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# Formal *aza*-Michael additions to tropone: addition of diverse aryl- and alkylamines to tricarbonyl(tropone)iron and $[(C_7H_7O)Fe(CO)_3]BF_4$

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ABSTRACT: A formal *aza*-Michael addition to tropone by way of tricarbonyl(tropone)iron and/or the tetrafluoroborate salt formed *via* protonation of the complex is reported. Tricarbonyl(tropone)iron smoothly undergoes the direct *aza*-Michael reaction with unhindered aliphatic amines under solvent free conditions in good yields. Meanwhile, the known cationic complex  $[(C_7H_7O)Fe(CO)_3]BF_4$  (whose reaction with a small number of nucleophiles was previously reported) undergoes addition with an even broader array of amine nucleophiles. Finally, it was discovered that protecting the *aza*-Michael adduct as a carbamate was necessary for oxidative demetallation of the complex.

Keywords: iron diene complexes, aza-Michael reaction, tropone, solvent free

Tropone and its  $\eta^4$  complex with an iron tricarbonyl fragment (tricarbonyl(tropone)iron (1) – readily synthesized from tropone<sup>1</sup>) are versatile synthetic building blocks that can be elaborated to a variety of complex scaffolds containing sevenmembered rings. Whereas tropone typically reacts with nucleophiles at the 2- and 7-positions<sup>2,3</sup> and also participates in cycloaddition reactions<sup>4–6</sup> at those positions, forming an  $\eta^4$ -diene complex with iron(0) fundamentally alters the reactivity of tropone. A notable illustration of the synthetic utility of 1 is Pearson and co-worker's stereocontrolled synthesis of heptitols<sup>7</sup> from 1, which was adapted by Soulié and co-workers in the synthesis of a polyhydroxylated nortropane skeleton.<sup>8,9</sup> Furthermore, the uncomplexed double bond of 1 has been shown to act as an enone equivalent in reactions with, for example, dienes,<sup>10,11</sup> tetrazines,<sup>12</sup> nitrile oxides,<sup>13</sup> diazoalkanes,<sup>14,15</sup> and organozinc reagents.<sup>16</sup> A similar addition of amine nucleophiles would furnish adducts containing several functional handles for further synthetic elaboration, whether in the form of the  $\eta^4$ -complexed diene or the corresponding free conjugated diene (Scheme 1). Thus, a formal *aza*-Michael addition to tropone and/or 1 serves as a potential starting point for the synthesis of complex amines containing a seven-membered carbocyclic ring common to a number of biologically active alkaloids (including several monoterpenoid indole alkaloids<sup>17</sup> and some *Daphniphyllum* alkaloids<sup>18</sup>).



Scheme 1. Aza-Michael adducts of tricarbonyl(tropone)iron: potential precursors for complex amines

Eisenstadt reported that the cationic complex **3** (synthesized from **1** in two steps<sup>19,20</sup>) could react with aniline or *tert*butylamine to give formal *aza*-Michael adducts of 1.<sup>21</sup> However, no other amine nucleophiles were investigated and demetallation of the products was also not reported. In addition to further exploring this chemistry, we were interested in developing a novel, *direct aza*-Michael addition of **1** without the need for pre-forming the cationic complex **3**. Herein, we describe our thorough exploration of the scope and reactivity of **3** toward various amine nucleophiles. In addition, we report the first direct *aza*-Michael addition of unhindered aliphatic amines to **1** as well as conditions for demetallation to reveal the dienone functionality.

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We began by exploring the reactivity of the dienyl tetrafluoroborate salt (3, Table 1) towards the sterically hindered nucleophile *o*-toluidine. We found that, in the presence of five equivalents of *o*-toluidine, such a reaction cleanly gave the desired formal *aza*-Michael adduct in moderate yield. We then proceeded to examine the effect of changing various reaction parameters (Table 1). We found that reducing the amount of toluidine to two equivalents resulted in no loss in yield and also facilitated chromatographic purification of the product. In addition, screening various aprotic solvents showed little impact on the isolated yield, and that anhydrous conditions appeared to decrease the yield. Thus, all subsequent reactions were carried out open to the atmosphere and no effort was made to exclude moisture. Finally, extending the reaction time resulted in enhanced yields.

Table 1. Optimization of nucleophilic addition to cationic complex 3.



Entry	<b>4</b> (equiv.)	Solvent	Time	Yield <b>2a</b> (%) <sup>b</sup>
1	2	diethyl ether	30 min	46
2	5	diethyl ether	30 min	43
3	2	CH <sub>2</sub> Cl <sub>2</sub>	30 min	45
4	2	$CH_2Cl_2^{c}$	30 min	29
5	2	THF	30 min	52
6	2	toluene	30 min	41
7	2	EtOAc	30 min	43
8	2	diethyl ether	24 h	63

<sup>a</sup>Reactions were conducted on a 0.1 mmol scale <sup>b</sup>Products were purified by column chromatography

<sup>c</sup>Reaction performed under an argon atmosphere with anhydrous solvent

We next sought to more broadly explore the scope of this formal *aza*-Michael reaction (see Table 2). Compound **3** was found to react cleanly with a wide variety of aryl and aliphatic amines, including reasonably hindered amines, in good yields. Particularly notable is the reactivity towards *o*-mono- and *o*-disubstituted aniline derivatives. Only with 2,6-diisopropylaniline (**2e**) (and, to a lesser extent, *o*-bromoaniline **2f**) was a significant reduction in yield observed. In line with Eisenstadt's findings, *tert*-butylamine was found to cleanly react, providing the corresponding adduct in 53% yield. Electron-withdrawal from the aniline derivative appears to be reasonably well-tolerated, with *p*-fluoroaniline reacting in 72% yield. On the other hand, electron-deficient aminopyridines undergo the reaction in low yields. We also found that carbamates such as BocNH<sub>2</sub> completely failed to react with **3**.<sup>22</sup> In each case, only a single diastereomer was obtained, with the Fe(CO)<sub>3</sub> fragment providing exceptional stereocontrol, as is well known with such diene complexes.<sup>23</sup> Indeed, we confirmed the stereochemical outcome of these additions *via* X-ray crystallographic analysis of the adduct of morpholine (**2l**; see ESI, CCDC No. 1853243).



 Table 2. Scope of nucleophilic addition to cationic complex 3.

Interestingly, we found that allowing 2,6-diisopropylaniline to react with **3** for 24 h gave an inseparable mixture of **1** and what was tentatively assigned as the product of a Friedel-Crafts type alkylation, with electrophilic attack occurring *para* to the aniline nitrogen (**6**, Scheme 2, right side). Shortening the reaction time to 30 min resulted in the formation of **2e** in low yield (see Scheme 2, left side, and Table 2). Thus, it appears that, at least with especially hindered nucleophiles, the addition to **3** is reversible under the reaction conditions and that the Friedel-Crafts product (**6**) is the thermodynamic product. This result is consistent with previous investigations into kinetic and thermodynamic additions of arylamines to tricarbonyliron-coordinated cyclohexadienyl cations.<sup>24-26</sup>



Scheme 2. Formation of *N*-alkylation product 2e (left) and Friedel-Crafts product 6 (right) from 3 and 2,6diisopropylaniline



Table 3. Direct aza-Michael reactions of 1

While we were pleased with the broad substrate scope of the addition to **3**, we hoped to develop a more streamlined route to these formal *aza*-Michael adducts, since the synthesis of **3** from **1** requires multiple synthetic operations (typically proceeding in 40-60% overall yield), where we found that variable (though relatively small) amounts of **1** were recovered alongside the desired tetrafluoroborate salt. Thus, to improve the overall yields of the adducts, we sought to explore a *direct aza*-Michael reaction of **1**. We were pleased to find that certain aliphatic amines rapidly underwent the desired reaction when mixed with **1** under solvent-free conditions at room temperature. Exploration of the scope of this direct *aza*-Michael addition (Table 3) revealed that only relatively unhindered primary amines and secondary cyclic amines underwent the desired reaction. Acyclic secondary amines and *tert*-butylamine did not react with **1** at room temperature and heating these reactions resulted in complex product mixtures. Presumably, the

secondary cyclic amines are locked in a favorable conformation in which the nitrogen is less crowded than in the acyclic cases. Anilines also did not undergo the desired direct addition to 1, likely because they are not sufficiently nucleophilic. Although the direct addition does not enjoy the same broad substrate scope as the addition to 3, it is the preferred method for preparing adducts such as 2k due to the higher yields and more direct route from 1.

The *aza*-Michael adducts contain a number of functional handles to further build up molecular complexity. However, the two olefins of the dienone moiety are masked by their complexation to the iron atom. Thus, exploiting these functional handles would be facilitated by demetallation of the complex to give the free ligand. A number of methods have been reported for the demetallation of  $(\eta^4$ -diene)tricarbonyliron(0) complexes, most of which involve oxidizing agents (*e.g.* Me<sub>3</sub>NO,<sup>27</sup> cerium ammonium nitrate (CAN),<sup>28</sup> CuCl<sub>2</sub>,<sup>29</sup> basic H<sub>2</sub>O<sub>2</sub>,<sup>30</sup> FeCl<sub>3</sub><sup>31</sup>), though photochemical methods<sup>32,33</sup> have also been reported. Despite a few examples of successful demetallations of amine-containing  $(\eta^4-diene)Fe(CO)_3$  complexes,<sup>34–36</sup> none of these methods proved successful with our adducts. We reasoned that oxidation of the nitrogen may be competitive with the desired demetallation. In a few cases we isolated tropone itself, resulting from oxidative elimination of the amino group in addition to demetallation. Therefore, we protected **2k** as a *tert*-butyl carbamate (Scheme 3) to prevent oxidation of the amino group. This compound reacted as expected with CAN to give compound 7. We also attempted to demetallate the unprotected adducts under acidic conditions, whereby protonation of the nitrogen would serve as temporary protection from oxidation. However, none of these efforts proved fruitful.



**Scheme 3**. Demetallation of *aza*-Michael adduct. Reagents and conditions: a) Boc<sub>2</sub>O, NaHCO<sub>3</sub>, EtOH, 64%; b) CAN, MeOH, 0 °C, 94%

In conclusion, we have developed a straightforward route to a diverse array of formal *aza*-Michael adducts of tropone. Key discoveries include: 1) thoroughly exploring and extending the scope of the reaction between dienyl tetrafluoroborate salt **3** and nitrogen-based nucleophiles as previously reported by Eisenstadt to include both electron-deficient and sterically hindered nucleophiles; 2) the development of a more efficient, *direct aza*-Michael reaction of **1** with unhindered aliphatic amines; 3) oxidative demetallation of Boc-protected adducts by CAN which required extensive exploration of known demetallation protocols. Notably, the demetallated products contain a number of functional groups (at minimum, a ketone and two olefins) which could serve as

handles for elaboration to more complex seven-membered ring-containing scaffolds which may be otherwise difficult to access. A complementary suite of potential reactions involving the iron-complexed diene<sup>16</sup> could further enhance the versatility of these *aza*-Michael adducts as platforms for synthesizing complex alkaloid-like scaffolds. Efforts towards such scaffolds are underway in our laboratory and will be reported in due course.

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#### Supplementary Material

Supplementary data associated with this article (experimental procedures, spectroscopic data for new compounds, and X-ray crystallographic data for compound **21**) can be found, in the online version, at https://doi.org/10.1016/j.tetlet.xxxx.xxx

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- - aza-Michael addition to tricarbonyl(tropone)iron under solvent-free conditions
  - Addition to the corresponding cationic dienyl complex has a broader substrate scope
  - Carbamates derived from aza-Michael adducts undergo smooth oxidative demetallation

