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Iodination of organic compounds using anion exchange resin supported peroxodisulfate under mild aprotic conditions

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ABSTRACT

Peroxodisulfate was simply supported on a weakly basic ion exchange resin by elution of a column containing the resin with an aqueous potassium peroxodisulfate solution. Resin supported peroxodisulfate was used for mild and selective α-iodination of 1,3-dicarbonyl and α,β-unsaturated carbonyl compounds in the presence of molecular iodine in acetonitrile at room temperature. Also direct and efficient iodination of activated aromatic compounds was performed in acetonitrile under reflux conditions.

Introduction

The use of polymer supported reagents and catalysts provides an attractive, clean and novel method for multi-step organic syntheses. Polymer supported reagents are reactive species which are associated with a polymeric material that perform many synthetic transformations.[1] The reagents usually may be either covalently or ionically attached to a polymer support. Ion-exchange resins, the first synthetic reactive polymers, are widely used as support for preparing polymeric reagents.[2]

Halogenation of organic substrates is an important reaction for the preparation of pharmaceutical and agrochemicals.[3a] Iodine-substituted aromatic compounds have found wide applications in medicine and biochemistry. Also they are important synthetic intermediates in various cross-coupling reactions, especially for carbon-carbon and carbon-heteroatom bond formations.[3b] A number of methods for direct iodination of aromatics have been reported more recently.[4] Examples are amine-iodine complexes in water,[5] triiodoisocyanuric acid in MeCN,[6] $Na_2S_2O_8/I_2/Me_4NI$ in MeCN,[7] H_2O_2/ KI/H_2SO_4 in MeOH,[8] HIO_4/Al_2O_3 in dioxane-water[9] and $(Bu_4N)_2S_2O_8/I_2$ in MeCN.[10] Acidic conditions and/or tedious workup are disadvantages of these procedures.

On the other hand, α-haloketones and α-haloenones are highly reactive intermediates for the generation of α-substituted ketones and enones.[11] The reactivity of α-iodinated carbonyl compounds is higher, especially in transition metal mediated reactions, than the corresponding bromo or chloro derivatives, while functionalization of the 5-position of uracils or uridines is important for the synthesis of chemotherapeutic agents[12a] and synthetic oligonucleotide probes.[12b] Various procedures published in the last years for preparation of α-iodoketones[13] include the use of I_2/CAN,[14] I_2/PDC,[15] I_2/CuO,[16] I_2/DME,[17] HIO_4/Al_2O_3,[9] I_2/oxone®,[18] poly[styrene-co-(4-vinylpyridinum dichloroiodate(-1)],[19] reaction of enol silyl ether with silver acetate-iodine[20] and reaction of enol acetate with N-iodosuccinimide.[21] Only a few reports on the preparation of α-iodoenones have been reported, which employ I_2/ bis(tetra-n-butylammonium)peroxodisulfate [22],[22] I_2/ bis-(trifluoroacetoxy) iodobenzene /pyridine,[23] I_2/amines[24] and I_2/pyridine/CCl_4.[25]

Recently, we used a polyvinylpyrrolidone supported reagent, PVP-H_2O_2 in the presence of I_2 or KI for clean and mild direct iodination of activated aromatic compounds.[26] Herein, we report the preparation of a novel polymer supported peroxodisulfate and it's application for the iodination of 1,3-dicarbonyls, α,β-unsaturated carbonyls and activated aromatic compounds in the presence of iodine at mild aprotic heterogeneous conditions in organic solvents. Due to simple work-up and easy separation of the polymeric reagents from reaction mixtures, applying these reagents in heterogeneous reactions has an important advantage over classic homogeneous ones.

Experimental

Ion exchanger II and other chemicals were obtained from Merck chemical company. The progress of the reactions was followed by GC on a Varian CP-3800instrument and TLC on commercial Merck precoated plates (silica gel 60 F_{254}). Melting points were determined by using open capillary tubes with a Buchi 510 apparatus and corrected. FT-IR and ^{1}HNMR spectra were recorded on a Perkin Elmer RXI spectrometer and a Brucker Avance 300 MHz, respectively.

Preparation of resin supported peroxodisulfate

Ion exchanger II (10 g) was packed into a chromatographic column. The column thoroughly eluted with an aqueous saturated potassium peroxodisulfate (2 L). Then the column was washed with water (1 L), acetone (500 cm^3), acetonitrile (500 cm^3) and dichloromethane (500 cm^3). The resin was dried in vacuo at 40 °C for 24 h. The loading of the polymeric reagent was determined by iodometric method after treating the reagent with saturated aqueous NaOH solution. 1 g of the reagent contains 1 mmol $S_2O_8^{2-}$.

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Iodination of uracil (entry 10, table 1)

To the mixture of uracil (0.224 g, 2 mmol) and iodine (0.508 g, 2 mmol) in 10 cm^3 of CH_3CN was added resin supported peroxodisulfate (1 g). The reaction mixture was stirred at room temperature. After 5 h, the mixture was filtered then was washed with aqueous 5% sodium thiosulfate (2 ×10 cm^3) and distilled water (2 ×10 cm^3). Organic layer was dried over $MgSO_4$ and the solvent was removed in vacuo. The crude product was purified by short column chromatography (silica gel, n-hexane/ ethyl acetate; 3:1). 5-iodo-uracil was obtained (0.428 g) with 90% isolated yield (m.p. 215-220 °C, Lit.[8] 225 °C). ^{1}HNMR ($CDCl_3$): 7.85 (s) ppm.

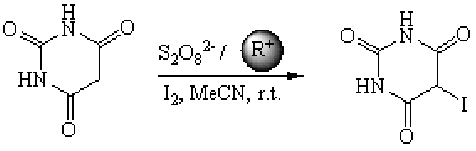
Iodination of anisole (entry 1, table 3)

To the mixture of anisole (0.108 g, 1 mmol) and iodine (0.254 g, 1 mmol) in 5 cm^3 of CH_3CN was added resin supported peroxodisulfate (0.5 g). The reaction mixture was refluxed. After 4 h, when the reaction complete, the mixture was cooled and filtered. Washing of the mixture was performed with aqueous 5% sodium thiosulfate (2 ×10 cm^3) and distilled water (2 ×10 cm^3). Organic layer was dried over $MgSO_4$ and the solvent was removed in vacuo. The crude product was purified by short column chromatography (silica gel, n-hexane/ ethyl acetate; 3:1). 4-iodo-anisole was obtained (0.224 g) with 96% isolated yield (m.p. 48-49 °C, Lit.[8] 46-48 °C). ^{1}HNMR ($CDCl_3$): δ 3.7 (s, 3H), 6.7 (d, J=9 Hz, 2H), 7.5 (d, J=9 Hz, 2H) ppm.

Results and discussion

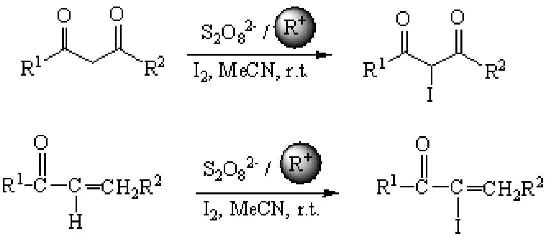
Resin supported peroxodisulfate was easily prepared from a weakly basic ion exchange resin (ion exchanger II) and aqueous saturated potassium peroxodisulfate solution. This reagent was used in iodination reactions after washing with distilled water and organic solvents, and drying. The reagent was stored at room temperature without loss of activity for several months. Loading of the polymeric reagent was determined by iodometric method after treating the reagent with saturated aqueous NaOH solution. 1 g of the reagent contains 1 mmol $S_2O_8^{2-}$. FT-IR spectrum (KBr) of supported peroxodisulfate shows that there is a pattern at the range of 500-1400 cm^{-1} similar to pattern of potassium peroxodisulfate but at slightly lower frequencies (1280, 1042 and 669 cm^{-1} vs. 1300, 1061 and 692 cm^{-1} respectively). This probably occurs due to the formation of hydrogen bonding between peroxodisulfate ion and ammonium groups on resin.

First we optimized reaction conditions including solvent, temperature, and amount of the iodine and polymeric reagent for iodination of barbituric acid (Scheme 1). We observed that iodination was efficiently performed by using 1 equiv. I_2 and 0.5 g polymeric peroxodisulfate in acetonitrile at room temperature. After 4 h, a complete conversion was noticed.



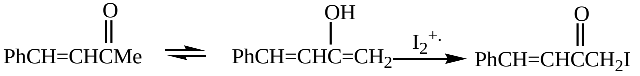
Scheme 1. Iodination of barbituric acid

These conditions were used for α-iodination of other carbonyl compounds including 1,3-dicarbonyl and α,β-unsaturated carbonyl compounds (Scheme 2, Table 1). Polymeric peroxodisulfate could be regenerated after filtering, washing with an aqueous thiosulfate solution, water, NaOH and finally with saturated potassium peroxodisulfate. As shown in table 1 (entry 2), barbituric acid was efficiently iodinated using regenerated resin (98% conversion rate).



Scheme 2. Iodination of 1,3-dicarbonyl and α,β-unsaturated carbonyl compounds

In the case of benzilidene acetone (Table 1, entry 6), an unsaturated methyl ketone, iodination occurs at methyl group instead of iodination of double bond. This reaction appears to proceed via its relatively stable enol form (Scheme 3).[22]

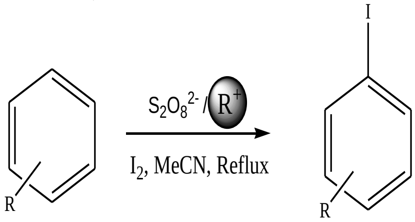


$$\mathrm{PhCH{=}CH\overset{O}{\overset{\|}{C}}Me} \rightleftharpoons \mathrm{PhCH{=}CH\overset{OH}{\overset{|}{C}}{=}CH_2} \xrightarrow{I_2^{+\cdot}} \mathrm{PhCH{=}CH\overset{O}{\overset{\|}{C}}CH_2I}$$

Scheme 3. Iodination of benzilidene acetone via its enol form

Conversion of barbituric acid to the corresponding iodo compound with potassium peroxodisulfate-iodine system is only 40% after 4 h at similar conditions (Table 2, entry 1). We also examined the iodination of barbituric acid by employing other sources of iodine such as KI and CuI in the presence of resin supported peroxodisulfate (Table 2, entries 2-4). After 6 h the conversions are 60% and 10%, respectively.

Also, we found that direct iodination of activated aromatic compounds can be efficiently performed using I_2 in the presence of resin supported peroxodisulfate in CH_3CN at reflux conditions (Scheme 4).



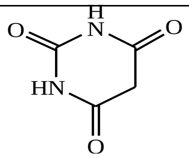
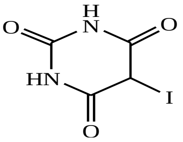
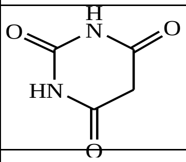
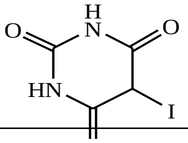
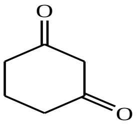
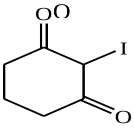
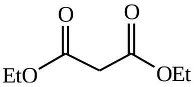
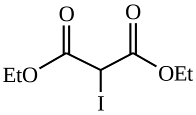
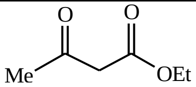
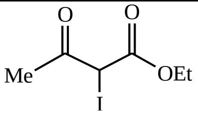
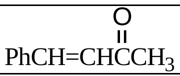
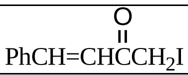
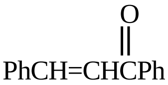
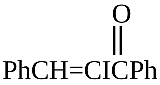
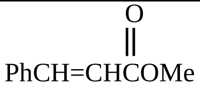
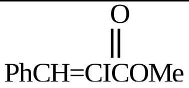
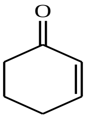
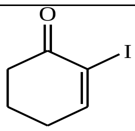
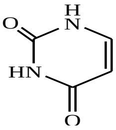
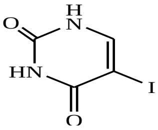
Scheme 4. Direct iodination of activated aromatic compounds

We first optimized the conditions for the iodination of anisole, and then applied them for other aromatic compounds. In these conditions, 4-iodo-anisol was obtained with 96% isolated yield after 4 h (Table 3, entry 1), while at room temperature conversion of the reaction is only 60% at same time. Our results for iodination of structurally different substrates including phenols and other activated aromatic compounds are shown in table 3. Iodination of benzene afforded low yields (Table 3, entry 10).

Conclusion

As shown above, resin supported peroxodisulfate were used for selective mono-iodination of 1,3-dicarbonyl and α,β-unsaturated carbonyl compounds, phenols and other activated aromatic compounds. Many reported methods in literature suffer poor selectivity because they yields di- or tri-iodinated products especially for 1,3-dicarbonyl and activated aromatic compounds.[5,9,27] Also having simple work-up and easy separation of the polymeric reagent from reaction mixture, our method has an important advantage over classic homogeneous ones. For some of mono-iodinated products, obtained yields are compared with some other methods in table 4. As shown in this table, our method has superior yields and/or shorter times in comparison with other method

Table 1. Iodination of carbonyl compounds using resin supported peroxodisulfate and iodine in acetonitrile at room temperature.

Entry	Carbonyl compound	Product [a]	Time (h)	Conversion (%)	Isolated yield (%)
1			4	100	95
2[b]			4	98	90
3			5	100	96
4			6	70	65
5			4.5	90	87
6	 $\mathrm{PhCH{=}CH\overset{O}{\overset{\|}{C}}CH_3}$	 $\mathrm{PhCH{=}CH\overset{O}{\overset{\|}{C}}CH_2I}$	5.5	90	83
7	 $\mathrm{PhCH{=}CH\overset{O}{\overset{\|}{C}}Ph}$	 $\mathrm{PhCH{=}CI\overset{O}{\overset{\|}{C}}Ph}$	6.5	75	70
8	 $\mathrm{PhCH{=}CH\overset{O}{\overset{\|}{C}}OMe}$	 $\mathrm{PhCH{=}CI\overset{O}{\overset{\|}{C}}OMe}$	5	80	74
9			4	85	81
10			5	95	90

[a] All products are known and identified by comparison of their physical and spectroscopic data with those of authentic samples.

[b] The oxidizing reagent was prepared using regenerated resin.

Table 2. Iodination of barbituric acid using different peroxodisulfate and iodine sources in acetonitrile at room temperature.

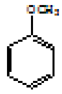
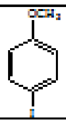
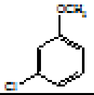
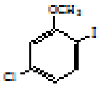
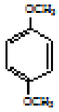
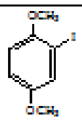
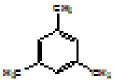
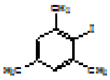
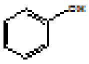
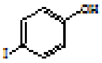
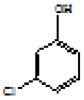
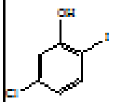
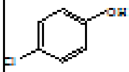
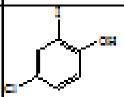
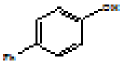
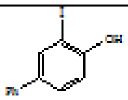
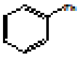
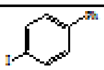
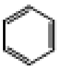
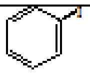
Entry	Reagents	Time (h)	Conversion (%)
1[a]	I_2 , $K_2S_2O_8$	4	40
2[b]	I_2, $S_2O_8^{2-}$ / R^+	4	100
3[c]	KI, $S_2O_8^{2-}$ / R^+	6	60
4[c]	CuI, $S_2O_8^{2-}$ / R^+	6	10

[a] 1 eq. I_2, 1eq. $K_2S_2O_8$

[b] 1 eq. I_2, 0.5 g resin supported $S_2O_8^{2-}$

[c] 2 eq. I^-, 0.5 g resin supported $S_2O_8^{2-}$

Table 3. Iodination of aromatic compounds using resin supported

Entry	Substrate	Product [a]	Time (h)	Isolated yield (%)
1			4	96
2			4	90
3			5	95
4			6	85
5			5.5	85
6			6.5	75
7			7	70
8			4.5	85
9			6	70
10			11	10

[†] References are shown in brackets. [‡] GC yields.

In conclusion, this procedure provides a selective, clean and simple route for efficient iodination of 1,3-dicarbonyl, α,β-unsaturated carbonyl and activated aromatic compounds. High yields, mild reaction conditions, simple workup and regenerablity of the polymeric reagent are other advantages of the method.

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