a period of 20 h. The completion of acetal formation is checked by TLC (silica gel $CHCl_3$), and the mixture is filtered into a solution of hydroxy(tosyloxy)iodobenzene[7] (2.4 g, 6 mmol) in trimethyl orthoformate (10 mL) and kept at r.t. for 12 h. The mixture is worked up as above to afford **8a**; yield: 1.25 g (94%).

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