JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

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Dihalo(imidazolium)sulfuranes: A Versatile Platform for the Synthesis of New Electrophilic Group-Transfer Reagents

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Supporting Information

ABSTRACT: The syntheses of imidazolium thiocyanates and imidazolium thioalkynes from dihalo(imidazolium) sulfuranes are reported and their reactivities as CN^+ and R-CC^+ synthons evaluated, respectively. The easy and scalable preparation of these electrophilic reagents, their operationally simple handling, broad substrate scope, and functional group tolerance clearly illustrate the potential of these species to become a reference for the direct electrophilic cyanation and alkynylation of organic substrates.

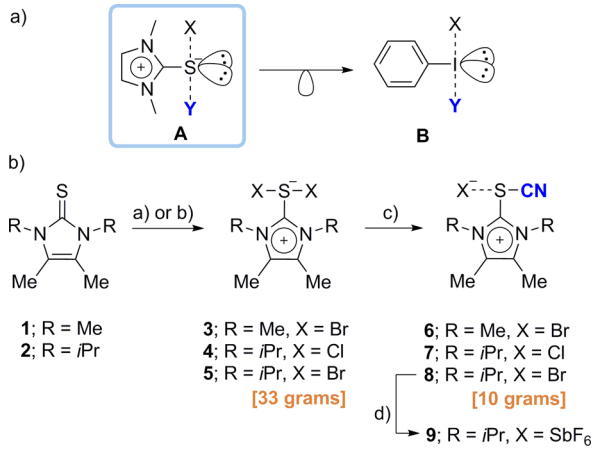
The unique ability of hypervalent iodine compounds to act as electrophilic group-transfer reagents has been extensively exploited during the last several years in a variety of synthetically useful transformations.[1] These include, among others, trifluoromethylation,[2] alkynylation,[3] arylation, amination,[4] halogenation, and cyanation[5] of a wide variety of electron-rich substrates under mild conditions. Considering this tremendous synthetic utility, it is surprising that other structurally related scaffolds, yet not based in iodine, have not been evaluated for similar purposes. In this regard, we envisaged that imidazolium sulfuranes **A**, which 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 new electrophilic group-transfer reagents (Scheme 1a). Herein, we report the successful implementation of this working hypothesis to the specific design of new sulfur-based direct cyanation and alkynylation reagents. The synthetic potential as CN^+ and R-CC^+ equivalents of the newly prepared species is also preliminary assessed.

As an extension of the pioneering research of Arduengo,[6] Kuhn[7] and Roesky[8] in the area of sulfurane chemistry, we submitted thioureas **1** and **2** to already described halogenation conditions and obtained the corresponding hypervalent sulfur compounds **3**−**5** as bright yellow to orange solids in high yields and analytic purity (Scheme 1).[9] Subsequent addition of one equivalent of Me_3SiCN caused the immediate disappearance of the color and formation of the desired imidazolium thiocyanates **6**−**8**. Compounds **6**−**8** were isolated as air stable pale yellow solids in excellent yields and can be stored at room temperature for months without evident decomposition. This synthetic route toward **6**−**8** could be scaled to multigram quantities.

The solid state structures of compounds **5**, **8**, and **9** (prepared from **8** after anion exchange with $AgSbF_6$) are depicted in Figure 1. As expected from a VSEPR analysis, **5** adopts the T-shape geometry that is also characteristic for I(III) species. The Br1−S1−Br2 distribution is nearly linear (177.5(2)°), and the three center four electron bond is characterized by two identical S−Br bond distances (2.505(3) Å) that are clearly elongated as compared with those in sulphenyl bromides (2.169(2) Å for Ph_3CSBr).[10] Formal substitution of one of the bromides by a less polarizable cyano group causes an elongation of the S1−Br1 distance in **8**. However, it is interesting to note that the measured Br1−S1 interatomic distance (3.087(3) Å) is 15% shorter than the sum of the van der Waals radii Br−S (3.650 Å). This speaks for a weak interaction between these two atoms, which can be described as the donation of electron density from the bromide to the low lying σ*(S1−C4) orbital. Not surprisingly, the noncoordinating nature of the hexafluoroantimonate anion in **9** cancels this interaction, and as result, the S1−C4 bond slightly shortens (1.702(2) Å) when compared to **8** (1.734(2) Å). In addition, the C1−S1−C4 angle slightly opens from 95.98(8)° in **8** to 98.61(9)° in **9**.

Once prepared, the ability of these species to transfer the CN group to organic nucleophiles was evaluated. We started our survey by studying the reaction of **8** with simple commercially available amines and found that the employment of DIPEA as

Scheme 1. Isolobal Relationship between I(III) Species and Imidazolium-Substituted Sulfuranes; Synthesis of 2-Thiocyanoimidazolium Salts[a]



[a]Reagents and conditions (yields): (a) Br_2, CH_2Cl_2, 0 °C → RT; **3** (97%); **5** (95%); (b) SO_2Cl_2, CH_2Cl_2, RT; **4** (74%); (c) TMSCN, CH_2Cl_2, RT; **6** (96%); **7** (94%); **8** (89%); (d) $AgSbF_6$, CH_3CN, RT; **9** (95%).

Received: May 21, 2015
Published: July 1, 2015

DOI: 10.1021/jacs.5b05287
J. Am. Chem. Soc. 2015, 137, 8704−8707

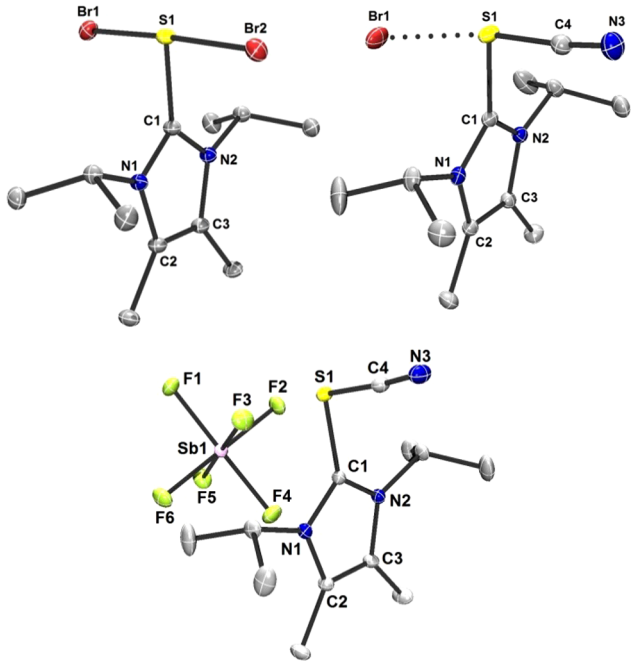


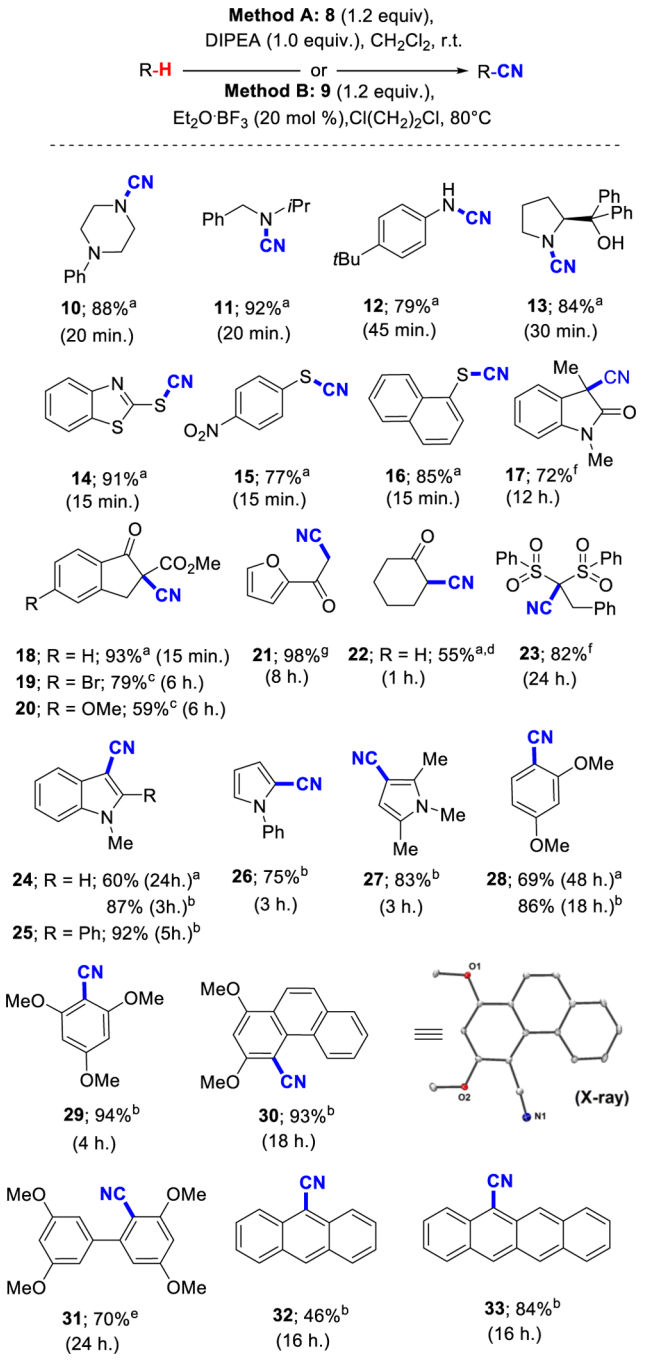
Figure 1. Molecular structures of compounds **5** (up, left), **8** (up, right), and **9** (down). Anisotropic displacement parameter shown at 50% probability level and hydrogen atoms omitted for clarity. Selected bond lengths [Å] and angles [deg] in **5**, C1−S1, 1.736(2); S1−Br1, 2.505(3); S1−Br2, 2.505(3); C1−S1−Br2, 88.78(1); in **8**, C1−S1, 1.744(2); S1−Br1, 3.087(3); S1−C4, 1.734(2); C1−S1−C4, 95.98(8); and in **9**, C1−S1, 1.750(2); S1−F3, 2.830(2); S1−C4, 1.702(2); C1−S1−C4, 98.61(9).[11]

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).[12] The presence of alcohol substituents, as in the case of *S*-diphenylprolinol, does not seem to be detrimental for the process (**13**). 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.[13,14] Note that for the preparation of **19** and **20**, compound **6** was preferred to **8** as cyanating reagent since thiourea byproduct **1** is easier to separate than **2** from the title products.

The direct cyanation of C−H bonds in aromatic compounds has a tremendous interest since (hetero)aromatic nitriles are really valuable intermediates not only in synthetic and medicinal chemistry but also in material science.[15] Therefore, we focused our efforts on these more challenging compounds. At the outset, we took *N*-methylindole as model substrate. As shown in Chart 1, using the procedure already described (Method A), *N*-methylindole was regioselectively cyanated at the C-3 position (**24**), albeit with moderate conversion. Assuming that additional activation of the cyanating reagent could be beneficial when less nucleophilic substrates were employed, we pursued the same transformation in the presence of catalytic amounts of Lewis acids. In these assays the employment of **9** (with hexafluoroantimoniate counteranion) as cyanating reagent is mandatory since the presence of halide anions cancels any catalyst effect.

After an extensive survey, the use of catalytic amounts of $BF_3{\cdot}OEt_3$ (20 mol %) was determined to be optimal to promote the cyanation of *N*-methylindole in terms of isolated yield and

Chart 1. Substrate Scope of the Electrophilic Cyanation Using 2-Thiocyanoimidazolium Salts 6−9



[a]Method A was applied. [b]Method B was used. [c]Method A was applied, but **6** was used as cyanating reagent. [d]The corresponding pyrrolidine enamine was used as starting material (see the SI). [e]Method B was applied, but the reaction was heated at 110 °C in a microwave oven. [f]Method A was applied, but NaH was used as base. [g]Method A was applied, but CH_3CN was used as solvent. All yields are of isolated products.[11]

reaction time, which was up to eight-fold reduced (Chart 1, compound **24**, Method B). Having found these new reaction conditions, the scope of the transformation was further explored. Gratifyingly, the range of additional substrates that could be also converted into the desired nitriles could be substantially expanded, including substituted pyrroles, electron rich benzene

DOI: 10.1021/jacs.5b05287
J. Am. Chem. Soc. 2015, 137, 8704−8707

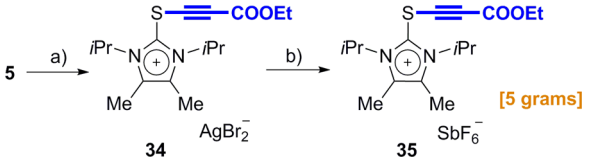
derivatives, and polycyclic aromatics (Chart 1, compounds **24**–**33**).[16]

To preliminarily elucidate some mechanistic aspects of this reaction, we carried out the cyanation of *N*-methylindole in the presence of typical radical inhibitors such as TEMPO or BHT (50 mol % each), finding no drop in the yield of the cyanated product. Moreover, the functionalization of *N*-methylindole is completely selective at the C-3 position, and no oxidative coupling products were detected. Combining these results suggests an electrophilic substitution mechanism rather than a radical pathway for this process.[17]

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 vapor pressure at room temperature warns off its use. Cyanating reagents based on hypervalent iodine reagents show strong exothermic decompositions on heating, and therefore, they must be handled with appropriate knowledge and safety measures.[11] In contrast, analysis of **8** by differential scanning calorimetry (DSC) up to 200 °C did not detect any sharp exothermic decomposition signal (see the Supporting Information).

In an attempt to further evaluate the utility of the imidazolium sulfurane platform **A** for the design of additional electrophilic group-transfer reagents and considering the analogue electronic structure between cyanides and alkynes decorated with electron withdrawing substituents, we speculated that imidazolium thioalkynes such as **34** might also be suitable reagents for the electrophilic alkynylation of organic substrates.[18] Hence, we first set up to prepare salt **34** by reaction of **5** with lithiated ethyl propiolate; however, only complex reaction mixtures were obtained. Conversely, addition of the softer silver propiolate to solutions of **5** afforded the desired alkynylated imidazolium **34** as dibromoargentate salt.[19] This primary product slowly decomposes in the presence of light. Hence, **34** was directly elaborated through anion exchange to **35**, which is a slightly orange powder insensitive to light or air (Scheme 2).

Scheme 2. Synthesis of 2-Imidazolium Thioalkynes[a]



[a]Reagents and conditions (yields): (a) AgCC–COOEt, CH_2Cl_2, RT; and then (b) $AgSbF_6$, CH_2Cl_2, RT; **35** (93%, two steps).

Figure 2 shows the X-ray structure of **35**. It features very similar attributes to those of **9**; a S1–C4 bond length of 1.684(9) Å and a C1–S1–C4 angle of (98.2(4)°). Of particular relevance are the short contacts that **35** depicts between the O1 of a molecule and the S1 and C4 atoms from an adjacent one (O1–S1, 2.871 Å; O1–C4, 2.955 Å). This intermolecular self-organization, which bridges the electrophilic and nucleophilic moieties of neighboring cations, indirectly supports the mechanistic picture already proposed (see the Supporting Information).

With **35** completely characterized, its potential as ethynylation reagent was preliminarily examined. In the presence of DIPEA, the alkynylation of aliphatic, electron rich, and electron poor

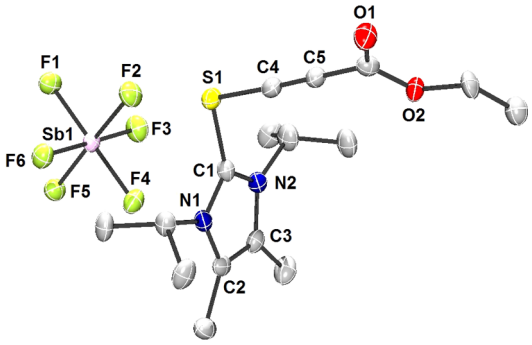
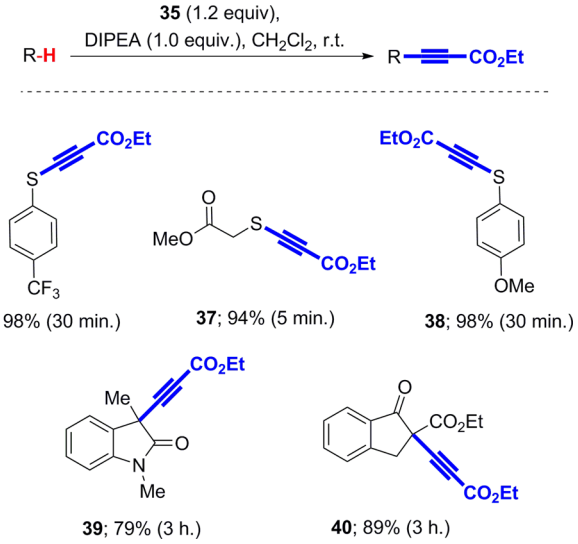


Figure 2. Molecular structures of compound **35** in the solid state. Anisotropic displacement parameter shown at 50% probability level and hydrogen atoms omitted for clarity. Selected bond lengths [Å] and angles [deg]: C1–S1, 1.758(8); S1–F3, 3.073(8); S1–C4, 1.684(9); C1–S1–C4, 98.2(4).[11]

aromatic thiols smoothly proceeded in excellent yields (Chart 2, **36**–**38**). Activated amides and ketoesters also afforded the

Chart 2. Substrate Scope of the Electrophilic Alkynylation Using 2-Imidazolium Thioalkyne 35[a]



[a]All yields are of isolated products.

desired alkynylated products (Chart 2, **39** and **40**); however, electron rich benzene derivatives or polycyclic aromatic compounds did not react with **35** even in the presence of catalytic $BF_3{\cdot}OEt_3$ or stoichiometric amounts of Brønsted acids.

In summary, this work illustrates the potential of imidazolium sulfuranes to become reference platforms for the development of new reagents able to promote the umpolung of synthetically useful organic groups. In this regard they might be interesting alternatives to hypervalent I(III) reagents. 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.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures including the characterization data for all new compounds, additional crystallographic information, and NMR spectra. The Supporting Information is available free of

DOI: 10.1021/jacs.5b05287
J. Am. Chem. Soc. 2015, 137, 8704–8707

charge on the ACS Publications website at DOI: 10.1021/jacs.5b05287.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

Generous financial support from the Fonds der Chemischen Industrie (Dozentenstipendium to M.A.) and the Deutsche Forschungsgemeinschaft (AL 1348/4-1) is gratefully acknowledged. We also thank Prof. A. Fürstner for constant support of our research programs, Prof. K. R. Pörschke for DSC measurements, and our X-ray crystallography department for assistance. G.T. thanks the regional government of the Basque Country (Spain) for support.

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DOI: 10.1021/jacs.5b05287
J. Am. Chem. Soc. 2015, 137, 8704−8707