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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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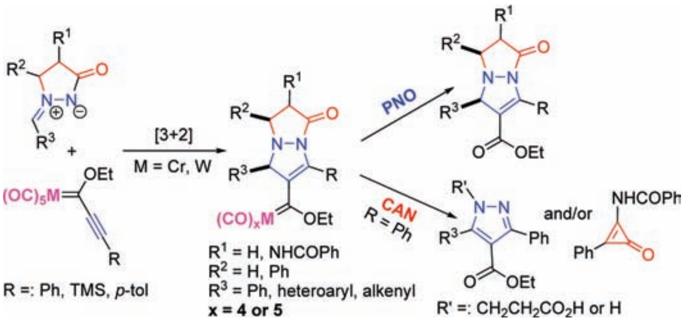
ABSTRACT



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-enone 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.[1] 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).[2,3] 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.[4] However, azomethine imines have been applied with limitations for synthetic purposes as compared with azomethine ylides and nitrones.[5] Only by means of

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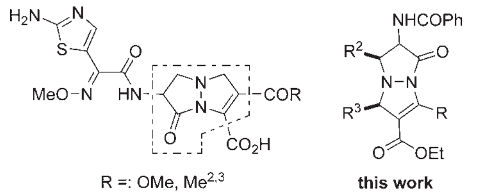
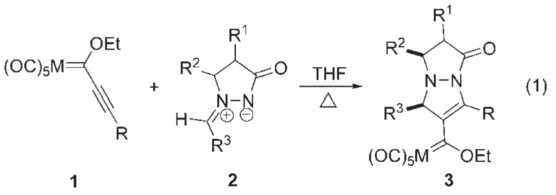
Scheme 1. Analogs of Penicillin and Cephalosporin Antibiotics,[2,3] and the Target Products in This Work



electron-poor terminal alkynes,[6] enones,[7] and benzynes,[8] 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.[2,6] Thus, exploration of new synthetic methods to functionalized *N*,*N*-bicyclic pyrazolidin-3-one derivatives is strongly desired.[9] Fischer carbene complexes have been used as versatile building blocks in organic synthesis.[10] The [3 + 2] cycloaddition of alkynyl Fischer carbene complexes with *N*-alkyl nitrones[11] and azides[12] 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.[10,13–16] In these 1,3-dipolar cycloaddition reactions, the metal pentacarbonyl moiety 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.[15] 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 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

Table 1. [3 + 2] Cycloaddition of Azomethine Imines **2** with **1**[a]



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

[a] Conditions: **1**, 1.0 mmol; **2**, 1.0 mmol; THF, 4 mL; 50 °C - reflux, atmospheric N_2. [b] Isolated yields. TMS = trimethylsilyl, *p*-tol = 4-MeC_6H_4.

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(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).

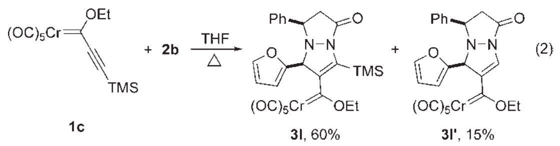
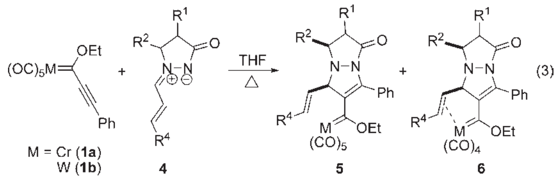


Table 2. [3 + 2] Cycloaddition of Alkenyl Azomethine Imines **4** with **1**[a]



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

[a] Reaction conditions: **1**, 1.0 mmol; **4**, 1.0 mmol; THF, 4 mL; 50 °C - reflux, atmospheric N_2. [b] 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-π 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 ^{13}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)$_5$ moieties were shown at *ca.* 223/216 ppm for Cr(CO)$_5$ and *ca.* 202/197 ppm (1:4 intensity) for W(CO)$_5$, respectively. For tetracarbonyl carbene complexes **6**, their ^{13}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)$_4$ moieties appeared as four discrete singlets with the same intensity at *ca.* 235/225/224/223 ppm for Cr(CO)$_4$ and *ca.* 216/210/205/203 ppm for W(CO)$_4$, respectively, suggesting no CO exchange in the M(CO)$_4$ moieties in solution on the NMR time scale.

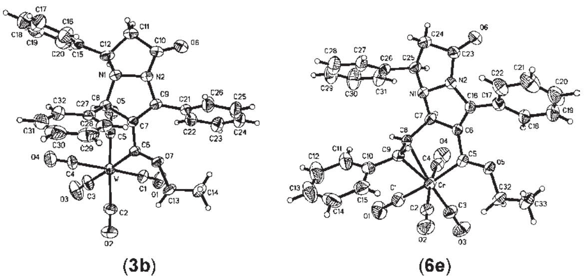


Figure 1. Molecular structures of **3b** and **6e**.

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),[16] and the distances between these vinylic carbons and the metal are 2.303(3) and 2.390(3) Å, respectively, revealing π-bonding between the metal and the CH=CH moiety. The molecular structures of **3b** and **6e** further confirmed that R^2 and R^3 groups in the products are arranged *syn* to each other. Because it is the δ-vinyl functional group coordinating to the metal in complex **6e** instead of the β-vinyl moiety coordinating to the metal as reported in Barluenga's constrained tetracarbonyl complexes,[17] 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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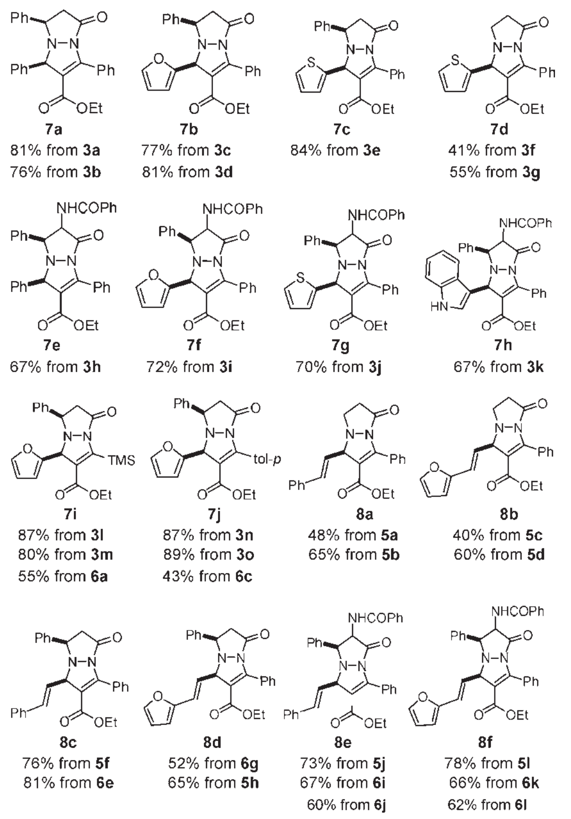
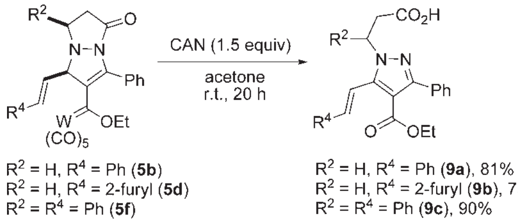


Conditions: 3, 5 or 6, 0.5 mmol; PNO, 1.1 equiv; 0.5-1.0 h; for oxidation of 3 and 5, CH_2Cl_2 (2 mL), 0 °C-r.t.; for oxidation of 6, THF (2 mL), 40 °C. Isolated yields.

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 **6i** 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.[17]

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.[18] 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.[3,9]



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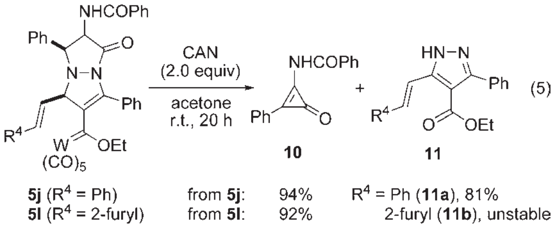

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In summary, regioselective [3 + 2] annulation of azomethine imines with 1-alkynyl Fischer carbene complexes has been successfully developed to synthesize versatile functionalized *N*,*N*-bicyclic pyrazolidin-3-ones. A remarkable metal effect was found 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.

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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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