The Synthesis and Chemoselective Reactivity of 3-Aminocyclopentadienones

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Iron and cobalt complexes of 3-aminocyclopentadienones have been synthesized from the \([2 + 2 + 1]\) cycloadditions of nitrogen acetylenes and pendant alkynes. Following decomplexation, the resulting 3-aminocyclopentadienones have been subjected to chemo- and regioselective cycloadditions with dienophiles and heterodiienes.

Introduction

Although cyclopentadienones are widely recognized as having a high degree of synthetic potential, their relative instability has limited their use in organic synthesis.\(^1\) Because of this, a significant amount of effort has targeted the synthesis and use of masked cyclopentadienones. A few of these are illustrated in Figure 1 and include the following: (a) cyclopentadienone-cyclopentadiene Diels–Alder adducts (e.g., 1);\(^2\) (b) 4-alkoxycyclopentadienones (e.g., 2);\(^3\) (c) oxime adducts (e.g., 3);\(^4\) (d) cyclopentadienone–transition metal complexes (e.g., 4).\(^5\)

While the masking strategies depicted in Figure 1 are cleverly designed and clearly of utility, from our perspective a better synthetic strategy would be one that used cyclopentadienones directly. With this as one of our goals, we have recently targeted and communicated the generation and use of 3-aminocyclopentadienones (e.g., 5, Figure 2).\(^6,7\) This came out of the notion that the divergent electronic properties of the two enones (one being a vinylogous amide) might enable us to use them in chemoselective reactions and ultimately in the synthesis of interesting alkaloids. As we are aware of very few examples of the use of cyclopentadienones in complex molecule synthesis,\(^8,9\) the success of these ventures would demonstrate that strategies incorporating cyclopentadienones are of merit.

Clearly, the aforementioned goals required that (a) we have an efficient entry into 3-aminocyclopentadienones (e.g., 5) and (b) that 5 be stable enough to isolate or to trap. With respect to the latter requirement, it has been well documented that substitution about the cyclopentadienone leads to its stabilization.\(^1\) As our ultimate interests included the use of 5 in the synthesis of interesting alkaloids, we placed the additional constraint on 5 that \(R, R',\) and P be of general synthetical utility.

With regard to their synthesis, we became fascinated with the generation of 3-aminocyclopentadienones from cobalt- and iron-mediated \([2 + 2 + 1]\) cycloaddition reactions of nitrogen acetylenes (ynamines) and pendant alkynes. While ynamines had not been utilized in this context prior to our work,\(^10,11\) they had been used by Witulski in cobalt-mediated Pauson–Khand reactions\(^12\) and in independent studies by Ficini\(^13\) and Witulski\(^14\) in Ni- and Rh-mediated cycloaromatization reactions, respectively. In addition to efficiency of synthesis, we were


\((9)\) Herndon has used lowered reduced cyclopentadienones in synthesis, see: Herndon, J. W.; Zhu, J. Org. Lett. 1999, 1, 15 and references contained therein.

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Figure 1.
attracted to the use of metal-mediated [2 + 2 + 1] cycloadditions because the cyclopentadienones would be generated as isolable metal complexes that might be interesting in their own right.15,16

Outlined herein is a full report of our investigations demonstrating that cobalt and iron complexes of [3.3.0]-, [4.3.0]-, and [5.3.0]aminocyclopentadienones can be synthesized from yne–ynamine cycloaddition reactions.6 Also described is the decomposition of the cyclopentadienones and their capture with dienophiles as well as dienes in chemo- and regioselective cycloaddition reactions.

Results and Discussion

Yne–Ynamine Synthesis. We have synthesized yne–ynamine cycloaddition precursors having 2-, 3-, and 4-carbon tethers between the alkyn and ynamine as depicted in Scheme 1. Yne–ynamine cyclization precursor 11 was synthesized in two steps from N-tosylaziridine. Namely, ring opening of N-tosylaziridine with lithium trimethylsilylacetylide followed by ynamine formation using Stang’s iodoacetylene salt provided yne–ynamine 11 synthetically useful yields.17 The homologous yne–ynamines 12 and 13 were synthesized from the corresponding alkynes. Mitsuobu coupling of (BOC)-NH(Ts) with 4-pentyn-1-ol and 5-hexyn-1-ol provided amino alkynes 6 and 7, respectively. Conversion of 6 and 7 into the corresponding ynamine precursors 8 and 9 involved TMS-alkyne formation and selective thermal removal of the Boc group.18 Ynamine formation provided 12 and 13, respectively.

Yne–Ynamine Cycloadditions to Cyclopentadienone Complexes. With access to yne–ynamine cycloaddition precursors, we investigated their conversion into the corresponding cobalt and iron cyclopentadienone complexes via [2 + 2 + 1] cycloaddition reactions. To our delight, when 11 was subjected to Vollhardt’s conditions for the corresponding all-carbon cycloaddition (CpCo(CO)2 and photolysis at low temperature)15b we isolated cobalt cyclopentadienone complex 14 as a dark red solid in 57% yield (Table 1). Yne–ynamine 11 also proved amenable to iron-mediated cycloaddition. Yellow cyclopentadienone complex 15 was generated in 84% yield upon exposure of 11 to Fe(CO)5 and elevated temperatures (Table 1).

Having generated iron and cobalt [3.3.0] complexes 14 and 15, we targeted the corresponding [4.3.0]- and [5.3.0]-cyclopentadienone complexes. Thus far, all of our attempts to generate [4.3.0]-cobalt complex 16 from 12 using the conditions that were successful for the synthesis of 14 have resulted in the formation of cyclobutadiene complex 17 (Scheme 2).

In contrast, the corresponding iron-mediated [2 + 2 + 1] cycloadditions provided iron [4.3.0]- and [5.3.0]-cyclopentadienone complexes in respectable yields (Table 2). When yne–ynamine 12 was subjected to Fe(CO)5 and heat, we isolated mono- and bis-TMS cobalt [4.3.0]-complexes in a 2.2:1 ratio in 96% overall yield.19 Similarly, the 3-amin[5.3.0]cyclopentadienone iron complex 20 was obtained in 54% yield from the cycloaddition of yne–ynamine 13.

These cycloadditions compare favorably with the corresponding all-carbon variants. In independent studies, both Pearson and Knölker have generated the all-carbon [4.3.0]- and [5.3.0]cyclopentadienone–iron complexes but in 57% and 50–59% yield (Pearson)20 and 82% and 15% (Knölker).
Table 2.

<table>
<thead>
<tr>
<th>entry</th>
<th>product</th>
<th>n</th>
<th>R</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>18</td>
<td>2</td>
<td>TMS</td>
<td>96(^a)</td>
</tr>
<tr>
<td>2</td>
<td>19</td>
<td>2</td>
<td>H</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>20</td>
<td>3</td>
<td>TMS</td>
<td>54</td>
</tr>
</tbody>
</table>

\(^a\) Ca. 2.1:1 ratio of 18:19 was isolated from the cycloaddition of 12.

Scheme 3

![Scheme 3 diagram]


Decomplexation and Cycloadditions of 3-Aminocyclopentadienones. With relatively efficient syntheses of metal cyclopentadienone complexes in hand, we were prepared to test our hypothesis that 3-aminocyclopentadienones might be valuable intermediates in complex molecule synthesis. We initially targeted decomplexation reactions using 3-amino- and 3-nitrocyclopentadienones because of the possibility that the divergent electronic properties of the two enone alkenes would enable us to carry these out chemo- and regioselectively.

Before examining the properties of 3-aminocyclopentadienones, it was necessary to find conditions to effect the decomplexation of 14, 15, 18, and 20. Upon exposure of cobalt complex 14 to ceric ammonium nitrate (CAN) at 0 °C for 1 h, we were able to generate a bright yellow solution of cyclopentadienone 22 (Scheme 3).\(^6\) We subsequently discovered that CAN had not only decomplexed the cobalt but that it had also chemoselectively protodevinylogously isomerized the vinylogous amide. While we have been able to access mixtures of mono-TMS cyclopentadienones 22 and bis-TMS cyclopentadienone 21 by subjecting 14 to CAN for shorter periods of time, we have not been able to selectively generate bis-TMS cyclopentadienone 21 from the CAN oxidative decomplexation of 14. In subsequent studies, we were able to isolate 21 from the decomplexation of iron cyclopentadienone 15 (vide infra).

Due to our lack of success in our early attempts to isolate 22 and its presumed instability to concentration, we chose to immediately subject 22 to cycloaddition reactions with dienophiles (Scheme 3 and Table 3) or heterodienes (eq 2). Aqueous workup and dilution of the yellow solution from decomplexation with an equal volume of benzene followed by exposure to methyl acrylate resulted in the formation of dihydroindolene 23 as a single regioisomer in 67% yield from 14 (Scheme 3).\(^2\) As it is widely accepted that C-5 substitution greatly stabilizes cyclopentadienones,\(^23\) the efficient entry into 23 is made all the more remarkable by the lack of vinylogous amide substitution in 22.

Similarly, when a solution of cyclopentadienone 22 was exposed to DMAD and heat indolene 24 was isolated in 78% yield from complex 14 (Table 3).\(^2\) Presumably, decarbonylation was occurring in the course of the synthesis of both 23 and 24 as we have not been able to isolate the adduct prior to loss of CO.

Having successfully carried out the decomplexation of cobalt complex 14 and subsequent cycloaddition of the corresponding cyclopentadienone we then took aim at iron cyclopentadienones 15, 18, and 20. As has been the experience of others,\(^2\) we have found the decomplexation of the iron complexes to be somewhat more problematic in comparison to cobalt complex 14 and have investigated a number of decomplexation protocols. Thus far, we have examined the oxidative decomplexation using trimethylamine N-oxide (TMANO) and morpholine N-oxide (NMO) along with the base-induced decomplexation using NaOH. In reactions that nicely complement the decomplexation of 14, the decomplexation of bis-TMS cyclopentadienone complex 15 with TMANO, NMO, or NaOH provided a solution of bis-TMS cyclopentadienone 21. As was the case in the cobalt decomplexation reaction, we did not isolate 21 but instead immediately subjected it to cycloaddition reactions with DMAD (Table 3) or unsaturated carbonyl compounds (Table 4). In a fashion similar to 22, the cycloaddition of 21 with DMAD resulted in the formation of indolene 25 in moderate yield. Higher yields were obtained when [3.3.0]- and [4.3.0]cyclopentadienones 18 and 20 were carried through the decomplexation and cyclization sequence with DMAD. Cycloaddition of [3.3.0]cyclopentadienone 26 gave a 54% overall yield of cycloadduct 27 while [4.3.0]cyclopentadienone 28 gave a 70% overall yield of adduct 29.

We believe that the facility with which the highly substituted aromatic heterocycles 24, 25, 27, and 29 have been generated will be of significance for the synthesis of these ring systems. Of interest is the observation that the methylene protons in the H \(_1\) NMR spectra of 25, 27, and 29 are magnetically inequivalent, implying a high inversion barrier at the nitrogen atom when the ortho position of the aryl ring is substituted with TMS.\(^2\)

Interestingly, the decomplexation of 18 using TMANO in acetone instead of CH\(_2\)Cl\(_2\) provided diene 30 as the only product in 82% yield (eq 1). Knölker and Pearson have observed a similar phenomenon in the decomplexation of the all carbon variant of 18.\(^2\)

Having utilized 3-aminocyclopentadienones as the 4π component in cycloadditions, we turned to their use as...
dienophiles in hetero-Diels–Alder cycloadditions with unsaturated aldehydes and ketones.\textsuperscript{28,29} We were thrilled to isolate adduct 31 in 82\% yield from cobalt complex 14 when cyclopentadienone 22 was condensed with acrolein (eq 2). This experiment truly demonstrates the utility of 3-aminocyclopentadienones as we have utilized them chemo- and regioselectively as both dienes and dienophiles.

Both bis-TMS-substituted cyclopentadienones 21 and 26 also acted as 2\(\pi\) components in their reaction with acrolein. In a fashion similar to 22, cyclopentadienone 26 reacted exclusively at the vinylogous amide to give 33 in 66\% yield for the two steps (Table 4, entry 3). The reaction of cyclopentadienone 21 was not as selective. While its reaction with acrolein resulted in the formation of vinylogous amide adduct 32 as the major product, it also gave a small amount of a byproduct whose structure we have tentatively assigned to the corresponding isolated enone adduct (Table 4, entries 1 and 2).\textsuperscript{30} While the enhanced selectivity of 22 relative to 21 can be rationalized as being due to the presence of the vinylogous amide TMS group in 21, at the present time it is not clear why 26 is more selective than 21. The reaction of 22 with heterodienes at the vinylogous amide appears to be general. Aminocyclopentadienone 22 reacts with methyl vinyl ketone (entry 4), crotonaldehyde (entry 5), and methacrolein (entry 6) to give adducts 34, 35, and 36, respectively in reasonable yields for the two-step process.

Surprisingly, 3-amino[5.3.0]cyclopentadienone 28 underwent cycloaddition with acrolein at the isolated enone instead of at the vinylogous amide to give 37 in 52\% yield (eq 3).\textsuperscript{31}


\textsuperscript{24} A similar vinylogous ester was unreactive in analogous cycloaddition reactions. See: Herndon, J. W.; Patel, P. P. Tetrahedron Lett. 1997, 38, 59.


\textsuperscript{26} The methylene signals did not coalesce at 80 °C.

\textsuperscript{27} See ref 21 and: Pearson, A. J.; Rosas, A. Organometallics 1995, 14, 5178.

\textsuperscript{28} For an example of the use of an enamine in a hetero-Diels–Alder cycloaddition reaction see: Stork, G.; Landesman, H. K. J. Am. Chem. Soc. 1956, 78, 5128.


\textsuperscript{30} Thus far, we have been unable to separate vinylogous amide adduct 32 from the corresponding enone adduct without selectively destroying the enone adduct. The structure of the enone adduct was assigned based upon the similarity of its \(^1\text{H}\) and \(^{13}\text{C}\) NMR spectra to 37.

\begin{table}[h]
\centering
\caption{Table 3.}
\begin{tabular}{cccccc}
\hline
entry & conditions\textsuperscript{a} & n & cyclopentadienone & R & product & yield (\%) \\
\hline
1 & CoCp A & 1 & 22 & H & 24 & 78 \\
2 & Fe(CO)\textsubscript{3} B & 1 & 21 & TMS & 25 & 36 \\
3 & Fe(CO)\textsubscript{3} B & 2 & 26 & TMS & 27 & 57 \\
4 & Fe(CO)\textsubscript{3} C & 2 & 26 & TMS & 27 & 48 \\
5 & Fe(CO)\textsubscript{3} C & 3 & 28 & TMS & 29 & 70 \\
6 & Fe(CO)\textsubscript{3} D & 3 & 28 & TMS & 29 & 36 \\
\hline
\textsuperscript{a} Key: A, CAN, B, TMANO; C, NMO; D, NaOH.
\end{tabular}
\end{table}

\begin{table}[h]
\centering
\caption{Table 4.}
\begin{tabular}{cccccccc}
\hline
entry & heterodiene & M & n & X & R & R' & R'' & adduct & yield\textsuperscript{d} (\%) \\
\hline
1 & acrolein & Fe(CO)\textsubscript{3}\textsuperscript{b} & 1 & TMS & H & H & H & 32 & 54\% \\
2 & acrolein & Fe(CO)\textsubscript{3}\textsuperscript{a} & 1 & TMS & H & H & H & 32 & 44\% \\
3 & acrolein & Fe(CO)\textsubscript{3}\textsuperscript{a} & 2 & 21 & TMS & H & H & 33 & 66 \\
4 & methylvinyl ketone & CoCp\textsubscript{a} & 1 & H & CH\textsubscript{3} & H & 34 & 74 \\
5 & crotonaldehyde & CoCp\textsubscript{a} & 1 & H & H & H & CH\textsubscript{3} & 35 & 36 \\
6 & methacrolein & CoCp\textsubscript{a} & 1 & H & H & CH\textsubscript{3} & H & 36 & 66 \\
\hline
\textsuperscript{a} Decomplexed with NMO. \textsuperscript{b} Decomplexed with TMANO. \textsuperscript{c} Decomplexed with CAN. \textsuperscript{d} Yield over two steps. \textsuperscript{e} 4:1 mixture with the corresponding enone adduct.
\end{tabular}
\end{table}
In addition to the heterodiene investigations described above, we have examined the cycloaddition of cyclopentadienone \(21\) with cyclopentadiene. To our delight, endo-adduct \(38\) was isolated in 57% yield when \(21\) was exposed to cyclopentadiene (eq 4). In contrast to our heterodiene results with \(21\), cyclopentadiene had reacted exclusively at the isolated enone of \(21\).

Conclusions

To conclude, we have demonstrated that 3-aminocyclopentadienones can be efficiently synthesized from metal mediated yne-ynamine \([2 + 2 + 1]\) cycloaddition reactions. In addition, we have shown that metal free 3-aminocyclopentadienones can serve as both the 4-\(\alpha\) and 2-\(\alpha\) component in chemoselective cycloaddition reactions. We are currently focused on the optimization of the reactions that have been discovered, the use of iron and cobalt complexed cyclopentadienones in addition reactions, and the use of the substrates from these reactions in the synthesis of interesting targets.

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Supporting Information Available: Experimental procedures and characterization data, along with \(^1\)H and \(^{13}\)C NMR spectra for compounds \(6 - 9, 12, 13, 15, 17, 18, 20, 25, 27, 29, 30, 32, 33,\) and \(37\). ORTEP figures, atomic coordinates, thermal parameters, bond lengths, and bond angles for \(14, 37,\) and \(38\). This material is available free of charge via the Internet at http://pubs.acs.org.