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The reductive etherification of carbonyl compounds using polymethylhydrosiloxane activated by molecular iodine

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ABSTRACT

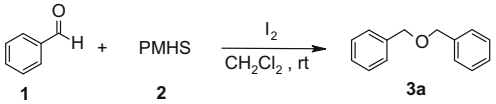
Aldehydes and ketones undergo a smooth reductive etherification by polymethylhydrosiloxane (PMHS) in the presence of a catalytic amount of molecular iodine under mild conditions to afford the corresponding symmetrical ethers in excellent yields. This new reagent system (PMHS/I_2) provides a simple and convenient route for the preparation of symmetrical ethers from carbonyl compounds.

The formation of carbon–oxygen bond is one of the most widely used functional group transformations in organic synthesis.[1,2] The classical methods for the preparation of ethers are the Williamson and Wurtz's synthesis.[3,4] The reductive etherification is one of the direct and simple method for the synthesis of symmetrical ethers. Typically, Lewis acids such as boron trifluoride, trifluoroacetic acid, ferric chloride and trimethylsilyltriflate are employed as catalysts for the reductive etherification of carbonyl compounds with triethylsilane.[5,6] Doyle et al. have reported an acid promoted reductive coupling of carbonyl compounds with trialkylsilanes as a route to symmetrical ethers.[7] This method requires several-fold excess of strong Bronsted acids, often used as solvents which limit its potential use in large scale synthesis. Other reagents such as pyridine–borane/trifluoroacetic acid and solid super acids/trialkylsilanes have also been employed for the reductive etherification of aldehydes to furnish symmetrical and unsymmetrical ethers.[8] However, many of these reagents are corrosive, moisture sensitive and are required in stoichiometric amounts. Therefore, the developments of simple and cost-effective reagents that are more efficient and provide convenient procedures with improved yields are desirable.

In recent years, molecular iodine has gained importance as inexpensive, non-toxic and a readily available catalyst for various organic transformations affording the corresponding products with high selectivity in excellent yields.[9] The mild Lewis acidity associated with iodine enhanced its usage in organic synthesis to perform several organic transformations using stoichiometric levels to catalytic amounts. Owing to advantages associated with this eco-friendly catalyst, molecular iodine has been explored as a powerful reagent in organic synthesis.[10]

In continuation of our interest on the catalytic use of molecular iodine for various organic transformations,[11] we herein report a mild, convenient and rapid method for the reductive etherification of both aldehydes and ketones with polymethylhydrosiloxane (PMHS), using a catalytic amount of elemental iodine. Initially, we attempted the reductive etherification of benzaldehyde (**1**) with PMHS (**2**) in the presence of a catalytic amount of (2.5 mol %) molecular iodine. The reaction was complete within 30 min and the desired product, dibenzyl ether **3a** was obtained in 90% yield (Scheme 1).

This result provided incentive for further study with various aldehydes such as phenylacetaldehyde, 2-phenylpropanaldehyde and 3-phenylpropanaldehyde. Interestingly, these aldehydes reacted equally well with PMHS to provide the corresponding symmetrical ethers (Table 1, entries b–d). In case of entry c, the product was obtained as a diastereomeric mixture in 1:1 ratio which was confirmed by GC and also by comparison with authentic



Scheme 1. Preparation of dibenzyl ether.

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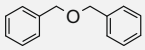
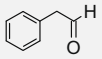
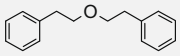
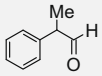
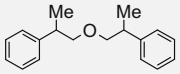
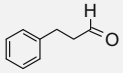
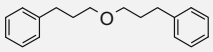
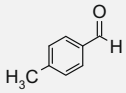
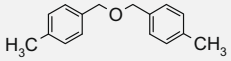
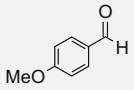
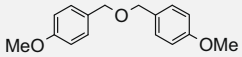
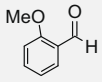
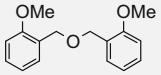
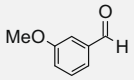
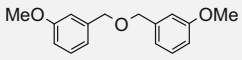
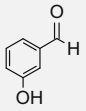
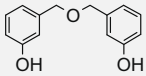
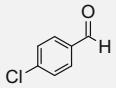
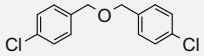
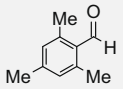
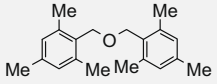
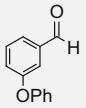
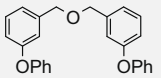
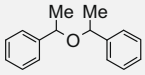
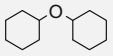
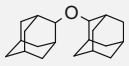
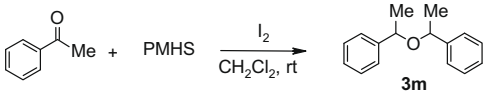
Table 1
PMHS/I2-Promoted reductive etherification of carbonyl compounds

Entry	Carbonyl compounds (**1**)	Ethers (**3**)[a]	Reaction time (min)	Yield[b] (%)
a			30	90
b			35	86
c			30	82[c]
d			25	85
e			30	88
f			20	89
g			35	87
h			35	87
i			30	85
j			25	86
k			45	82
l			40	87
m			30	85[d]
n			30	70
o			15	84
p			15	86[d]

[a] All products were characterized by IR, ^{1}H, ^{13}C NMR and mass spectroscopy.
[b] Yield refers to pure products after chromatography.
[c] The product was obtained as a diastereomeric mixture in 1:1 ratio which was determined by GC.[12]
[d] A single diastereomer was formed.[2]

samples.[12] Similarly, substituted aromatic aldehydes such as *p*-methylbenzaldehyde, *p*-anisaldehyde, *o*-anisaldehyde, *m*-anisaldehyde, *m*-hydroxybenzaldehyde, *p*-chlorobenzaldehyde, 2,4,6-trimethylbenzaldehyde and *m*-phenoxybenzaldehyde were converted into their corresponding symmetrical ethers in high yields by using this procedure (Table 1, entries e–l). Next, we examined the reactivity of ketones such as acetophenone and cyclohexanone. Ketones



Scheme 2. Preparation of di-2-phenethyl ether.

also participated well in this reaction (Table 1, entries m and n, Scheme 2).

The products were characterized by ^{1}H, ^{13}C NMR, IR and mass spectrometry and also by comparison with authentic compounds.[8] In cases of entries m and p, a single diastereomer was obtained, which was confirmed by ^{1}H NMR spectrum of the crude products and also by comparison with authentic samples.[2] The reactions are operationally simple and highly efficient for the production of symmetrical ethers from carbonyl compounds. There are several advantages in the use of iodine as the catalyst for this transformation, which include high yields of products, operational simplicity, enhanced rates, cleaner reaction profiles and easy availability of the catalyst at low cost. In addition, the reaction conditions are amenable for scale-up. Among various catalysts such as $Sc(OTf)_3$, $Yb(OTf)_3$, $Ce(OTf)_3$, $In(OTf)_3$ $InCl_3$ and $InBr_3$ employed for this conversion, molecular iodine was found to be the most effective catalyst in terms of yields and reaction rates. As solvent, dichloromethane gave the best results. The scope and generality of this process is illustrated with respect to various carbonyl compounds and the results are presented in Table 1.[13]

Mechanistically, it is known that iodine may react with PMHS to produce trimethylsilyl iodide which might be responsible for initiating the reaction and unstable reducing reagent, which rapidly reacts with carbonyl compounds to promote the reduction.[9a] To test this hypothesis; we carried out the reaction with trimethylsilyl iodide (0.25 equiv) and PMHS under otherwise identical conditions. The products were identical to those that were obtained with iodine. However, the products were obtained in low to moderate yields (45–60%) when TMSI was employed as the catalyst. Thus, the combination of PMHS and 2.5 mol % of molecular iodine ($PMHS/I_2$) was found to be effective for this conversion. The use of molecular iodine as a catalyst for the activation of polymethylhydrosiloxane (PMHS), which is an inexpensive and soluble hydrogen source, for the reduction of carbonyl compounds makes this quite simple, more convenient and practical.

In conclusion, iodine has proved to be an effective catalyst for the reductive etherification of various aldehydes with polymethylhydrosiloxane under extremely mild conditions. This method describes a novel use of molecular iodine for the activation of polymethylhydrosiloxane to provide symmetrical ethers from carbonyl compounds. The procedure is very simple, quick and convenient which may find use in organic synthesis.

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13. *Experimental procedure*: To a mixture of benzaldehyde (0.212 g, 2 mmol) and polymethylhydrosiloxane (0.390 g, 6 mmol, Sigma Aldrich) in dichloromethane (10 mL) was added 2.5 mol % of iodine at 0 °C under nitrogen atmosphere. The reaction mixture was stirred at room temperature for specified time in Table 1. After complete conversion, as indicated by TLC, the reaction mixture was diluted with water (10 mL) and washed with $Na_2S_2O_3$ solution and extracted with dichloromethane (2 × 15 mL). The organic layers were dried over anhydrous Na_2SO_4 and purified by column chromatography on silica gel (Merck, 100–200 mesh, 1% ethyl acetate in *n*-hexanes) to afford pure ether. Spectral data for selected products: **3a**: liquid, IR (KBr): ν 2934, 1631, 1490, 1197, 769 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.52 (s, –O–CH_2Ph, 4H), 7.21–7.35 (m, Ar-*H*, 10H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 75.1, 127.4, 128.2, 129.4, 132.3. ESI-MS: *m*/*z* (%): 199 (M+1). Compound **3f**: Liquid, IR (KBr): ν 2925, 1635, 1219, 1054, 772 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.80 (s, –O–CH_3, 6H), 4.58 (s, –O–CH_2Ph, 4H), 6.85 (d, *J* = 8.6 Hz, *m*-Ar-*H*, 4H), 7.25 (d, *J* = 8.6 Hz, *p*-Ar-*H*, 4H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 55.5, 79.5, 114.3, 129.5, 131.2, 159.5. ESI-MS: *m*/*z* (%): 259(M+1). Compound **3j**: Solid, mp 54–55 °C, IR (KBr): ν 2996, 1633, 1439, 1195, 775 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.41 (s, –O–CH_2Ph, 4H), 7.25–7.34 (m, Ar-*H*, 8H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 71.2, 128.8, 129.3, 131.8, 138.5. ESI-MS: *m*/*z* (%): 268 (M+1). Compound **3m**: Liquid, IR (KBr): ν 2923, 1618, 1218, 771 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.66 (d, *J* = 7.0 Hz, –CHCH_3, 6H), 4.24 (q, *J* = 7.0 Hz, –CHCH$_3$, 2H), 7.19–7.37 (m, Ar-*H*, 10H).^{13}C NMR (50 MHz, $CDCl_3$): δ 26.1, 80.1, 126.6, 127.8, 128.7, 145.4. ESI-MS: *m*/*z* (%): 227(M+1).