Tropylium Ion Mediated \( \alpha \)-Cyanation of Amines

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Supporting Information

**ABSTRACT:** Tropylium ion mediated \( \alpha \)-cyanation of amines is described. Even in the presence of KGN, tropylium ion is capable of oxidizing various amine substrates, and the resulting tropylium ion undergoes fast metathesis with cyanide to tropylium cyanate ion. The byproducts of this transformation are simply cycloheptatriene, a volatile hydrocarbon, and water-soluble potassium tetafluoroborate. Thirteen total substrates are shown for the \( \alpha \)-cyanation procedure, including a gram scale synthesis of 175-cycloheptatetraene. In addition, a tropylium ion mediated oxidation of a Cope rearrangement is demonstrated.

Tropylium ions are a functional group with broad utility for the formation of carbon—carbon bonds and amine stereocenters. Unfortunately, the traditional approach to tropylium 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 tropylium ion formation. When coupled with subsequent nucleophilic trapping, amine oxidation also offers a useful means to achieve amine desylation functionalization. In this communication, we describe the use of tropylium ions as a powerful reagent for amine oxidation and \( \alpha \)-cyonation.

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.5, 6 DDQ,7 Br2/OMe8,9 or singlet oxyger8 as oxidants. On the other hand, the substrate scope reported with metal oxidants has been notably narrow, and is often limited to N-Methyl derivatives or tetryl hydrazinyl nitro compounds. 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 to provide diverse products, these reagents are not highly amenable to broader structural modifications. For these reasons, the development of mild and selective new approaches to amine oxidation stands as an important goal.

As a highly emerging conceptual alternative, the use of carbocations, such as tropylium and tropylium ions, 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 array of synthetic and electronic tunability, we have become interested in the development of cyanating agents, such as tropylium ion, as versatile hydrocarbon-based oxidizing agents.

Tropylium ion (Figure 1) the first electron-carrying homologue of benzene, was first prepared by Doering and Knox in 1954.9 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.

With this in mind, we first examined the action of tropylium ion on an amine substrate that would not be prone to enamine formation/\( \alpha \)-alkylation, namely, tetrabutylamine (eq 1). After stirring 18H9 (1) and tropylium tetrafluoroborate for 30 min in acetonitrile, we observed quantitative formation of tropylium ion 2, along with cycloheptatriene. Notably, when potassium cyanide was added to the reaction mixture prior to oxidation, we observed the \( \alpha \)-cyano adduct 3 in 81% yield (eq 2). The compatibility of tropylium and cyanide ion was surprising, since Doering had reported the poor separation of cycloheptatrienyl cyanide by this ketone.

Nevertheless, we recognized that the fact that tropylium did not undergo quenching by cyanide under these conditions offered a practical means to achieve the mild and selective 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 tetafluoroborate.

Our rationale for the success of the reaction shown in eq 2 is centered on the fact that KGN is essentially insoluble in acetonitrile, which therefore prevents the formation of cycloheptatrienyl cyanide (9) and allows tropylium ion to oxidize the amine substrate (Figure 2, cf. 4 \( \rightarrow \) 5). Indeed, the addition of...
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Previous Amine Oxidations Reports

• Iminiums traditional approach: **carbonyl-amine condensation**

  ![Chemical Reaction](image)

  «challenges in terms of scope, efficiency and substrate compatibility.»

Alternative: **amine oxidation.**

• Main promoters are TM, DDQ, PhI(OAc)\(_2\) and singlet oxygen.

This work: **tropylium ion.**

- 6π-electron aromatic system
- first prepared by Doering and Knox in 1954
- aromatic carbocation

**TpBF\(_4\): 60€/5g**
Previous Amine Oxidations Reports

• Iminiums traditional approach: *carbonyl-amine condensation*

  \[
  \text{NH} \quad R^1 \quad R^2 + \quad O=H \quad R^3 \xrightarrow{H^+ \quad H_2O} \quad \text{N}^+ \quad R^1 \quad R^2 \quad R^3
  \]

  "challenges in terms of scope, efficiency and substrate compatibility."

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For a review on tropylium ion see F. Pietra Chem. Rev. 1973, 73, 293.
The Cycloheptatrienylium (Tropylium) Ion

BY W. VON E. DOERING AND L. H. KNOX

RECEIVED APRIL 8, 1954

Thermal elimination of hydrogen bromide from dibromotropolilene produces cycloheptatrienylium bromide, the structure of which follows from its salt-like character, its hydrogenation to cycloheptane and its conversion by phenyllithium to 7-phenylcycloheptatriene. This stable cation is the parent of a new aromatic system which has been foreshadowed theoretically by the molecular orbital treatment of aromatic character and experimentally by the behavior of tropone, tropolone and azulene.

\[
\begin{align*}
\text{Cycloheptatrienylium Ion} & \quad \text{Cycloheptane} \\
\text{Bromination} & \quad \text{Conversion by phenyllithium}
\end{align*}
\]
Reactions of the Cycloheptatrienylium (Tropylium) Ion

BY W. VON E. DOERING AND L. H. KNOX

RECEIVED JUNE 25, 1956

The tropylium ion, whose preparation has been made more convenient, reacts as an electrophilic reagent with the bases water, hydrogen sulfide and ammonia to give ditropyl ether, sulfide and amine, respectively, with the bases acetamide, benzamide and succinimide to form the N-tropyl derivatives and with cyanide ion to give tropyl cyanide which can be hydrolyzed to an amide identical with Buchner’s norcaradiene carboxamide and which reacts with phenylmagnesium bromide to give desoxybenzoin. The tropylium ion is converted both by chromic acid and silver oxide to benzaldehyde. In a reaction of some theoretical significance because it probably proceeds by way of the cycloheptatrienyl (tropyl) free radical, tropylium ion is reduced by zinc dust to ditropyl.

\[ \text{Cyclic structure} \rightarrow \text{Intermediate structure} \rightarrow \text{Final product} \]
Action of some bases on the tropylium cation

S. G. McGeachin

Department of Chemistry, University of Alberta, Edmonton, Alberta

Received September 3, 1968

The tropylium cation has been treated with the hindered bases triphenylmethyl sodium, 2,6-dimethoxyphenyl lithium, and 2,4,6-tri-t-butylphenyl lithium to give substituted cycloheptatrienes. Where possible its reaction with tertiary amines follows Reaction Scheme 1 to give immonium salts which can be hydrolyzed to tropylated aldehydes and ketones. Its reaction with trimethylamine gives the quaternary ammonium salt which on exposure to the atmosphere is decomposed to trimethylammonium fluoborate and a mixture of tropone and ditropyl ether.

Canadian Journal of Chemistry, 47, 151 (1969)
Hydride Transfer. Reactions of Triphenylcarbonium Fluoroborate and Triphenylmethyl Bromide with Tertiary Amines

RALPH DAMICO AND C. D. BROADDUS

The Procter and Gamble Company, Miami Valley Laboratories, Cincinnati, Ohio 45239

Received February 7, 1966

Trialkylamines undergo hydride transfer reactions with triphenylcarbonium fluoroborate and triphenylmethyl bromide in chlorinated hydrocarbons, acetonitrile, excess amine solvents, and diluents at room temperature. If an amine contains only α hydrogens the corresponding ternary iminium salt can be isolated. When β-hydrogen atoms are present the intermediate ternary iminium salt reacts with tertiary amine to produce an enamine and amine hydroanion salt. Enamines transfer hydride ions very rapidly to triphenylcarbonium fluoroborate and triphenylmethyl bromide. A mechanism is proposed to account for high yields of amine hydroanion salts and triphenylmethane from reactions of trialkylamines and trityl salts.

\[
(CH_3)_2NC_{12}H_25 + Ph_3C^+BF_4^- \rightarrow \frac{H}{(CH_3)_2NC_{12}H_{25}BF_4^- + Ph_3CH}
\]

100% (70%) (62%)
This Work

\[ \text{MeCN, r.t., 30 min} \quad \text{BF}_4^- \quad \text{i-Bu}_2\text{N}=\text{Me} \quad \text{MeCN, r.t., 3 h} \quad \text{KCN} \quad \text{BF}_4^- \]

1. \( \text{i-Bu}_2\text{N} \rightarrow \text{i-Bu}_2\text{N} = \text{Me} \quad \text{BF}_4^- \quad 100\% \text{ conv.} \)

2. \( \text{MeCN, r.t., 30 min} \quad \text{BF}_4^- \quad \text{i-Bu}_2\text{N} = \text{Me} \quad \text{MeCN, r.t., 3 h} \quad \text{KCN} \quad \text{BF}_4^- \)

3. \( \text{CN} \quad \text{i-Bu}_2\text{N} \quad \text{Me} \quad \text{MeCN, r.t., 3 h} \quad \text{KCN} \quad \text{BF}_4^- \)

b.p. = 116 °C

81% yield

\[ + \text{KBF}_4 \]
Substrate Scope Studies

\[
\begin{align*}
R_1'N &\begin{array}{c} \text{BF}_4^- \\ \text{KCN} \\ \text{MeCN} \end{array} \rightarrow R_1N &\begin{array}{c} \text{CN} \\ \text{R}_3 \\ \text{R}_2 \end{array}
\end{align*}
\]

(1) \(\text{CN} \quad \begin{array}{c} \text{Me} \\ \text{i-Bu} \\ \text{Me} \end{array} \quad \begin{array}{c} \text{Me} \\ \text{Me} \end{array} \quad 120 ^\circ \text{C}, \quad 12 \text{ h} \quad 78\% \text{ yield} \quad 5.9:1 \text{ regioselectivity}

(2) \(\text{O}_2\text{N} \quad \begin{array}{c} \text{Me} \\ \text{i-Bu} \\ \text{Me} \end{array} \quad \begin{array}{c} \text{Me} \\ \text{Me} \end{array} \quad 120 ^\circ \text{C}, \quad 12 \text{ h} \quad 77\% \text{ yield} \quad >20:1 \text{ regioselectivity}

(3) \(\begin{array}{c} \text{O}_2\text{N} \\ \text{Me} \end{array} \quad \begin{array}{c} \text{Me} \\ \text{i-Bu} \\ \text{Me} \end{array} \quad \begin{array}{c} \text{Me} \\ \text{Me} \end{array} \quad 100 ^\circ \text{C}, \quad 12 \text{ h} \quad 43\% \text{ yield} \quad 3.7:1 \text{ regioselectivity}

(4) \(\text{Me} \quad \begin{array}{c} \text{CN} \\ \text{Me} \end{array} \quad \begin{array}{c} \text{Me} \\ \text{Me} \end{array} \quad 80 ^\circ \text{C}, \quad 12 \text{ h} \quad 71\% \text{ yield}

(5) \(\text{CN} \quad \begin{array}{c} \text{Me} \\ \text{Me} \end{array} \quad \begin{array}{c} \text{Me} \\ \text{Me} \end{array} \quad 23 ^\circ \text{C}, \quad 2 \text{ h} \quad 90\% \text{ yield}

(6) \(\text{CN} \quad \begin{array}{c} \text{Me} \\ \text{Me} \end{array} \quad \begin{array}{c} \text{Me} \\ \text{Me} \end{array} \quad 80 ^\circ \text{C}, \quad 3 \text{ h} \quad 84\% \text{ yield}


Substrate Scope Studies

Reactions:

- (7) $R_1\sim N\sim R_3 \xrightarrow{\text{KCN, MeCN}} R_1\sim N\sim R_3$
  - $23^\circ\text{C}, 0.25\text{ h}$, 73% yield

- (8) $\text{MeO}_2\text{C} \sim N \sim \text{Me} \xrightarrow{\text{KCN, MeCN}} \text{MeO}_2\text{C} \sim N \sim \text{Me}$
  - $120^\circ\text{C}, 12\text{ h}$, 75% yield

- (9) $\text{H} \sim N \sim \text{N} \xrightarrow{\text{KCN, MeCN}} \text{H} \sim N \sim \text{N}$
  - $23^\circ\text{C}, 3\text{ h}$, 90% yield, 1 g scale

- (10) $\text{Ph} \sim N \sim \text{NBn}_2$
  - $80^\circ\text{C}, 12\text{ h}$, 42% yield

- (11) $\text{Ph} \sim N \sim \text{Me}$
  - $80^\circ\text{C}, 2\text{ h}$, 62% yield

- (12) $\text{Ph} \sim N \sim \text{CN}$
  - $80^\circ\text{C}, 12\text{ h}$, 34% yield
Oxydative Aza-Cope Rearrangement

Secondary amine

\[ \text{24} \xrightarrow{120 \, ^\circ \text{C}, \text{MeCN}} \text{25} \]

73% yield

oxidative aza-Cope rearrangement
Mechanistic Analysis
Mechanistic Alternatives
Outlook

• Tropylium ion mediated $\alpha$-cyanation of amines.

1 Broad scope of amine oxidation (13 total substrates).
2 Resulting imininiums undergo salt metathesis with cyanide (+ 1 aza-Cope rear. example).
3 It produces aminonitriles.

• Byproducts are simply:
  • cycloheptatriene (volatile hydrocarbon)
  • potassium tetrafluoroborate (water-soluble).
Thank you STeRéo!
References


(7) For the oxidation with trityl ion, see: Damico, R.; Broaddus, C. D. J. Org. Chem. 1966, 31, 1607. As an issue of practicality, we note that, in contrast to tropylium ion, the byproduct of hydride abstraction by trityl ion is triphenylmethane, which is a nonvolatile, non water-soluble compound.


