

Synthesis, characterisation, and reactivity of novel pseudocyclic hypervalent iodine reagents with heteroaryl carbonyl substituents

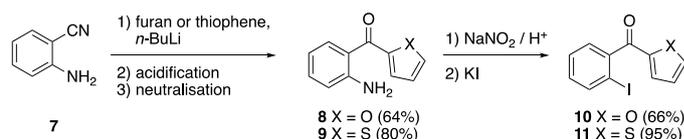
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Two new hypervalent iodine reagents containing furan and thiophene moieties in addition to a carbonyl group in the vicinity of the iodine atom were synthesised and characterised. The X-ray analysis of both compounds revealed a strong intramolecular contact between the carbonyl oxygen and the hypervalent iodine atom with tosylate as a counter ion. The two reagents showed a broad range of synthetic applications and proved to be versatile oxidizing agents.

The chemistry of hypervalent iodine compounds has expanded largely during the last two decades. Due to their readily availability, easy handling and diversity, organic hypervalent iodine reagents are widely used in modern synthetic organic chemistry. Their electrophilic nature, in addition to their superior leaving group ability ($\sim 10^6$ times triflate) are the key features behind their unique reactivity.^{1,2} Hence, hypervalent iodine reagents found a wide range of synthetic applications, especially selective oxidative transformations including, but not limited to, oxidative C–C, C–heteroatom and heteroatom–heteroatom couplings,^{3–6} oxidative rearrangements,^{7–10} difunctionalisation of alkenes,^{11–13} and dearomatisation of phenols.^{14–18} Moreover, hypervalent iodine compounds are environmentally friendly alternatives to heavy metal oxidants as a result of their low toxicity and mild reaction conditions. As hypervalent iodine reagents are electrophilic in nature, heteroatoms in the vicinity of the electrophilic iodine centre affect the structural features, reactivity and selectivity of hypervalent iodine reagents.^{19–21} Various reagents incorporating nitrogen-containing heterocyclic units of various classes have been reported in literature (Figure 1).^{20–26}

Figure 1. Some hypervalent iodine reagents containing heterocycles.

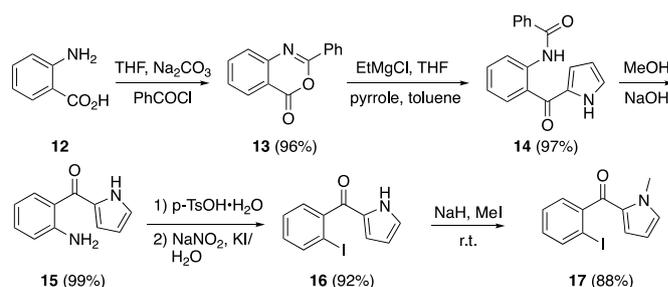
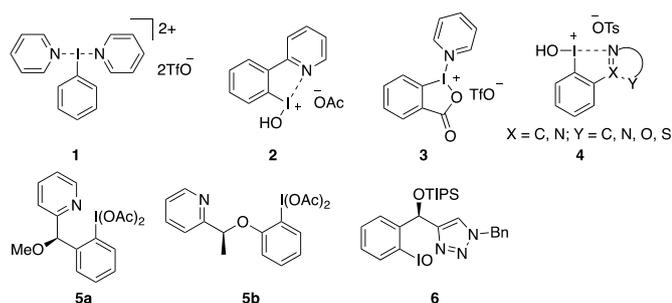
Herein, we report the synthesis of new hypervalent iodine containing 5-membered heterocyclic moieties. The aromatic iodoketone precursors **10** and **11** were prepared in 44% and 77% yield, respectively, over two steps starting from 2-aminobenzonitrile (**7**) as shown in Scheme 1.²⁷



Scheme 1. Synthesis of iodoketones bearing furan and thiophene moieties.

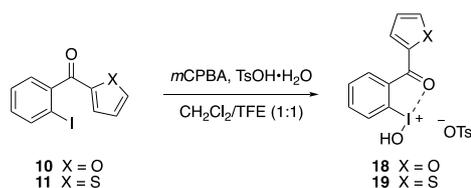
On the other hand, the pyrrole analogue **16** was prepared following a different synthetic route (Scheme 2).^{28,29} Iodoketone **16** was obtained in 85% overall yield starting from anthranilic acid over four steps. *N*-methylation of **16** afforded the iodoketone **17** in 88% yield.

Having the iodoketones **10**, **11** and **17** in hand, their oxidation to the corresponding hypervalent iodine reagents was investigated. Although the oxidation of simple iodoarenes usually proceeds smoothly, the oxidation of **10**, **11** and **17** was cumbersome. A wide range of oxidants and oxidation protocols were investigated, but either there was no reaction at all, or the reaction mixture was very complex to isolate the oxidized products in a pure form, although the ¹H NMR of the crude reaction mixture showed an evidence of the formation of the corresponding iodine(III) species in many attempts.



Scheme 2. Synthesis of iodoketones bearing a pyrrole moiety.

Only the oxidation of iodoarenes **10** and **11** using *m*-chloroperbenzoic acid (*m*CPBA)³⁰ in the presence of *p*-toluenesulfonic acid monohydrate was successful and the products **18** and **19** were isolated in a pure form in 86% and 85% yield, respectively (Scheme 3). The oxidation products of **10** and **11** were recrystallised from hexane-dichloromethane and characterised by single crystal X-ray crystallography. The solid-state structure of the products ruled out the initially expected Koser's³¹ type structures with a close tosylate – iodine distance and confirmed the pseudocyclic^{32,33} forms **18** and **19** manifesting the Lewis-base assisted activation^{21,32} of the iodine centre.



Scheme 3. Oxidation of iodoketones **10** and **11**.

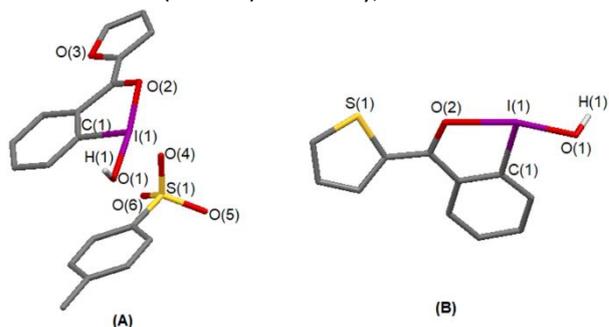
Analysis of the X-ray data of tosylate **18** (Figure 2A) showed the presence of a strong intramolecular interaction of 2.342 Å between the carbonyl oxygen and the hypervalent iodine atom besides one short iodine-oxygen covalent bond [I(1)-O(1) = 1.945 Å] and the iodine-carbon covalent bond [I(1)-C(1) = 2.080 Å]. The observed angle [O(1)-I(1)-O(2)] of the iodonium ion fragment of **18** (167.7°) is in good agreement with the distorted T-shaped geometry characteristic to hypervalent iodine(III) compounds.^{21,34,35}

Although a single crystal of high quality of product **19** could not be obtained, a crystal structure showing only the cationic fragment of product **19** was obtained (Figure 2B). Similar to product **18**, the analysis of the X-ray data of product **19** showed the presence of a strong intramolecular interaction of 2.326 Å between the carbonyl oxygen and the hypervalent iodine atom besides one short iodine-oxygen covalent bond [I(1)-O(1) = 1.943 Å] and iodine-carbon covalent bond [I(1)-C(1) = 2.155 Å] with an observed angle [O(1)-I(1)-O(2)] of 166.7° indicating a distorted T-shaped geometry characteristic to hypervalent iodine(III) compounds.^{21,34,35} The iodonium ion of **19** showed a secondary interaction (2.830 Å) between the coordinated carbonyl oxygen (O(2)) and the sulfur atom (S(1)) of the thiophene ring which is not observed in the case of its furan analogue **18**.

Figure 2. X-ray crystal structure of compound **18** (A) and the cationic fragment of compound **19** (B). Hydrogen atoms bound to carbon atoms were removed for clarity. Selected bond lengths and angles: **18**: I(1)-O(1) 1.945 Å, I(1)-O(2) 2.342 Å, I(1)-C(1) 2.080 Å, O(1)-I(1)-O(2) 167.7°; **19**: I(1)-O(1) 1.943 Å, I(1)-O(2) 2.326 Å, I(1)-C(1) 2.155 Å, O(1)-I(1)-O(2) 166.7°.

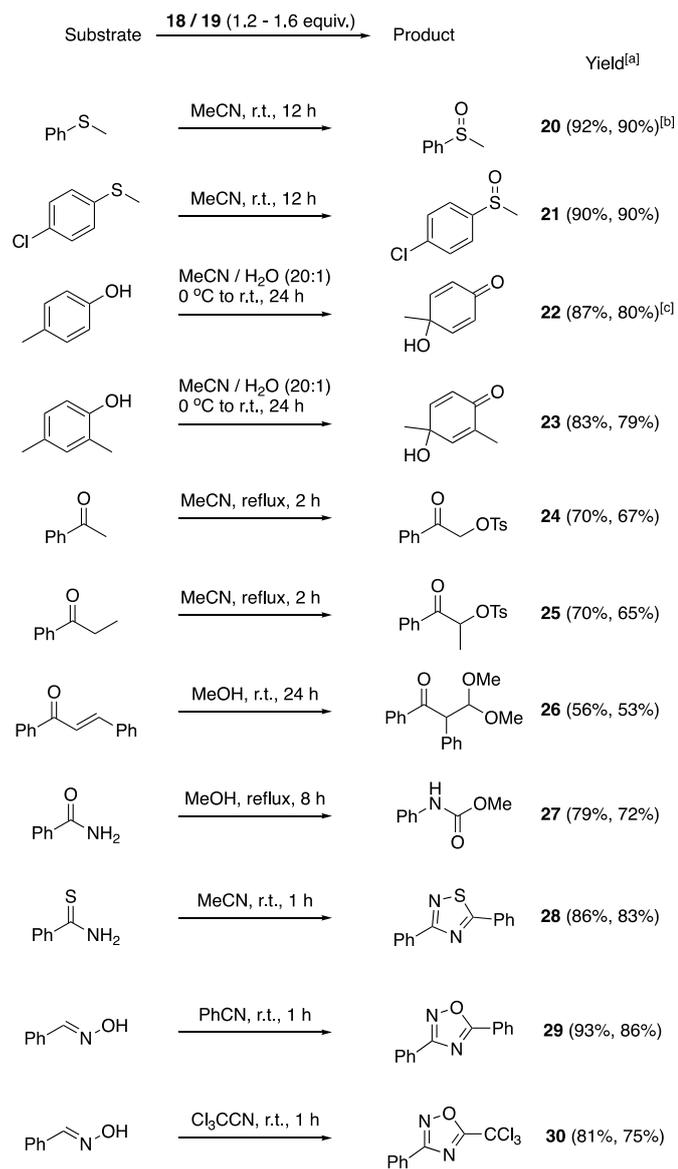
A broad range of potential synthetic applications of hypervalent iodine reagents **18** and **19** as versatile oxidizing reagents is

demonstrated (Table 1). Generally, all the reactions with both



reagents lead to the formation of the expected products in moderate to excellent yields. The furan-derived reagent **18** proved to be more reactive than its thiophene analogue **19** which might be attributed to the presence of additional secondary interaction in the case of compound **19** (*vide supra*) rendering it more stable and hence less reactive.

Sulfoxides **20** and **21** were obtained in excellent yields (90-92%) *via* the oxidation of the corresponding sulfides using **18** and **19**. Oxidizing thioanisole under the same conditions with Koser's reagent led to the isolation of **20** in 80% yield. Phenol dearomatisation of *p*-cresol and 2,4-dimethylphenol lead to the corresponding ketones **22** and **23** in 76 - 83% yield. When Koser's reagent was used as the oxidant for the oxidative dearomatisation of *p*-cresol, the corresponding ketone **22** was obtained in 74% yield. Both compounds **18** and **19** affected the α -tosyloxylation of acetophenone and propiophenone in good yields. Performing the α -tosyloxylation of propiophenone in a catalytic manner using 10 mol% of **10**, **11**, and **17** as organocatalysts in the presence of *m*CPBA as the terminal oxidant led to the formation of product **25** albeit in low yields, 21%, 10%, and 13%, respectively. In addition, the oxidative rearrangement of benzalacetophenone mediated by **18** and **19** in methanol afforded the corresponding α -aryl ketone **26** in 56% and 53% yield, respectively. Moreover, Hofmann rearrangement⁹ of benzamide in methanol led to the corresponding carbamate **27** in good yield. Reagents **18** and **19** are efficient oxidants for oxidative heterocyclisations. 3,5-Diphenyl-1,2,4-thiadiazole (**28**) was obtained in 86% and 83% yield *via* oxidative dimerization of thiobenzamide using reagents **18** and **19**, respectively. In the same context, the reaction of benzaldehyde oxime with **18** and **19** in acetonitrile and 2,2,2-trichloroacetonitrile proceed smoothly to afford 1,2,4-oxadiazoles **29** and **30** in high yields.



^[a] Using **18** and **19**, respectively; ^[b] 80% using Koser's reagent; ^[c] 74% using Koser's reagent.

Table 1. Synthetic applications of reagents **18** and **19**.

Conclusions

In conclusion, the synthesis and structural elucidation of two new hypervalent iodine reagents **18** and **19** is reported. The X-ray analysis of **18** and **19** showed the presence of strong intramolecular interaction (2.342 and 2.326 Å) between the carbonyl oxygen and the hypervalent iodine atom of compounds **18** and **19**. Reagents **18** and **19** are versatile reagents for a wide range of oxidative transformations such as oxidation of sulfides, phenol dearomatisation, oxidative rearrangements and heterocyclisations. In general, both reagents lead to the formation of the products in moderate to excellent yields. Moreover, the furan derived reagent **18** shows higher reactivity than its thiophene analogue **19** in most cases.

Conflicts of interest

The authors declare no conflicts of interests.

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