

# Highly Regioselective [3 + 2] Annulation of Azomethine Imines with 1-Alkynyl Fischer Carbene Complexes to Functionalized *N,N*-Bicyclic Pyrazolidin-3-ones

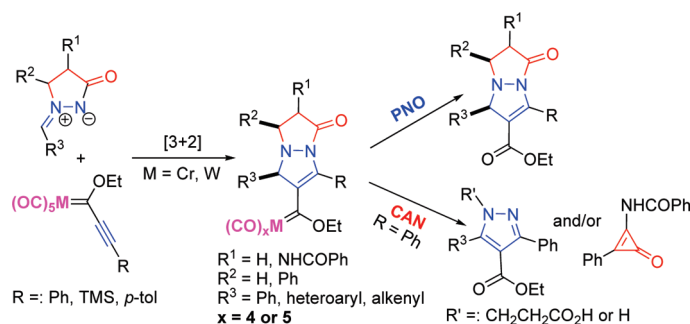
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Received April 29, 2011

## ABSTRACT



The highly regioselective [3 + 2] cycloaddition of azomethine imines to 1-alkynyl Fischer carbene complexes has been successfully realized under mild conditions. Oxidative demetalation of the newly formed pyrazolo-pyrazolone carbene complexes with pyridine-*N*-oxide or ceric ammonium nitrate efficiently afforded pyrazolo-pyrazolone derivatives as well as cycloprop-2-ene and trisubstituted 1*H*-pyrazoles in some cases, providing a novel route to versatile functionalized *N,N*-bicyclic pyrazolidin-3-ones.

*N,N*-Bicyclic pyrazolidin-3-ones, i.e., pyrazolo-pyrazolone derivatives, usually exhibit distinct bioactivity, and some of them have attracted much attention in drug development.<sup>1</sup> For example, tetrahydropyrazolo[1,2-*a*]pyrazolones have been studied as the analogs of penicillin and cephalosporin antibiotics over the past two decades

(Scheme 1).<sup>2,3</sup> To date, construction of such a *N,N*-bicyclic core has become a challenging task in organic synthesis, and the most possible route to reach this goal seems to be 1,3-dipolar cycloaddition of azomethine imines with alkynes.<sup>4</sup> However, azomethine imines have been applied with limitations for synthetic purposes as compared with azomethine ylides and nitrones.<sup>5</sup> Only by means of

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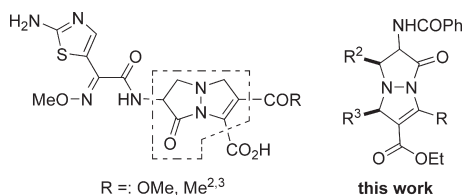
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**Scheme 1.** Analogs of Penicillin and Cephalosporin Antibiotics,<sup>2,3</sup> and the Target Products in This Work



electron-poor terminal alkynes,<sup>6</sup> enones,<sup>7</sup> and benzynes,<sup>8</sup> 1,3-dipolar [3 + 2] cycloadditions of azomethine imines can occur, forming a less substituted *N,N*-bicyclic core than that described in Scheme 1.<sup>2,6</sup> Thus, exploration of new synthetic methods to functionalized *N,N*-bicyclic pyrazolidin-3-one derivatives is strongly desired.<sup>9</sup> Fischer carbene complexes have been used as versatile building blocks in organic synthesis.<sup>10</sup> The [3 + 2] cycloaddition of alkynyl Fischer carbene complexes with *N*-alkyl nitrones<sup>11</sup> and azides<sup>12</sup> was reported for the synthesis of *N*-heterocyclic compounds. Although Fischer carbene complexes have been extensively applied to construct six-membered rings via [4 + 2] cycloaddition, their successful [3 + 2] annulations to five-membered heterocycles have been limited to a few examples.<sup>10,13–16</sup> In these 1,3-dipolar cycloaddition reactions, the metal pentacarbonyl moiety

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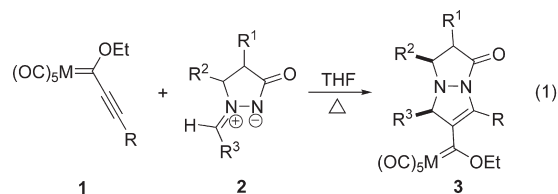
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of a Fischer carbene substrate usually accelerates the reaction and enhances the selectivity of the desired product. Recently, we disclosed [3 + 2] cycloadditions of 1-alkynyl Fischer carbene complexes with pyrazolinones for the preparation of *N,N*-bicyclic bimanes featuring strong luminescence.<sup>15</sup> Herein, we report the novel [3 + 2] cycloaddition of azomethine imines (**2**) with internal alkynes, i.e., 1-alkynyl Fischer carbene complexes (**1**), to synthesize potentially bioactive functionalized *N,N*-bicyclic pyrazolidin-3-one derivatives.

The reaction of 1-alkynyl Fischer carbene complex **1a** with azomethine imine **2a** was initially carried out under a nitrogen atmosphere. At rt–50 °C, the reaction seldom

**Table 1.** [3 + 2] Cycloaddition of Azomethine Imines **2** with **1**<sup>a</sup>

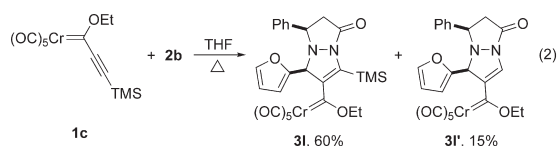


entry	M, R ( <b>1</b> )	R <sup>1</sup> , R <sup>2</sup> , R <sup>3</sup> ( <b>2</b> )	time (h)	yield <sup>b</sup> (%)
1	Cr, Ph ( <b>1a</b> )	H, Ph, Ph ( <b>2a</b> )	2	<b>3a</b> (71)
2	W, Ph ( <b>1b</b> )	<b>2a</b>	0.5	<b>3b</b> (75)
3	<b>1a</b>	H, Ph, 2-furyl ( <b>2b</b> )	7	<b>3c</b> (68)
4	<b>1b</b>	<b>2b</b>	3	<b>3d</b> (66)
5	<b>1a</b>	H, Ph, 2-thienyl ( <b>2c</b> )	14	<b>3e</b> (61)
6	<b>1a</b>	H, H, 2-thienyl ( <b>2d</b> )	7	<b>3f</b> (62)
7	<b>1b</b>	<b>2d</b>	4	<b>3g</b> (78)
8	<b>1b</b>	PhCONH, Ph, Ph ( <b>2e</b> )	36	<b>3h</b> (51)
9	<b>1b</b>	PhCONH, Ph, 2-furyl ( <b>2f</b> )	28	<b>3i</b> (46)
10	<b>1b</b>	PhCONH, Ph, 2-thienyl ( <b>2g</b> )	19	<b>3j</b> (45)
11	<b>1b</b>	PhCONH, Ph, 3-indolyl ( <b>2h</b> )	21	<b>3k</b> (25)
12	Cr, TMS ( <b>1c</b> )	<b>2b</b>	10	<b>3l</b> (60)
13	W, TMS ( <b>1d</b> )	<b>2b</b>	8	<b>3m</b> (86)
14	Cr, <i>p</i> -tol ( <b>1e</b> )	<b>2b</b>	8	<b>3n</b> (78)
15	W, <i>p</i> -tol ( <b>1f</b> )	<b>2b</b>	4	<b>3o</b> (82)

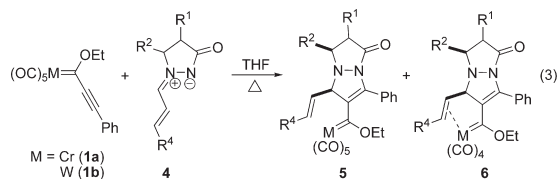
<sup>a</sup> Conditions: **1**, 1.0 mmol; **2**, 1.0 mmol; THF, 4 mL; 50 °C - reflux, atmospheric N<sub>2</sub>. <sup>b</sup> Isolated yields. TMS = trimethylsilyl, *p*-tol = 4-MeC<sub>6</sub>H<sub>4</sub>.

occurred in chloroform or benzene, whereas it underwent completion in THF within 2 h, forming a [3 + 2] cycloaddition product, i.e., pyrazolo-pyrazolone **3a**, in 71% yield as the only product (Table 1, entry 1). In a similar fashion, products **3b–g** were isolated in 61–78% yields (entries 2–7). Using PhCONH-substituted azomethine imines **2e–h**, compounds **3h–k** were collected in 25–51% yields (entries 8–11). Fischer carbene complex **1a** was much less reactive than **1b** in the reactions with azomethine imines **2e–h**, resulting in no measurable amount of the target products. With 1-alkynyl Fischer carbene complexes **1c–f**, the same type of [3 + 2] cycloaddition products **3l–o** were obtained in 60–86% yields

(entries 12–15). It is noteworthy that, in the reaction of **1c** with azomethine imine **2b**, a desilylating product **3l'** was also isolated in 15% yield (eq 2).



**Table 2.** [3 + 2] Cycloaddition of Alkenyl Azomethine Imines **4** with **1**<sup>a</sup>

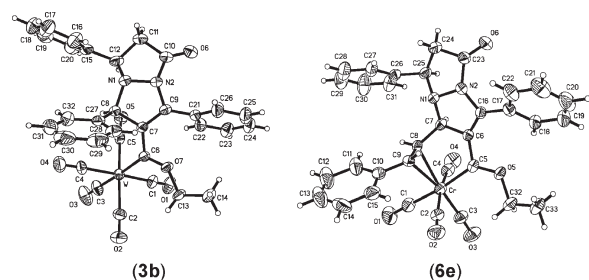


entry	<b>1</b>	R <sup>1</sup> , R <sup>2</sup> , R <sup>4</sup>	time (h)	yield <sup>b</sup> (%)
1	<b>1a</b>	H, H, Ph ( <b>4a</b> )	1	<b>5a</b> (45) <b>6a</b> (53)
2	<b>1b</b>	<b>4a</b>	0.3	<b>5b</b> (84) <b>6b</b> (–)
3	<b>1a</b>	H, H, 2-furyl ( <b>4b</b> )	2	<b>5c</b> (37) <b>6c</b> (57)
4	<b>1b</b>	<b>4b</b>	1	<b>5d</b> (79) <b>6d</b> (–)
5	<b>1a</b>	H, Ph, Ph ( <b>4c</b> )	1	<b>5e</b> (–) <b>6e</b> (75)
6	<b>1b</b>	<b>4c</b>	0.5	<b>5f</b> (74) <b>6f</b> (–)
7	<b>1a</b>	H, Ph, 2-furyl ( <b>4d</b> )	2	<b>5g</b> (–) <b>6g</b> (85)
8	<b>1b</b>	<b>4d</b>	1	<b>5h</b> (85) <b>6h</b> (–)
9	<b>1a</b>	PhCONH, Ph, Ph ( <b>4e</b> )	4	<b>5i</b> (–) <b>6i</b> (44)
10	<b>1b</b>	<b>4e</b>	3	<b>5j</b> (63) <b>6j</b> (18)
11	<b>1a</b>	PhCONH, Ph, 2-furyl ( <b>4f</b> )	4	<b>5k</b> (–) <b>6k</b> (52)
12	<b>1b</b>	<b>4f</b>	4	<b>5l</b> (54) <b>6l</b> (14)

<sup>a</sup> Reaction conditions: **1**, 1.0 mmol; **4**, 1.0 mmol; THF, 4 mL; 50 °C-reflux, atmospheric N<sub>2</sub>. <sup>b</sup> Isolated yields.

Next, the reactions of **1** with alkenyl azomethine imines **4** were investigated (Table 2). Two new Fischer carbene complex products **5a** (45%) and **6a** (53%) were isolated from the [3 + 2] cycloaddition of **1a** with **4a** in THF under heating conditions (entry 1). **5a** is a pentacarbonyl carbene complex featuring the same *N,N*-bicyclic core as **3** has, while **6a** is a tetracarbonyl carbene complex with Cr- $\pi$  bonding. Under the same conditions, cycloaddition of **1b** with **4a** afforded **5b** (84%) as the only product (entry 2). A remarkable metal effect led to the predominant formation of products **5** (54–84%) from the reactions of tungsten carbene complex **1b** with **4** (entries 2, 4, 8, and 10), whereas increasing the steric hindrance on the bicyclic ring of an azomethine imine substrate favored the formation of products **6** (44–85%) from the reactions of **1a** with **4** (entries 1, 3, 5–7, and 9).

The characteristic <sup>13</sup>C NMR signals of the carbene carbons in complexes **3** and **5** appeared at 335.0–338.5 ppm for Cr=C and 305.5–310.3 ppm for W=C, and those of the M(CO)<sub>5</sub> moieties were shown at *ca.* 223/216 ppm for Cr(CO)<sub>5</sub> and *ca.* 202/197 ppm (1:4 intensity) for W(CO)<sub>5</sub>,



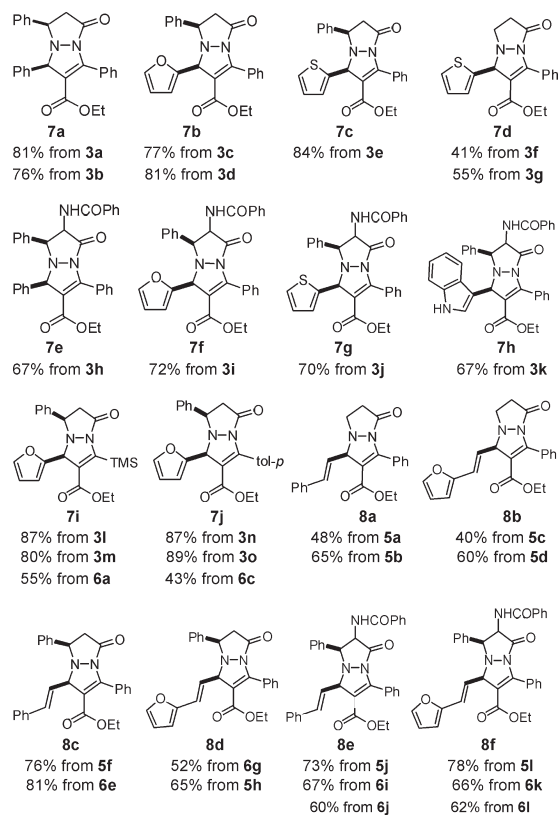
**Figure 1.** Molecular structures of **3b** and **6e**.

respectively. For tetracarbonyl carbene complexes **6**, their <sup>13</sup>C NMR signals were situated in the region 320.8–321.6 ppm for Cr=C and 294.7–295.2 ppm for W=C, and those of the M(CO)<sub>4</sub> moieties appeared as four discrete singlets with the same intensity at *ca.* 235/225/224/223 ppm for Cr(CO)<sub>4</sub> and *ca.* 216/210/205/203 ppm for W(CO)<sub>4</sub>, respectively, suggesting no CO exchange in the M(CO)<sub>4</sub> moieties in solution on the NMR time scale.

The molecular structures of **3b** and **6e** were further confirmed by X-ray crystallographic determinations (see the Supporting Information (SI)), and their perspective views are presented in Figure 1. Complex **3b** exists as a typical pentacarbonyl carbene complex with a metal carbene bond (W–C, 2.189(5) Å), featuring an *N,N*-bicyclic pyrazolo-pyrazolone core. Complex **6e** presents a molecular structure containing the same *N,N*-bicyclic core as **3b** has, and its Cr–C bond length is 2.034(3) Å. The bond distance between the two alkenyl carbons coordinated to the metal, i.e., C(8)–C(9) bond length in **6e**, is 1.364(4) Å which is longer than the common C=C bond (*ca.* 1.34 Å),<sup>16</sup> and the distances between these vinylic carbons and the metal are 2.303(3) and 2.390(3) Å, respectively, revealing  $\pi$ -bonding between the metal and the CH=CH moiety. The molecular structures of **3b** and **6e** further confirmed that R<sup>2</sup> and R<sup>3</sup> groups in the products are arranged *syn* to each other. Because it is the  $\delta$ -vinyl functional group coordinating to the metal in complex **6e** instead of the  $\beta$ -vinyl moiety coordinating to the metal as reported in Barluenga's constrained tetracarbonyl complexes,<sup>17</sup> complexes **6** are stable in the solid state or solution.

Interconversion between complexes **5** and **6** was investigated to explore their stability. Heating in vacuo (*ca.* 1 mmHg) made most of the pentacarbonyl carbene complexes **5** decompose to the corresponding tetracarbonyl carbene complexes **6** (see the SI). For example, **5a** and **5c** were quantitatively converted to **6a** and **6c** upon heating at 50 °C/1 mmHg for 8 h, respectively. Partial decomposition of **5h** and **5j** occurred in vacuo after heating at 90 °C for 8 h, resulting in their corresponding tetracarbonyl complexes **6h** and **6j** in *ca.* 50% yields, while **5b** and **5d** withstood the heating conditions, exhibiting very high stability. However,

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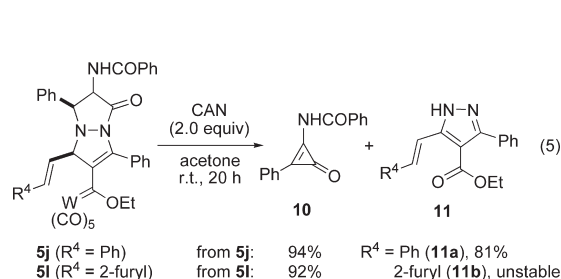
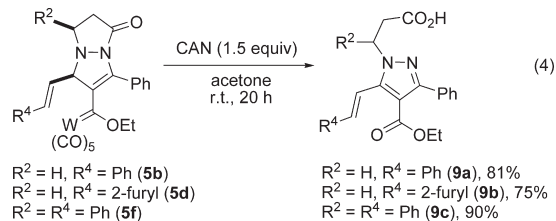
Conditions: **3**, **5** or **6**, 0.5 mmol; PNO, 1.1 equiv; 0.5–1.0 h; for oxidation of **3** and **5**, CH<sub>2</sub>Cl<sub>2</sub> (2 mL), 0 °C-r.t.; for oxidation of **6**, THF (2 mL), 40 °C. Isolated yields.

**Figure 2.** Oxidative demetalation of complexes **3**, **5**, and **6**.

conversion of **6** to **5** took place under mild conditions. In the presence of atmospheric CO, violet **6a** was quantitatively converted to orange **5a** in dichloromethane at ambient temperature over a period of 24 h. Upon exposure of **6c**, **6g**, and **6i** to a CO atmosphere, they were only partially converted to the corresponding pentacarbonyl analogues **5c**, **5g**, and **5i** in 50–80% yields. It should be noted that **6h** and **6j** were unreactive with CO and stayed unchanged in THF under the CO atmosphere at 50 °C over a period of 20 h. These results suggest that the present tetracarbonyl carbene complexes **6** are much more stable than those tetracarbonyl aminovinylcarbene complexes reported by Barluenga et al.<sup>17</sup>

Demetalation of the newly formed Fischer carbene complexes was carried out in dichloromethane or THF at 0–40 °C by using pyridine-*N*-oxide (PNO) as the oxidant.<sup>18</sup> Thus, oxidative demetalation of **3** with PNO afforded *N,N*-bicyclic pyrazolidin-3-ones **7a–h** in 41–84% yields, and that of **5** and **6** produced the same type of organic products **8a–f** in 40–81% yields (Figure 2). It was found that complexes **6** are less reactive to PNO than their corresponding pentacarbonyl analogs **5** and their oxidative demetalation should be carried out at 40 °C. Ceric ammonium nitrate (CAN) also showed potential in

oxidatively demetalating these Fischer carbene complexes. Subsequently, oxidative demetalation of **5b**, **5d**, and **5f** with CAN led to cleavage of their amide C–N bonds, forming the ring-opening products, i.e., tetrasubstituted pyrazoles **9a–c** (75–90%) (eq 4). In a similar fashion, oxidation of the fully substituted pyrazolo-pyrazolone Fischer carbene complexes **5j** and **5l** with CAN efficiently afforded cycloprop-2-enone **10** (92–94%) and trisubstituted 1*H*-pyrazoles **11** (eq 5). Formation of **10** is presumably attributed to sequential C–N bond cleavages and intramolecular carbon–carbon coupling in **5**. These results suggest a promising route to multisubstituted pyrazoles for biochemical purposes.<sup>3,9</sup>



In summary, regioselective [3 + 2] annulation of azomethine imines with 1-alkynyl Fischer carbene complexes has been successfully developed to synthesize versatile functionalized *N,N*-bicyclic pyrazolidin-3-ones. A remarkable metal effect was found to direct formation of the pentacarbonyl and tetracarbonyl carbene complexes from the reactions of alkenyl azomethine imines with 1-alkynyl Fischer carbene complexes. Oxidative demetalation of the newly formed *N*-heterocyclic carbene complexes afforded *N,N*-bicyclic pyrazolidin-3-ones by using pyridine-*N*-oxide and produced cycloprop-2-enone and multisubstituted pyrazoles with ceric ammonium nitrate as the oxidant. These results suggest a novel alternative route to potentially bioactive functionalized *N,N*-bicyclic pyrazolidin-3-ones, cycloprop-2-enone, and functionalized pyrazoles under mild conditions.

**Acknowledgment.** We are grateful to the National Natural Science Foundation of China (20772124, 20972157), 973 Program (2009CB825300), Natural Science Foundation of Liaoning Province (20102225), and the Innovation Program of CAS (DICP K2009D04) for support of this research.

**Supporting Information Available.** Experimental procedures, analytical data and copies of NMR spectra, and X-ray crystallographic files for **3b** and **6e**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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