

Design and synthesis of new electrophilic group transfer reagents

Introduction: The general reactivity of I(III) compounds is determined by the hypervalent, weak nature of the I-R bonds and the partial positive charge localized at the iodine atom, which makes Ar-IX₂ compounds highly electrophilic. Hence, typical reactions of hypervalent I(III)-compounds are substituent transfer to organic compounds or reductive coupling of these same groups (Figure 1). This reactivity has made I(III) compounds very popular reagents in organic synthesis where they are often used as electrophilic transfer reagents for late-stage modifications.[1] Examples of this versatility are the already developed trifluoromethylation, alkynylation, arylation, amination, halogenation and cyanation protocols that are efficient for a wide variety of non-prefunctionalized substrates under quite mild conditions.[2]

Despite of their tremendous synthetic potential, the use of hypervalent I(III) reagents faces serious disadvantages: Their synthesis requires the use of highly reactive and

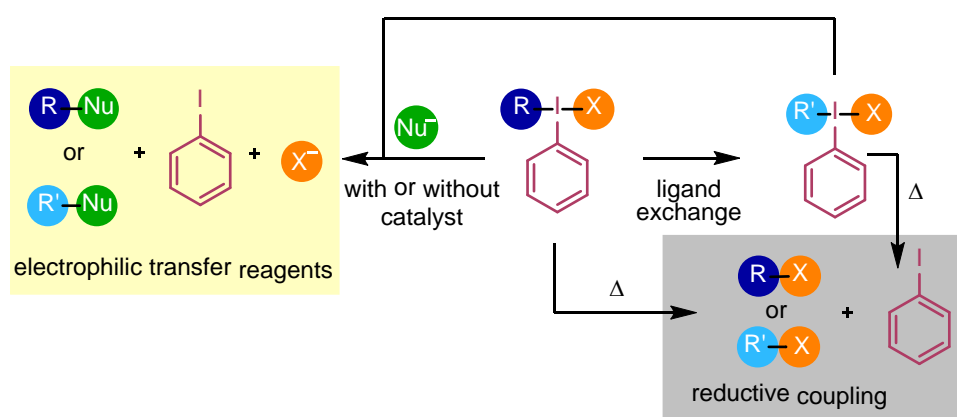


Figure1: Typical reactivity of I(III) compounds

potentially explosive peroxides, and in fact, I(III) derivatives show themselves strong exothermic decompositions on heating. Therefore, they must be handled with an appropriate knowledge and under strict safety measures, especially if big scale reactions are planned. **These shortcuts justify further research** aimed to develop more other electrophilic group-transfer reagents based on more user-friendly platforms.

In this regard, it is surprising that other structurally related scaffolds, yet not based in iodine, have not been evaluated for similar purposes. Hence, we recently envisaged that **imidazolium sulfuranes A**, that are isolobal to I(III) species **B**, and also depict the key three-center four-electron bond motive, might be considered alternative platforms for the development of a new family of

electrophilic group-transfer reagents (Figure 2). Moreover, these species

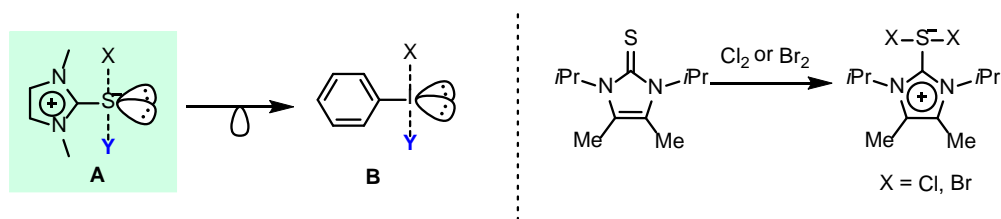


Figure2: Isolobal relationship between I(III) species and imidazolium-substituted sulfuranes . Synthesis of hypervalent sulfur derivatives.

can be very easily obtained as bright yellow to orange solids in high yields and analytic purity by direct halogenation of available thioureas.[3]

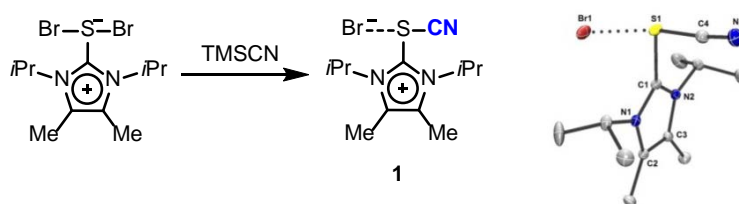


Figure 3: Synthesis and structure of 2-thiocyanimidazolium salts.

-Electrophilic cyanation: In order to test our hypothesis, we first prepared compound **1** and studied its ability to transfer the CN group to organic nucleophiles (Figure 3).

We started our survey by studying the reaction of **1** with simple commercially available amines, and found that the employment of DIPEA as base in dichloromethane efficiently promoted the N-cyanation to afford the desired cyanamides in good isolated yields and short reaction times (Figure 4). The same protocol was also applicable to the cyanation of other substrates such as aromatic thiols, enolates, enamines and activated methylenes providing the corresponding aromatic thiocyanates, β -amido or keto nitriles, and β -cyano sulphones in good to excellent yields. Moreover, the scope of the transformation could be also extended to the cyanation of pyrroles, indoles, electron rich benzene derivatives and polycyclic aromatics.[4]

Our cyanation protocol distinguishes itself by operational simplicity, safeness and a broad reactivity profile if compared with alternative electrophilic cyanating reagents: Cyanogen bromide has a comparable substrate scope; however, its toxicity and low

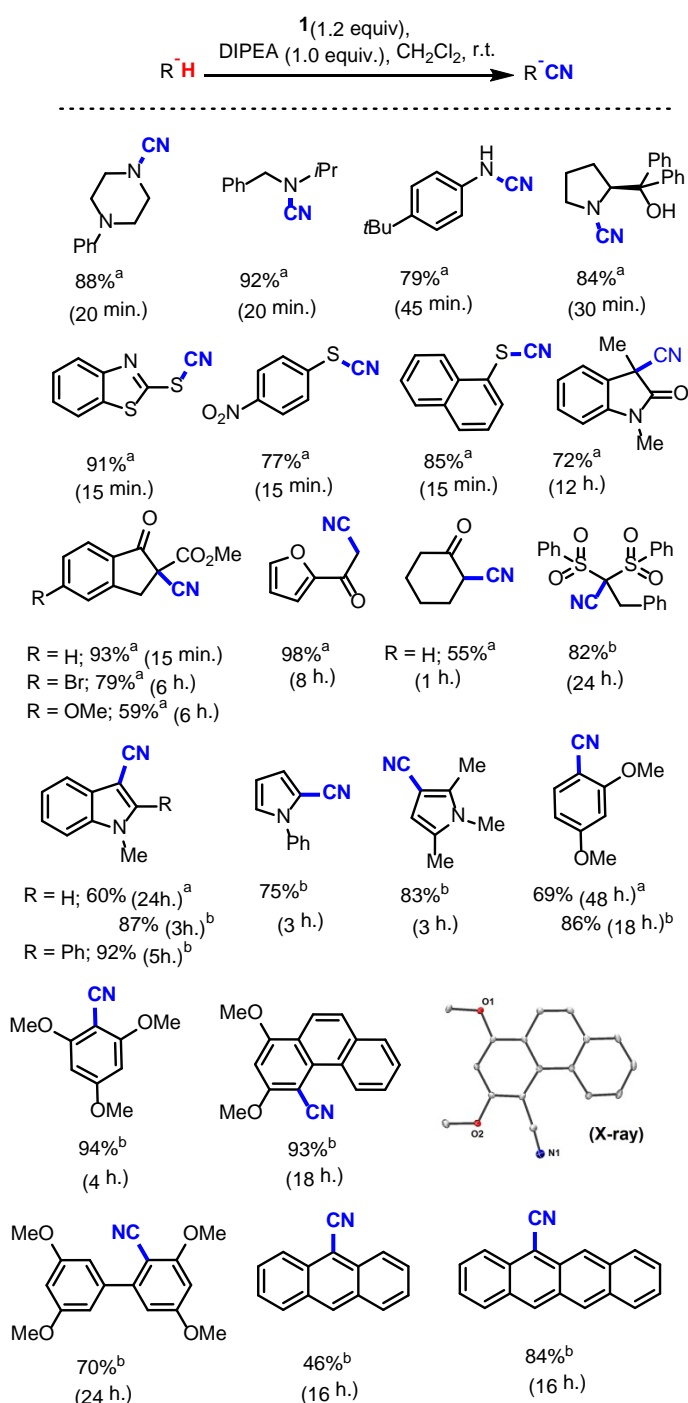


Figure 4: Substrate scope of the electrophilic cyanation using 2-thiocyanimidazolium salt **1**.

yield: Cyanogen bromide has a comparable substrate scope; however, its toxicity and low

vapor pressure at room temperature warns off its use. On the other hand, as already mentioned, cyanating reagents based on hypervalent iodine reagents show strong exothermic decompositions on heating. Analysis of **1** by differential scanning calorimetry (DSC) up to 200°C did not detect any sharp exothermic decomposition signal.

Encouraged by this discovery we set up to explore whether alkynylthioimidazolium salts **2a-k** could also participate in this transformation. Thus, a series of these compounds bearing different functionalizations on the alkyne rests was prepared by reaction of the dihalosulfurane precursor with the desired alkynylzinc bromide. However, already during preliminary investigations, we came across an unexpected finding: simple commercially available Grignards regioselectively attack these salts *at the sulfur atom* affording the corresponding alkynylthioethers **3a-f** in excellent yields (Figure 5). This unique behavior renders alkynylthioimidazolium salts as convenient synthetic equivalents of a formal $[R - C \equiv C - S]^+$ cation.[5]

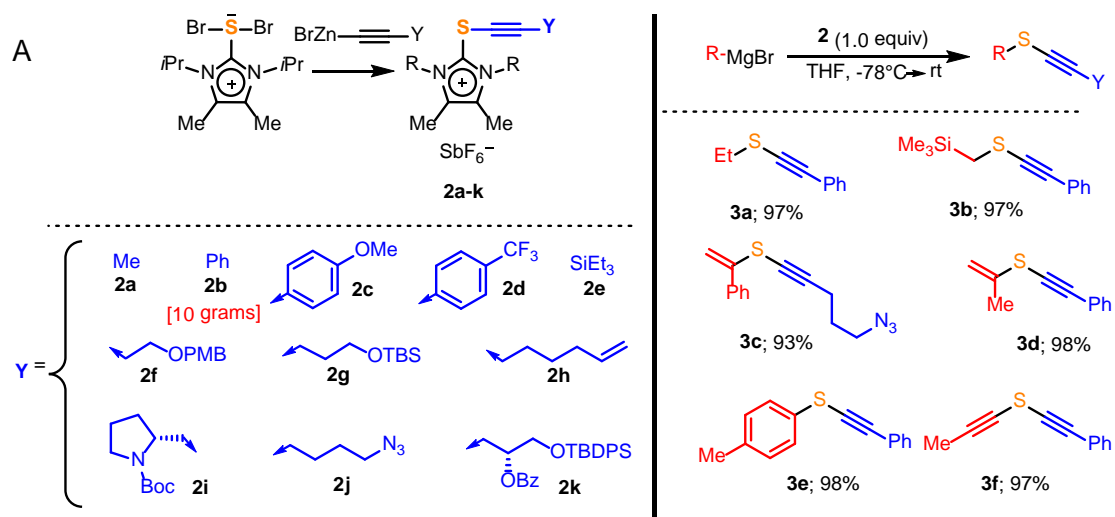


Figure 5: Substrate scope of the electrophilic thioalkynylation using **2a-k**.

Alkyl-, aryl-, alkenyl- and even alkynylgrignards were found to smoothly react under optimized conditions with salts **2a-k** providing a library of alkynylsulfides **3a-f** in good to excellent yields. Specifically, the robustness and applicability of this transformation is highlighted by the successful preparation of fairly hindered thioethers, vinylthioacetylenes, and a series of asymmetric bis(alkynyl)thioacetylenes that are non-obvious to obtain through other routes. Note however, that the preparative significance of this method is limited at this stage by the use of Grignard reagents.

Conclusions and future perspectives:

The potential of imidazolium sulfuranes to become platforms for the development of new reagents able to promote the umpolung of synthetically useful organic groups has been demonstrated. Ongoing studies in our laboratory are aimed to demonstrate the generality of the concept, and to further evaluate the synthetic utility of the new reagents prepared.

References:

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