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2,4,6-Tris(4-iodophenoxy)-1,3,5-triazine as a new recyclable “iodoarene” for in situ generation of hypervalent iodine(III) reagent for α-tosyloxylation of enolizable ketones

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ABSTRACT

The synthesis of 2,4,6-tris[(4-iodo)phenoxy)]-1,3,5-triazine **6**, as a new recyclable nonpolymeric analogue of iodobenzene is achieved using the reaction of 2,4,6-trichloro-1,3,5-triazine with 4-iodophenol in the presence of KOH. The application of **6** as a recyclable ‘iodoarene’ is demonstrated for α-tosyloxylation of enolizable ketones via in situ generation of hypervalent iodine(III) species using PTSA and MCPBA as the terminal oxidant. The recyclability of the reagent **6** was possible owing to the facile recovery and reuse from the reaction mixture due to its near insolubility in methanol.

Hypervalent iodine(III) and iodine(V) reagents have occupied a firm place in modern organic synthesis due to their low toxicity, ready availability, mild conditions, excellent selectivity, and reactivities with those of heavy metal (Pb, Tl, and Hg) oxidants.[1] The hypervalent iodine(III) reagent such as [hydroxy(tosyloxy)iodo]benzene (HTIB) is the sole efficient reagent for inducing α-tosyloxylation of enolisable ketones.[2] The combination of *p*-toluenesulphonic acid (PTSA) with other trivalent iodine reagents such as (diacetoxyiodo)benzene[3] and iodosylbenzene[4] have been also demonstrated for α-tosyloxylation of enolizable ketones. The resulting α-tosyloxyketones are useful doubly electrophilic building blocks and are considered as environmentally benign alternatives to the toxic and lachrymatory α-haloketones. Since it is generally not necessary to isolate the α-tosyloxyketone, they can be utilized in situ as strategic precursors for the one-pot synthesis of a wide range of heterocycles such as thiazoles, selenazoles, oxazoles, imidazoles, pyrazoles, and benzofurans.[5]

The HTIB and other hypervalent iodine reagents are commonly used as stoichiometric oxidants in synthesis and after the reactions, equimolar quantity of iodoarenes are produced as by-products. This demands extensive chromatographic purifications to recover and reuse the relatively expensive iodoarenes from the reaction mixture and a quantitative recovery of the iodoarene is seldom achieved. In view point of Green Chemistry, the formation of iodoarene as by-product is one of the important shortcomings of the process involving hypervalent iodine reagents as it diminishes the overall atom-economy of the reaction.[6] For example, the atom-economy of only 58.7% is achieved in the α-tosyloxylation of acetophenone using HTIB as the oxidant without quantitative recovery of iodobenzene through column chromatographic purification.[7] This particular problem of atom-economy associated with hypervalent iodine reagents has been resolved by using polymer supported hypervalent iodine reagents which promotes the recovery and recycling of iodoarenes due to simple filtration technique.[8] Thus, the preparation of polymer supported HTIB and its application for α-tosyloxylation of enolizable ketones are known in the literature.[9] However, these polymer supported hypervalent iodine reagents require multi-step cumbersome preparation and have poor solubility in various solvents. Furthermore, the repeated use of polystyrene resin leads to the degradation of the polymeric backbone due to benzylic oxidation of the polystyrene chain which may affect the overall yield of the recyclability process. Another progress for recovery and reuse of iodoarene has been achieved by using room-temperature ionic liquid supported HTIB.[10] In this case, iodobenzene anchored to ionic liquid was recovered from the reaction mixture up to 75% using acetonitrile as the eluent. Apart from these strategies, Kita and coworkers have meticulously identified recyclable non-polymeric trivalent iodine reagents based on adamantane[11] and tetraphenylmethane[12] structures. The recyclability of these reagents is due to the near practical insolubility

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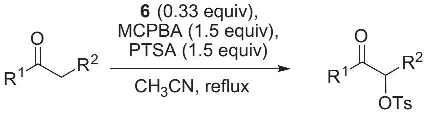
of 'polyiodo derivatives' in hexane or methanol. Based on this concept, 4,4′-bis[(hydroxy)(tosyloxy)iodo]biphenyl has been also demonstrated as the recyclable reagent for α-tosyloxylation of enolizable ketones due to insolubility of 4,4′-diiodobiphenyl in hexane.[13]

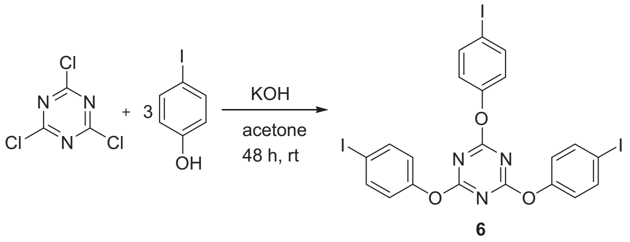
The pioneering work of Ochiai et al. related to the in situ generation of hypervalent iodine(III) reagent using MCPBA as the terminal oxidant has made this field more versatile.[14] Accordingly, a number of methods demonstrating in situ generation of hypervalent iodine(III) using a catalytic[15] as well as stoichiometric quantity of iodoarenes for α-tosyloxylation of enolizable ketones have appeared in the literature. The various polymer[16] as well as ionic liquid[17] supported 'recyclable iodoarenes' have been documented for the α-tosyloxylation of enolizable ketones via the in situ generation of hypervalent iodine(III) using MCPBA as the terminal oxidant (Fig. 1).

Recently, we reported the synthesis and applications of 2,4,6-tris[(4-dichloroiodo)phenoxy)]-1,3,5-triazine as a new recyclable nonpolymeric analogue of (dichloroiodo)benzene for chlorination reaction and the oxidative synthesis of heterocycles.[18] In this case, the recyclability of 2,4,6-tris[(4-dichloroiodo)phenoxy)]-1,3,5-triazine was possible owing to the facile recovery and reuse of the co-produced 2,4,6-tris(4-iodophenoxy)-1,3,5-triazine **6** from the reaction mixture due to its near insolubility in methanol. Herein, we wish to take advantage of this fact for α-tosyloxylation of enolizable ketones via in situ generation of hypervalent iodine(III) species from **6** using MCPBA as the terminal oxidant. Accordingly, the α-tosyloxylation of enolizable ketones was carried out using **6** as a recyclable 'iodoarene', PTSA and MCPBA as the terminal oxidant (Scheme 1).

Our initial studies started with the preparation of 2,4,6-tris(4-iodophenoxy)-1,3,5-triazine **6**.[19] Thus, the reaction of 2,4,6-trichloro-1,3,5-triazine (1 equiv) with a mixture of 4-iodophenol (3 equiv) and KOH in acetone, under stirring condition, at room temperature for 48 h, furnished 2,4,6-tris(4-iodophenoxy)-1,3,5-triazine **6** in 93% yield (Scheme 2).[20]



Scheme 1. α-Tosyloxylation of enolizable ketones.



Scheme 2. Synthesis of 2,4,6-tris[(4-dichloroiodo)phenoxy)]-1,3,5-triazine **6**.

Next, the optimum reaction conditions for α-tosyloxylation were investigated by using the model reaction of acetophenone with various equivalents of triiodo derivative **6**, PTSA, and MCPBA as the terminal oxidant in CH_3CN under reflux. It is observed from Table 1 that the formation of α-tosyloxyacetophenone **8a** took place using 0.1, 0.2, 0.5, and 1.0 equiv of **6** in combination with PTSA (1.5 equiv) and MCPBA (1.5 equiv) as the terminal oxidant. However, the maximum yield of 81% was achieved using 1.5 equiv of **6** in shorter reaction time (4 h).[21] It is important to note that the formation of **8a** did not take place in the absence of **6** which means it acts as the catalyst. Under the present reaction conditions, the formation of Baeyer–Villiger oxidation product was not observed.

The recyclability of the triiodo derivative **6** was achieved using the solubility criteria which was previously reported for the polyiodo derivatives based on adamantane[11] **3**, tetraphenylmethane[12] **4**, and 4,4′-diiodobiphenyl[13] **5**, structures. It was observed that **6** is nearly insoluble (0.02 mg/mL) in methanol.[22] Thus, after the completion of α-tosyloxylation of ketones, the reaction solvent (CH_3CN) was evaporated under reduced pressure followed by addition of methanol. The triiodide **6** was found to be insoluble

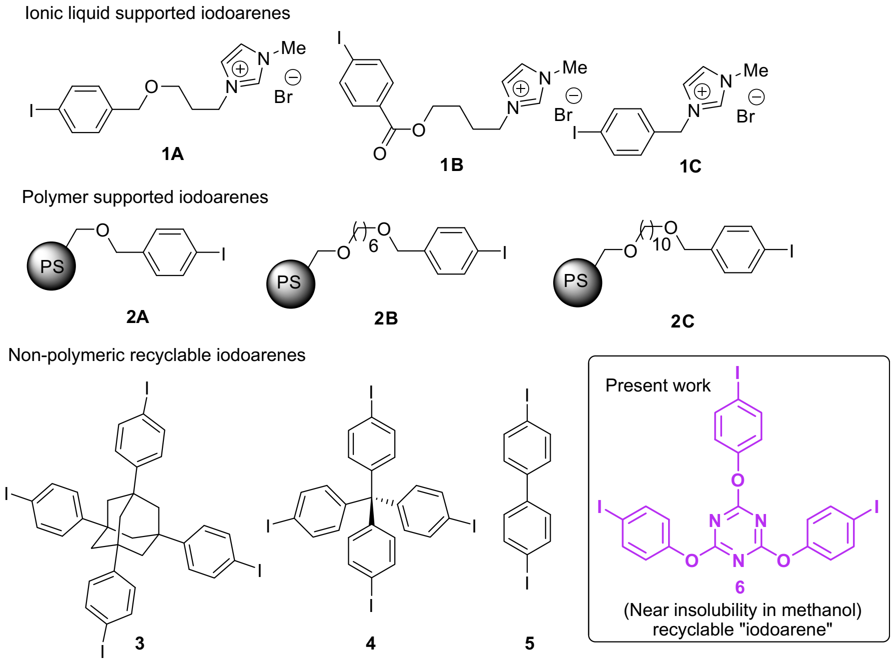


Figure 1. Recyclable 'iodoarenes' used for α-tosyloxylation of enolizable ketones.