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Iodine induced transformations of alcohols under solvent-free conditions

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Abstract—Iodine has been shown to be an efficient catalyst for transformations of alcohols under solvent-free conditions. In the presence of 5% of iodine, tertiary alcohols underwent dehydration forming the corresponding alkenes, while in the case of 2-phenylpropane-2-ol cyclodimerisation to 1,1,3-trimethyl-3-phenylindane took place. Secondary and primary benzyl alcohols under the same conditions gave the corresponding ethers.

1. Introduction

Increasing demand for appropriate, economic, but eco-friendly processes have in recent decades culminated in research efforts following the principles accepted under the term 'green chemistry'.[1] In this context water has become an important reaction medium for organic reactions,[2] and nowadays it is no longer surprising to conduct organometallic chemistry[3] or free-radical functionalisation[4] in aqueous media. Sharpless and co-workers reported an unusual effect of water on the reactivity of organic molecules which do not react in solvent-free systems, while chemical transformation proceeded in the presence of water on its surface, that is, 'on water'.[5] However, solvent-free systems[6] remain an attractive option for achieving more eco-friendly protocols. In this case, the aggregate state of substrates and reagents plays an important role and should be carefully analyzed regarding liquid–liquid, solid–liquid or solid–solid interactions, and moreover the situation becomes even more complex when catalysts are used.

The regioselectivity of iodofunctionalisation of organic molecules using iodine could be significantly influenced by the solvent and this effect is often expressed when reactions in acetonitrile and methanol are compared. It was shown recently that iodination of benzene derivatives bearing an alkyne and amino functionality underwent an iodocyclisation process, resulting in the formation of quinolines in MeCN and indoles in MeOH.[7] Acetophenone derivatives underwent regiospecific ring iodination using the I_2/F–TEDA–BF_4 system in CH_3CN, and side chain iodination with the same reagent occurred in CH_3OH,[8] while enhanced iodine atom economy has been achieved when I_2/H_2O_2 was used for the iodination of alkenes in methanol or water.[9] Equimolar I_2/Ph_3P mixtures were used for conversion of alcohols to iodides under solvent-free conditions and microwave irradiation,[10a] while in CH_2Cl_2, various cyclohexanol derivatives were dehydrated.[10b]

In recent years molecular iodine has become an important environmentally benign reagent for organic functional group conversions,[11a] including Hibbert's work,[11b] and as an attractive mild Lewis catalyst for various functionalisations of organic molecules.[11c,d] A catalytic amount of iodine is able to activate the hydroxy group and elimination processes are usually accompanied by rearrangements or intramolecular cyclisations,[12] while acylation under solvent-free conditions with acetic anhydride,[13a,b] vinyl acetate[13c] or propenyl acetate[13d] was reported. We demonstrated that iodine as a catalyst is able to discriminate between CH_3OH, H_2O and H_2O_2, and methoxy-hydroperoxides and dihydroperoxides were formed from ketones and aldehydes.[14]

In order to understand better the role of iodine as a mild catalyst in the functionalisation of organic molecules, we now report the use of phenyl-substituted alcohols as

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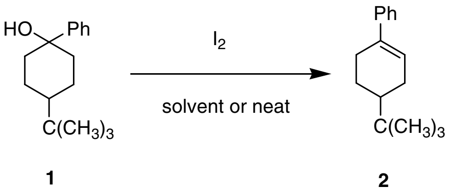
model compounds which offer, following appropriate activation of the hydroxy group, the possibility of formation of carbonium ions.[15] The phenyl-substituted alkenes possibly formed are usually very sensitive to reaction conditions and often undergo polymerisation.[15] Phenyl substituted alcohols could undergo at least three different reaction pathways, often competing among themselves, that is, transformation to phenyl-substituted alkenes, dimerisation or cyclodimerisation, and formation of ethers; however, the course of transformation strongly depends on the reaction conditions and substituents. For effective formation of phenyl-substituted alkenes a strong acid is usually required, but the reaction can proceed further undergoing dimerisation or cyclodimerisation yielding substituted indanes, while the formation of ethers strongly depends on the catalyst and reaction conditions.[15] Herein, we report our investigation of the effect of the amount of iodine (1%, 5%, 10%), solvent (CH_3COOH, CH_3OH, CH_3CN), and reactions on water or under solvent-free conditions on the transformation of phenyl-substituted alcohols.

First we investigated the effect of the reaction conditions (Table 1) on the transformation of 4-*tert*-butyl-1-phenylcyclohexanol (**1**, *trans–cis* mixture) induced by various amounts of iodine. In all the cases studied, only the dehydration process took place and 1-phenyl-4-*tert*-butyl-cyclohexene (**2**) was formed. We found that the presence of 1% of iodine was not sufficient to induce dehydration (entries 1, 3, 5, 9 and 12), while the solvent importantly influenced the elimination process when 5% of iodine was used. After 60 min in CH_3CN or CH_3COOH, complete conversion to **2** occurred at room temperature (entries 2 and 4). Transformation in CH_3OH required 4 h heating at 60 °C (entry 7, 85%), while 95% conversion was observed when 10% of iodine was used (entry 8). Since **1** is insoluble and iodine is only slightly soluble in water, the studied transformation actually proceeded on water, but in the presence of 1% of iodine after 60 min at room temperature and vigorous stirring (1000 rpm^{-1}) no transformation took place. On the other hand, 70% elimination was observed after 3 h in the presence of 5% of iodine (entry 10), while for complete conversion to **2** (entry 11) the reaction temperature had to be raised to 60 °C. Finally, we attempted the reaction under solvent-free conditions and in a typical experiment **1** (1 mmol, solid) and various amounts of iodine (1%, 5%) were triturated in a glass mortar for 1 min and then left for various times at room temperature (25 °C). In the presence of 1% of iodine, no transformation took place after 60 min, while complete dehydration was achieved when 5% of iodine was used (entry 13) and a reaction time of 15 min was sufficient to obtain 96% of pure **2** after flash chromatography (SiO_2, CH_2Cl_2).

Table 1. The effect of the amount of iodine and reaction conditions on the conversion of 4-*tert*-butyl-1-phenyl-cyclohexanol **1** to 4-*tert*-butyl-1-phenyl-cyclohexene **2**



Entry	Solvent	I_2 (%)	Time (min)[a]	Conversion (%)[c]
1	CH_3COOH	1	60	—
2		5	60	100
3	CH_3CN	1	60	—
4		5	60	100
5	CH_3OH	1	60	—
6		5	60	—
7		5	240[b]	85
8		10	240[b]	95
9	H_2O	1	60	—
10		5	180	70
11		5	180[b]	100
12	Neat	1	60	—
13		5	15	100

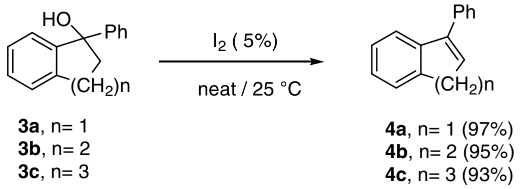
[a] Reactions were carried out at 25 °C.

[b] Reaction at 60 °C.

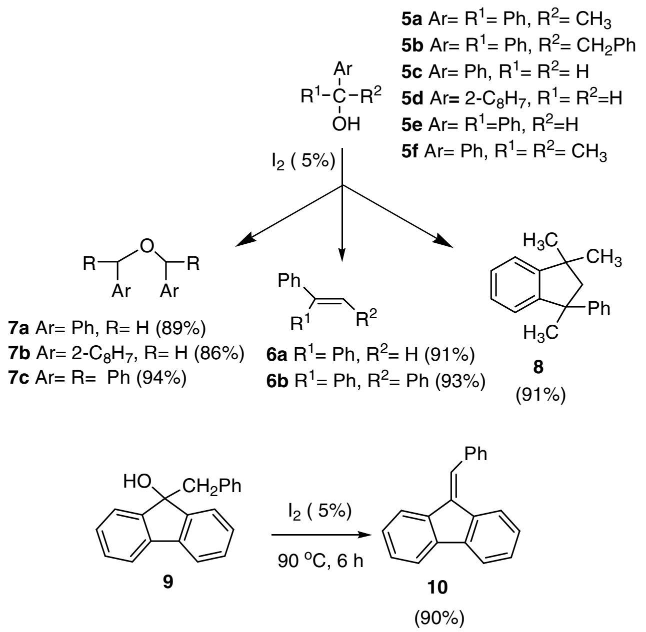
[c] Conversion determined from ^1H NMR spectra; mass balance was greater than 90%.

Encouraged by these results, we further studied the effect of ring size and aggregate state of the substrate on the course of transformation under solvent-free conditions. Benzocycloalcohols (**3a** liquid, **3b** liquid and **3c** solid, Scheme 1) were even more reactive than **1**, and after 2 min, elimination of water took place to give benzocycloalkenes **4** in high yields (90–100%).

The fact that introduction of a second phenyl group into the alcohol increased the rate of dehydration irrespective of the ring size stimulated us to study the effect of the conformational stability of acyclic systems on the rate of dehydration. 1,1-Diphenylethanol (**5a**, Scheme 2) required a longer reaction time for complete conversion to 1,1-diphenylethylene (**6a**, 25 °C, 45 min), while introduction of an additional phenyl group (**5b**) significantly diminished the rate of dehydration. Treatment of 1,1,2-triphenylethanol **5b** for 6 h at 25 °C gave no result, but by increasing the temperature to 60 °C, quantitative conversion to triphenylethylene (**6b**) was observed after 4 h. 9-Benzyl-9*H*-fluoren-9-ol (**9**) was chosen as a substrate because the cationic intermediate at position nine could be considered as an anti aromatic unit,[16] which can decrease the reactivity if carbocationic intermediates are formed during the transformation process. In fact, **9** required an even higher temperature and longer reaction time, but dehydration was still the exclusive process, and excellent conversion to alkene **10** took place at 90 °C in 6 h.



Scheme 1.



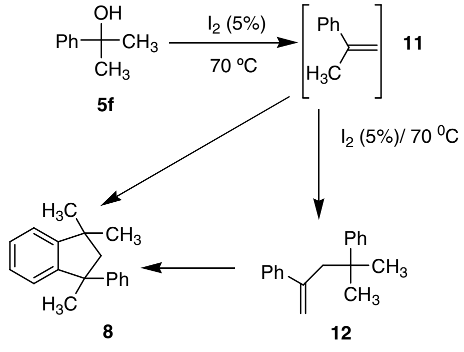
Scheme 2.

The observed results suggested that iodine is involved in the generation of a cationic intermediate and for this reason we changed the substituents on alcohol (**5**) so that a less stable carbonium ion would be formed. Benzyl alcohol (**5c**) when heated at 70 °C in the presence of 5% of iodine underwent a different type of transformation and dibenzyl ether **7a** was isolated in high yield. A similar transformation to **7b** was also observed with solid 2-naphthylmethanol **5d**. Introduction of a second phenyl group did not change the type of transformation and diphenylmethanol **5e** was readily converted to the di(diphenylmethyl)ether **7c** under the same conditions. In order to verify the role of the benzylic position in the transformation, we examined two structurally related alcohols: 2,2-diphenyl ethanol (5% of iodine, 70 °C, 3 h) and 9*H*-fluoren-9-yl-methanol (5% of iodine, 90 °C, 5 h), but both remained unchanged under these conditions.

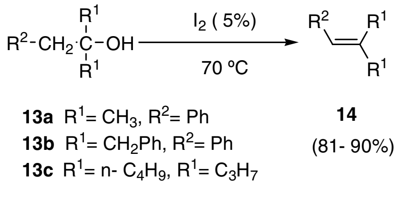
Introduction of a methyl group at the benzylic position can significantly change the stability of a carbonium ion.[16] In fact, 2-phenyl-propan-2-ol (**5f**, Scheme 2) underwent a third type of transformation in the presence of 5% of iodine under solvent-free conditions. After 3 h at 70 °C, a liquid product was isolated in 91% yield, for which HRMS indicated the presence of a dimeric $C_{18}H_{20}$ unit formed through dehydration of **5f**. Careful analyzes of the ^1H and ^{13}C NMR spectra indicated the formation of (±)-1,1,3-trimethyl-3-phenyl-indane (**8**). In order to obtain further insight into the dimerisation process, we reduced the reaction time to 5 min at 70 °C for **5f** and the absence of 2-phenyl-propene as a possible primary product was confirmed, but the presence of the dimeric alkene 4-methyl-2,4-diphenyl-pent-1-ene (**12**)[17] was established, as well as the indane derivative **8**. In the next experiment, we heated 2- phenylpropene **11** in the presence of 5% of iodine for 15 min at 70 °C and complete conversion to indane derivative **8** was achieved. These results indicate the following reaction scenario (Scheme 3): 2-phenyl-propan-2-ol **5f** underwent rapid dehydration to 2-phenyl-propene **11**, further transformation to dimeric alkene **12** and then finally cyclisation to indane derivative **8**.

Finally, we studied the effect of the presence of a phenyl ring at the reactive centre in alcohols on the reaction pathway. The tertiary alcohols studied (**13a–c**, Scheme 4) underwent only the dehydration process to give the corresponding alkenes **14** at 70 °C in the presence of 5% of iodine, however, longer reaction times (5–7 h) were needed for complete conversion. In the case of secondary alcohols (4-*tert*-butyl-cyclohexanol or cycloheptanol) and the primary alcohol 1-octanol, only starting material was recovered under the abovementioned reaction conditions.

In the present work, we have demonstrated that iodine is an efficient catalyst for transformation of alcohols under solvent-free conditions and elimination–substitution–cyclodimerisation processes were established. Dehydration in the presence of 5% of iodine under solvent-free conditions to the corresponding alkenes was observed in the case of substituted tertiary alcohols, except for 2-phenyl-propan-2-ol which underwent an elimination–cyclodimerisation process to give a derivative of indane. Phenyl-substituted secondary alcohols (diphenylmethanol) or primary benzyl alcohols resulted in the formation of ethers. Iodine was also found to be a convenient catalyst for cyclodimerisation of phenyl-substituted alkenes and formation of a substituted indane was established in this case. Further investigations on the mechanism of these transformations as well as of the effect of the structure of the alcohol on the regioselectivity and stereoselectivity and the amount of iodine and temperature for the transformation of primary



Scheme 3.



Scheme 4.

and secondary alcohols are now in progress. The scope and structural limitations of alkene dimerisation in the presence of a catalytic amount of iodine are also under investigation.

2. Typical procedure for solvent-free transformations of alcohols with iodine

Alcohol **5f** (solid) (1 mmol) and 5% of iodine (0.05 mmol, 12.7 mg) were triturated in a glass mortar for 1 min, transferred to a 15 ml flask and heated at 70 °C for 3 h. An aqueous solution of $Na_2S_2O_3 \cdot 5H_2O$ (10%, 20 ml) was then poured into the cooled mixture and the crude product was extracted with *tert*-butyl-methyl-ether (35 ml) and washed with water. Pure 1,1,3-trimethyl-3-phenyl-indane (**8**, colourless oil) was obtained by column chromatography (SiO_2, hexane: CH_2Cl_2 4:1) in 91% yield.

^{1}H NMR ($CDCl_3$): δ_H 1.03 (s, 3H), 1.34 (s, 3H), 1.69 (s, 3H), 2.19 (d, $J = 13.0$ Hz, 1H), 2.50 (d, $J = 13.0$ Hz, 1H), 7.10–7.28 (m, 9H); ^{13}C NMR (76 MHz; $CDCl_3$): δ_C 30.4, 30.6, 30.9, 42.8, 50.8, 59.5, 122.5, 125.0, 125.4, 126.6, 127.2, 127.9, 148.7, 151.0, 152.1; IR (NaCl, cm^{-1}): 3061, 3021, 2959, 2863, 1599, 1445, 1312, 1202, 1028. 757, 700; *m/z* (EI, 70 eV): 236 (45%, M^+), 221 (100), 143 (35), 91 (32); HRMS (EI): Calcd. Mass for $C_{18}H_{20}$: 236.1565, Found mass 236.1574; Elemental analysis: Calcd. For $C_{18}H_{20}$: C 91.47; H 8.53. Found C 91.73; H 8.41.

In the case of liquid substrates, 1 mmol of alcohol and 5% of iodine were mixed together in a 15 ml flask for 1 min and then left for various times at 25 °C or heated at 60–70 °C.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.09.154.

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