

Technology Offer

Substituted Imidazolium Sulfuranes and their use as novel Electrophilic Group-Transfer Reagents

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The ability of hypervalent iodine compounds to act as electrophilic group-transfer reagents has been extensively exploited during the last several years in a variety of synthetically useful transformations

like cyanations and alkynylations. Now it was found, that novel imidazolium sulfuranes, which are isolobal to I(III) species and also depict the key three-center four-electron bond motive, can be used as an alternative platform for the development of new electrophilic group-transfer reagents.

Imidazolium thiocyanates could be synthesized in multigram quantities with high yields and isolated as air stable solids that can be stored at room temperature for months without evident decomposition. Used in cyanating reactions, these novel reagents distinguish themselves by operational simplicity, safeness and a broad reactivity profile.

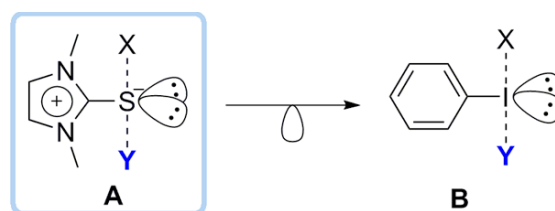
Additionally 2-Imidazolium thioalkynes, which can be used as novel alkynylation reagents, could be synthesized and were tested.

Background

The ability of hypervalent iodine compounds to act as electrophilic group-transfer reagents has been extensively exploited during the last several years in a variety of synthetically useful transformations.

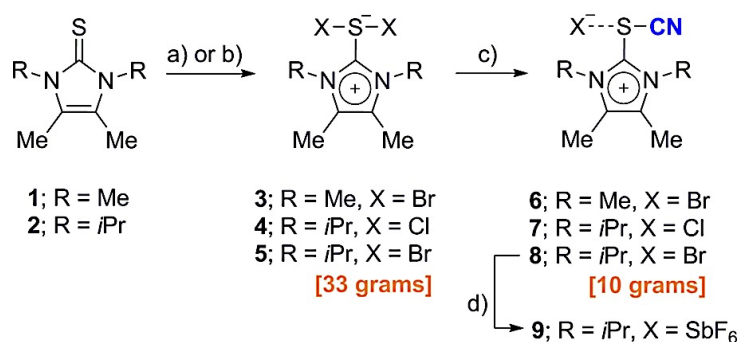
These include trifluoromethylation, alkynylation, arylation, amination, halogenation, cyanation. As cyanating reagents based on hypervalent iodine reagents show strong exothermic decompositions on heating - and therefore, must be handled with appropriate knowledge and safety measures - the development of novel cyanating reagents - distinguishing themselves by operational simplicity, safeness and a broad reactivity profile - would be desirable.

Imidazolium sulfuranes (A), which are isolobal to I(III) species (B) and also depict the key three-center four-electron bond motive, might be alternative platforms for the development of new electrophilic group-transfer reagents.



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By submitting thioureas 1 and 2 (Scheme 1) to well known halogenation conditions, the corresponding hypervalent sulfur compounds 3–5 are obtained as solids in high yields and analytic purity. Subsequent addition of one equivalent of Me₃SiCN caused the formation of the desired imidazolium thiocyanates 6–8.



Scheme 1:
Synthesis of 2-Thiocyanimidazolium Salts
Reagents and conditions (yields):
(a) Br₂, CH₂Cl₂, 0 °C → RT;
3 (97%); 5 (95%);
(b) SO₂Cl₂, CH₂Cl₂, RT;
4 (74%);
(c) TMSCN, CH₂Cl₂, RT;
6 (96%); 7 (94%); 8 (89%);
(d) AgSbF₆, CH₃CN, RT;
9 (95%).

Compounds 6–8 were isolated as air stable solids in excellent yields and can be stored at room temperature for months without evident decomposition. DSC analysis of 8 up to 200 °C did not detect any sharp exothermic decomposition signal.

The synthetic route toward 6–8 could be scaled to multigram quantities.

The reaction of 8 with commercially available amines with the employment of DIPEA as base in dichloromethane efficiently promoted the N-cyanation to afford the desired cyanamides 10–13 in good isolated yields and short reaction times (Chart 1). The presence of alcohol substituents, as in the case of S-diphenylprolinol, does not seem to be detrimental for the process.

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 14–16, β-amido or keto nitriles 17–22, and β-cyano sulphones 23 in good to excellent yields.

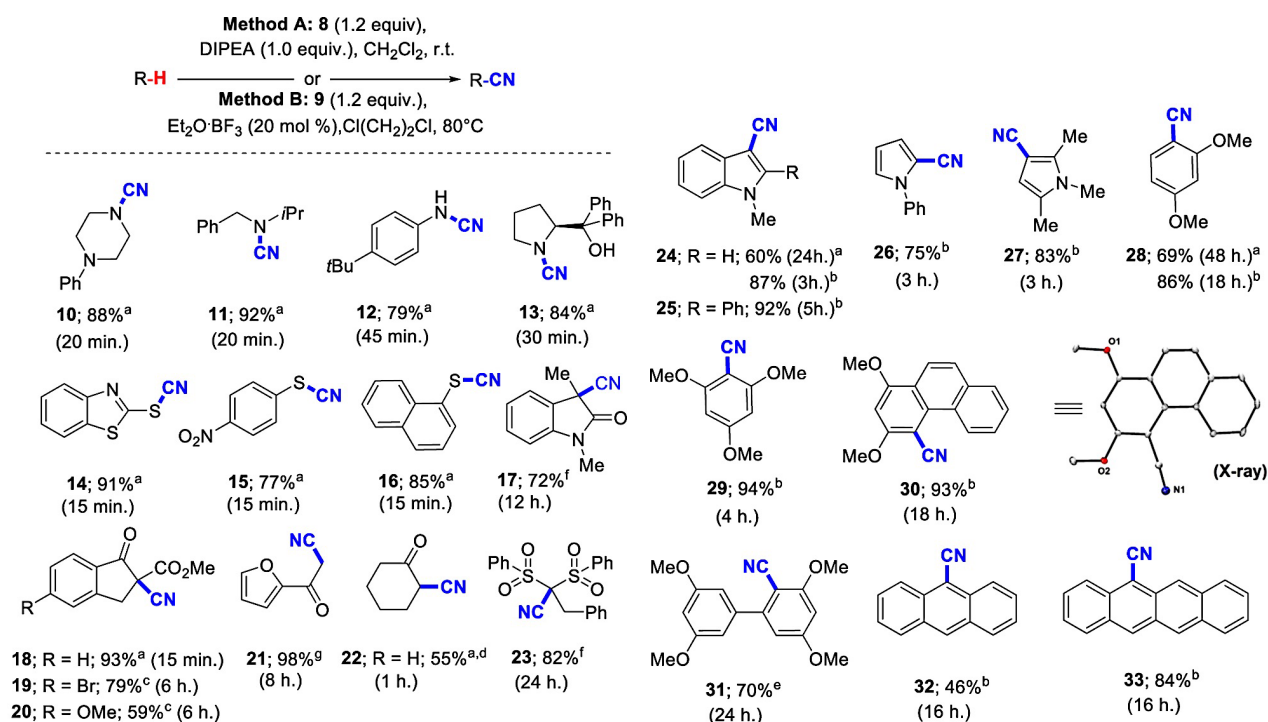
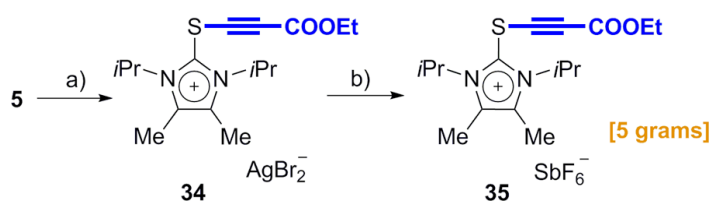


Chart 1: Substrate Scope of the Electrophilic Cyanation Using 2-Thiocyanimidazolium Salts 6–9.
aMethod A was applied. bMethod B was used. cMethod A was applied, but 6 was used as cyanating reagent. dThe corresponding pyrrolidine enamine was used as starting material. eMethod B was applied, but the reaction was heated at 110 °C in a microwave oven. fMethod A was applied, but NaH was used as base. gMethod A was applied, but CH₃CN was used as solvent. All yields are of isolated products.



To further prove the utility of the novel imidazolium sulfurane platform for the design of electrophilic group-transfer reagents, also 2-Imidazolium Thioalkynes like 34 and 35 were prepared.



Reagents and conditions (yields): (a) AgCC-COOEt, CH₂Cl₂, RT; (b) AgSbF₆, CH₂Cl₂, RT; 35 (93%, two steps)

In the presence of DIPEA the alkynylation of aliphatic, electron rich, and electron poor aromatic thiols proceeded in excellent yields.

Several activated amides and ketoesters also afforded the desired alkynylated products.

In summary, imidazolium sulfuranes could become a platform for the development of new reagents able to promote the umpolung of synthetically useful organic groups and hence will be interesting alternatives to hypervalent I(III) reagents.

Literature

Garazi Talavera, Javier Peña, Manuel Alcarazo: "Dihalo(imidazolium)sulfuranes: A Versatile Platform for the Synthesis of New Electrophilic Group-Transfer Reagents", J. Am. Chem. Soc. 2015, 137, 8704–8707

Patent Information

EP priority patent application filed in June 2015.
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