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Tropylium Ion Mediated α-Cyanation of Amines

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Supporting Information

ABSTRACT: Tropylium ion mediated α-cyanation of amines is described. Even in the presence of KCN, tropylium ion is capable of oxidizing various amine substrates, and the resulting iminium ions undergo salt metathesis with cyanide ion to produce aminonitriles. The byproducts of this transformation are simply cycloheptatriene, a volatile hydrocarbon, and water-soluble potassium tetrafluoroborate. Thirteen total substrates are shown for the α-cyanation procedure, including a gram scale synthesis of 17β-cyanosparteine. In addition, a tropylium ion mediated oxidative aza-Cope rearrangement is demonstrated.

Iminium ions are a functional group with broad utility for the strategic formation of carbon−carbon bonds and amine stereocenters. Unfortunately, the traditional approach to iminium ion formation by way of carbonyl-amine condensation presents significant challenges in terms of scope, efficiency, and substrate compatibility. In this regard, amine oxidation represents a highly attractive conceptual alternative to the condensation approach for iminium ion formation.[1] When coupled with subsequent nucleophilic trapping, amine oxidation also offers a useful means to achieve amine α-functionalization. In this communication, we describe the use of tropylium ion as a powerful reagent for amine oxidation and α-cyanation.

The value of amine oxidation has long been recognized, and a variety of amine oxidation methods have been reported that make use of transition metals,[2] DDQ,[3] $PhI(OAc)_2$,[4] or singlet oxygen[5] as oxidants. On the other hand, the substrate scope reported with metal oxidants has been notably narrow, and is often focused on *N*,*N*-dialkylaniline or tetrahydroisoquinoline motifs. In addition, circumstances often exist in which the use of metal reagents is undesirable, either for reasons of cost or toxicity. While the use of DDQ or singlet oxygen for amine oxidation has been shown in more diverse contexts, these reagents are not highly amenable to broad structural modification. For these reasons, the development of mild and selective new approaches to amine oxidation stands as an important goal.[6]

As a highly intriguing conceptual alternative, the use of carbocations, such as trityl[7] and tropylium ions,[8] to oxidize amines via hydride abstraction has been demonstrated in a limited context, although the synthetic utility of such processes has not been broadly explored. Because of their wide steric and electronic tunability, we have become interested in the development of aromatic cations, such as tropylium ion, as versatile hydrocarbon-based oxidizing agents.

Tropylium ion,[9] (Figure 1) the 6π-electron one-carbon homologue of benzene, was first prepared by Doering and Knox in 1954[10] and is now commercially available as one of several stable and easily handled salts. Our interest in this reagent was piqued by a report that tropylium ion could effect the conversion of amines to the corresponding α-tropylated iminium ions.[11] Although of rather limited synthetic utility, this finding led us to consider whether the hydride abstracting ability of tropylium ion could be employed in synthetically useful ways.

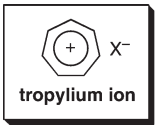
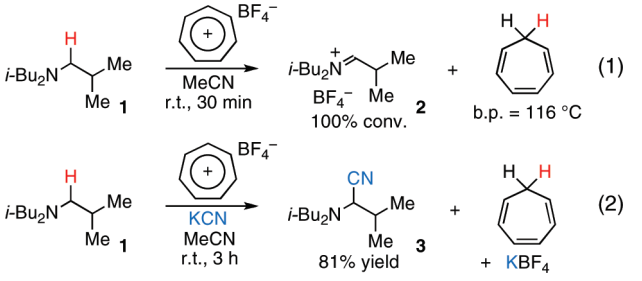


Figure 1. Tropylium ion.

With this aim, we first examined the action of tropylium ion on an amine substrate that would not be prone to enamine formation/α-alkylation, namely, triisobutylamine (eq 1). After stirring *i*-Bu_3N (**1**) and tropylium tetrafluoroborate for 30 min in acetonitrile, we observed quantitative formation of iminium ion **2**, along with cycloheptatriene. Notably, when potassium cyanide was added to the reaction mixture *prior to oxidation*, we observed the α-cyanated product **3** in 81% yield (eq 2). The compatibility of tropylium and cyanide ions was surprising, since Doering had reported the preparation of cycloheptatrienylnitrile by this very combination.[12] Nevertheless, we recognized that the fact that tropylium did not undergo quenching by cyanide under these conditions offered a practical new means to achieve the mild and convenient α-cyanation of amines. Indeed, it is worth noting that the only byproducts of this transformation were cycloheptatriene, a volatile hydrocarbon (bp 116 °C), and the water-soluble salt potassium tetrafluoroborate.



Our rationale for the success of the reaction shown in eq 2 is centered on the fact that KCN is essentially insoluble in acetonitrile, which therefore prevents the formation of cycloheptatrienylnitrile (**9**) and allows tropylium ion to oxidize the amine substrate (Figure 2, cf. **4** → **5**). Indeed, the addition of

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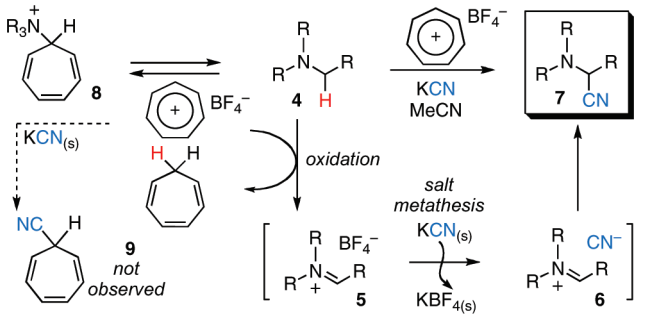
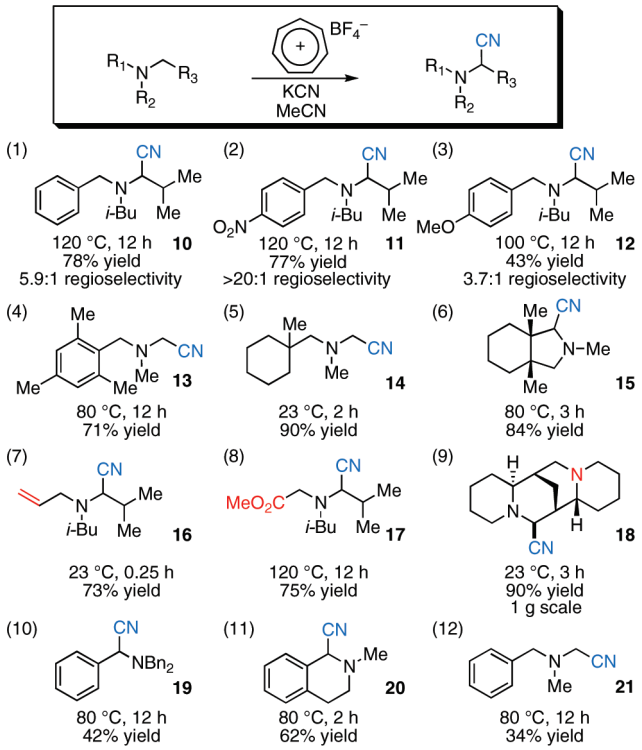


Figure 2. Mechanistic analysis of amine α-cyanation.

Table 1. Substrate Scope Studies for Amine α-Cyanation.[a]



[a] Reactions were performed by combining the substrate, 1 equiv tropylium salt, and 2 equiv KCN in MeCN in a sealed vial. Yields determined on isolated and purified products.

18-crown-6 to the reaction mixture or the use of TMSCN as the cyanide source resulted in rapid formation of nitrile **9** and complete suppression of amine oxidation. In the presence of the insoluble cyanide source, however, iminium ion **5** can undergo salt metathesis with KCN to produce an iminium cyanide intermediate **6**, which then collapses to the aminonitrile product **7**. It is not clear at present why iminium ion **5** is capable of solubilizing cyanide ion whereas tropylium ion is not.

We have found that the substrate scope of tropylium-mediated amine α-cyanation is usefully broad, and displays some intriguing regioselective preferences (Table 1). For example, benzyl diisobutylamine **10** underwent α-cyanation in good yield at elevated temperature with a 5.9:1 selectivity for aliphatic oxidation (entry 1), presumably reflecting an inherent ~3:1 selectivity of aliphatic versus benzylic positions. This selectivity is opposite that which would be expected from a comparison of C−H bond dissociation

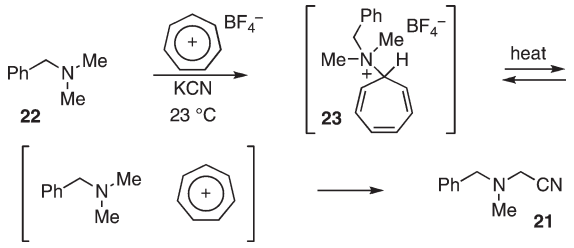


Figure 3. Competitive but reversible *N*-alkylation of amines.

energies, but appears instead to reflect selective oxidation of the most electron-rich methylene. (For comparison, DDQ in the presence of KCN and 18-crown-6 effected α-cyanation of the same substrate in 32% yield over the same time frame, with a 1.7 to 1 selectivity for the benzylic position, see Supporting Information.) In support of this notion, a nitro substituent in the para position of the benzyl group increased the selectivity for oxidation at an aliphatic position to >20:1 (entry 2), while a methoxy subsituent decreased the ratio somewhat and rendered the reaction much less efficient (entry 3).

The reaction also appears to be sensitive to steric factors. Thus, for example, *N*,*N*-dimethylmesitylamine was found to undergo methyl cyanation to furnish nitrile **13** (entry 4). Similar selectivity was observed with a neopentyl substrate, which notably reacted with high efficiency at room temperature (entry 5). In contrast, however, the bicyclic amine giving rise to adduct **15** was found to oxidize exclusively at a more sterically encumbered methylene rather than the *N*-methyl group (entry 6).

In an effort to explore some of the functional group compatibility of this method, we investigated substrates that gave rise to nitrile products **16**−**18**. Interestingly, *N*,*N*-diisobutylallylamine underwent extremely facile reaction in only 15 min at room temperature and with a complete regioselective preference for oxidation at an aliphatic position (entry 7). An amino ester displayed a similar selectivity (entry 8), although more forcing conditions were required. We also found it possible to obtain α-cyanate (−)sparteine (**18**) in high yield on a preparative scale (1 g) at ambient temperature without complication from the second amine functionality (entry 9).[5]

Interestingly, substrates that proved to be more problematic included those that possessed only benzylic hydrogens (entry 10) or for which the aliphatic positions were unreactive (entry 11). Dimethylbenzylamine was a particularly poor substrate in part for the reasons discussed below, although it should be noted that the nitrile **21** was produced with a significant preference for methyl oxidation (entry 12).

A number of the substrates in Table 1 required heating in part because at ambient temperature they were prone to *N*-alkylation by tropylium ion to form *N*-tropylammonium salts (cf. **8**, Figure 2).[13] For example, when benzyldimethylamine **22** was combined with an equivalent of tropylium·BF_4 at room temperature, ammonium salt **23** was observed by ^{1}H NMR (Figure 3). Heating **23**, which presumably allowed for reversion to amine and tropylium ion, in the presence of KCN then slowly produced the nitrile product **21**. That this competitive *N*-alkylation is subtly affected by steric and electronic factors can be seen by the variable temperatures required by the substrates in Table 1.

With an eye toward expanding the potential synthetic application of this amine oxidation, we decided to explore whether tropylium ion mediated oxidation could be employed for carbon−carbon bond formation in alternative contexts. Toward this goal, we prepared

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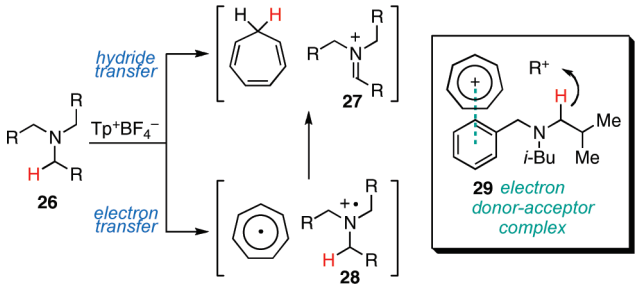
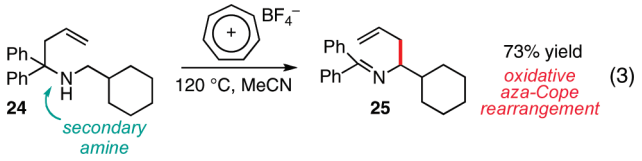


Figure 4. Mechanistic alternatives for tropylium ion mediated amine oxidation.

the homoallylic amine substrate **24** via allylation of *N*-cyclohexylmethyl benzophenone imine. In the presence of 1.5 equiv of tropylium BF_4^- at 120 °C in acetonitrile (sealed vial), **24** underwent facile oxidation/aza-Cope rearrangement to provide imine **25** in 73% yield. It is notable that this oxidative procedure was successful even in the presence of a secondary amine. We presume *N*-alkylation by tropylium ion was suppressed due to significant steric encumbrance by the *gem*-diphenyl group.



Finally, in regard to the mechanism of tropylium-mediated amine oxidation, we recognize two likely possibilities, the first being direct hydride abstraction from amine **26** and the second involving initial electron transfer to produce an amine radical cation intermediate **28** and tropyl radical (Figure 4).[14] Although at present we cannot say which of these two possibilities might be operative, we reemphasize that oxidation of substrate leading to product **10** (Table 1) with DDQ, typically a single electron oxidant,[3] resulted in a significantly different ratio of regioisomers for benzylic versus aliphatic oxidation.

Another important consideration is the possibility of electron donor−acceptor (EDA) complexes (cf. **29**) with substrates possessing aryl rings. Such EDA complexes with tropylium ion are known[15] and their formation might be expected to drastically alter the reactivity and selectivity of aromatic substrates. Positing intermediates of the type **29** would also help explain the relatively poor efficiency of the benzylic oxidations in Table 1 relative to the purely aliphatic substrates. In this regard, it is noteworthy that the efficiency of formation of the *p*-methoxybenzyl product **12** (Table 1) was especially poor, since a more stable EDA complex would be expected to form in this case. Further experiments to determine the presence and potential impact of these putative structures are underway.

As demonstrated here, aromatic cations such as tropylium ion have the capacity to serve as useful reagents for amine oxidation. The broad structural and electronic tunability of these reagents should offer unique opportunities for reaction design and the pursuit of novel selectivities. Mechanistic investigations and further development of aromatic cation oxidations will be the focus of our future efforts.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. Experimental procedures and product characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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