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Hypophosphorous acid–iodine: a novel reducing system. Part 1: Reduction of diaryl ketones to diaryl methylene derivatives

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Abstract

A mixture of hypophosphorous acid (H_3PO_2) and iodine in hot acetic acid reduces diaryl ketones quickly and aryl alkyl ketones slowly to the corresponding methylene derivatives. The active reducing agent is hydrogen iodide, generated by reaction between iodine and hypophosphorous acid. © 2000 Elsevier Science Ltd. All rights reserved.

Hypophosphorous acid (H_3PO_2), although often used for the reductive deazoniation of aryldiazonium ions ($ARN_2^+ \rightarrow ArH + N_2$),[1] has only rarely been used as a synthetic reagent in organic chemistry.[2–4] We have found that a mixture of hypophosphorous acid and a catalytic amount of iodine in refluxing acetic acid converts diaryl ketones to the corresponding diarylmethylenes (Eq. (1)) in high yield (Table 1). Diaryl ketones are reduced considerably faster than arylalkyl ketones (compare runs 1 or 2 with runs 11 and 14). The latter are in turn reduced much faster than dialkyl ketones; in fact, cyclohexanone undergoes self-aldol condensation under the reaction conditions faster than it can be reduced to cyclohexane (run 13). Benzaldehyde undergoes the known adduct formation of H_3PO_2 with aldehydes (run 12).[5] 4-Bromobenzophenone is readily reduced without hydrogenolysis of the bromine atom (run 3). Reduction of 4-hydroxybenzophenone proceeds readily, except that the product is partially esterified under the reaction conditions (run 8). Interestingly, this reagent system also readily reduces the carbon–carbon bond of α,β-unsaturated ketones: the carbon–carbon double bond of benzalacetophenone (**1**) is quickly reduced, affording dihydro derivative **2**, which then undergoes slow reduction of its carbonyl group (run 14). Dibenzosuberenone (**6**), in which the double bond

$$\text{ArCOAr}' \xrightarrow[\substack{I_2\ (\text{cat.}) \\ \text{HOAC, reflux}}]{H_3PO_2} \underset{97\text{–}100\%}{\text{ArCH}_2\text{Ar}'} \tag{1}$$

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Table 1
Reduction of carbonyl compounds with hypophosphorous acid–iodine in refluxing acetic acid

Run	Ketone	Product(s), yield[a]
1	Fluorenone	Fluorene, 99%
2	Benzophenone	Diphenylmethane, 100%
3	4-Bromobenzophenone	4-Bromodiphenylmethane, 97%
4	3,4-Dimethylbenzophenone	3,4-Dimethyldiphenylmethane, 100%
5	Dibenzosuberone (**3**)	Dibenzosuberane (**4**), 98%
6	Dibenzosuberenone (**6**)	Dibenzosuberane (**4**), 35%; dibenzosuberene (**5**), 64%
7[b]	Dibenzosuberenone (**6**)	Dibenzosuberane (**4**), 100%
8	4-Hydroxybenzophenone	4-Hydroxydiphenylmethane, 81%; 4-acetoxydiphenylmethane, 19%
9	1,4-Dibenzoylbenzene	1,4-Dibenzylbenzene, 99%
10[c]	1,4-Dibenzoylbenzene	4-Benzylbenzophenone, 30%; 1,4-dibenzylbenzene, 70%
11	Acetophenone	Ethylbenzene, 11%[d]
12	Benzaldehyde	0% Toluene[e]
13	Cyclohexanone	0% Cyclohexane[f]
14	Benzalacetophenone (**1**)	2,3-Dihydrobenzalacetophenone (**2**), 97%; 1,3-diphenylpropane, 3%

[a] Carbonyl cpd (4 mmol), iodine (0.4 mmol), 50% aq. hypophosphorous acid (19.3 mmol) acetic acid (65 mL) 24 h reflux under N_2.

[b] Extended heating (72 h).

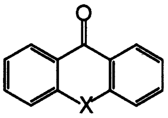
[c] Reaction carried out in air.

[d] Plus 89% starting material.

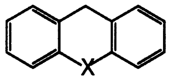
[e] See text.

[f] Trimer **7** is produced in 95% yield.

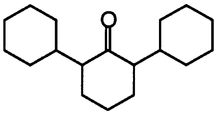
is formally conjugated with the carbonyl group, undergoes reduction of the double bond competitively with the carbonyl group to produce dibenzosuberane (**4**) in substantial yield in competition with simple reduction of the carbonyl group (run 6). Longer heating converts **6** to **4** (run 7). Incomplete reduction in run 10 may be a result of consumption of H_3PO_2 by reaction with air. Cyclohexanone underwent double aldol condensation to afford known trimer **7**[6] as a ca 98:2 mixture of stereoisomers in >95% yield under our standard conditions. We are exploring this surprising reaction further.



3, X = CH_2CH_2
6, X = CH=CH



4, X = CH_2CH_2
5, X = CH=CH



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Reductions effected by a mixture containing iodine, an oxidizing agent, are of obvious mechanistic interest. We believe that the active reducing agent in these reactions is hydrogen iodide, generated through reduction of iodine by hypophosphorous acid (Scheme 1).[7] In this proposed scheme, hydride transfer from HI to a protonated carbonyl group generates the secondary alcohol and an ‘I^+’ equivalent (e.g. IOAc or similar positive iodine species), which then combines with iodide to regenerate iodine. Hypophosphorous acid then again reduces iodine to continue the catalytic cycle; H_3PO_2 is therefore the ultimate source of reducing equivalents. However, an iodine source is necessary: we found in a control experiment less than 2% conversion of benzophenone into diphenylmethane when iodine was omitted from the reaction medium. Hydrogen iodide has previously been shown to reduce aryl carbinols to the corresponding aralkanes in acidic solution.[8] Indeed, we have found that our postulated intermediate benzhydrol is reduced much faster than benzophenone under our standard conditions.[9]

$$\begin{aligned}
2I_2 + H_3PO_2 + 2\,HOAc &\longrightarrow 4\,HI + O{=}P(OAc)_2OH \\
Ar_2C{=}O + 4\,HI &\longrightarrow Ar_2CH_2 + 2\,\text{"}I^+\text{"} + 2\,I^- + H_2O \\
2\,\text{"}I^+\text{"} + 2\,I^- &\longrightarrow 2\,I_2
\end{aligned}$$

Net reaction:

$$ArCOR + H_3PO_2 + 2\,HOAc \longrightarrow ArCH_2R + O{=}P(OAc)_2OH + H_2O$$

Scheme 1.

Summary. An acetic acid solution of hypophosphorous acid containing a catalytic quantity of iodine reduces diaryl ketones to the corresponding diarylmethylene compounds ($ArCOAr' \rightarrow ArCH_2Ar'$) in close to quantitative yield. This reaction is competitive in terms of yield, convenience, and general synthetic utility with the traditional processes for this conversion, e.g. the Wolff–Kishner[10] and Clemmensen[11] reductions, and with more recent processes such as reduction by silanes.[12,13] Arylalkyl ketones are reduced more slowly, and dialkyl ketones slowest of all. The carbon–carbon double bond of some α,β-unsaturated ketones such as benzalacetophenone (**1**) is reduced much faster than the carbonyl group by H_3PO_2–I_2; we will report further on this reaction later because we are still exploring several unusual processes we have observed with activated alkenes.

Aqueous hydrogen iodide, either alone, in refluxing acetic acid, or with added elemental phosphorus, has previously been found to reduce quinones, hydroquinones, polycyclic aromatic phenols, and a few aryl ketones to the corresponding arenes.[14] The reactions in Table 1 occur substantially more slowly when aqueous hydrogen iodide is substituted for iodine. This may possibly be due to the higher water content of the medium. Finally, the present procedure has an economic advantage, with hydriodic acid and hypophosphorous acid currently selling for ca $60/mole and $10/mole, respectively.

Reduction of 4-bromobenzophenone (representative experiment): Iodine (1.00 g, 4.0 mmol) and acetic acid (50 mL) were stirred together under N_2 in a flask fitted with a condenser and a dropping funnel. Hypophosphorous acid, 50% aq. (2 mL, 19.3 mmol) was added and the mixture was heated to reflux. A solution of 4-bromobenzophenone (3.18 g, 12.0 mmol) in 15 mL of acetic acid was added over a period of 1–2 h. The mixture was then stirred and refluxed for an additional 24 h, cooled, diluted with water and extracted with hexane. The hexane was dried of $MgSO_4$. Analysis by GC-mass spectrometry showed that the hexane contained only a single constituent, 4-bromodiphenylmethane. The hexane was concentrated and purified by flash chromatography to afford 4-bromodiphenylmethane[15] (2.70 g, 84%); ^1H NMR (300 MHz, $CDCl_3$: δ 3.95 (s, 2H), 7.06–7.43 (m, 9H); mass spectrum: 246, 248 (25, p^+); 167 (100, p-Br).

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