Synthetic Methods

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Sequential Five-Component Construction of the Cyclopenta[*e*]-[1,3]oxazine Skeleton using Stable 2-Azetine Derivatives**

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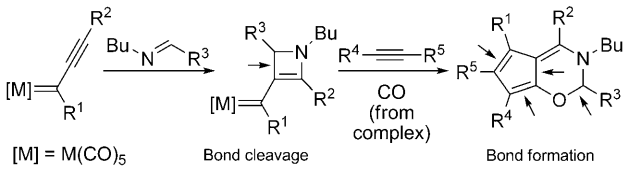
Dedicated to Professor Julius Rebek, Jr. on the occasion of his 65th birthday

Small-ring heterocycles are of prominent importance because of their potential as bioactive compounds and synthetic building blocks. Whilst the chemistry of three-membered nitrogen heterocycles has been widely reported, studies on their four-membered counterparts have focused primarily on 2-azetidinones and, to a much lesser extent, azetidine rings.[1] The 2-azetine system 1,2-dihydroazete, which has a strained cyclic enamine ring, is particularly elusive.[2] Most 2-azetine compounds undergo spontaneous electrocyclic ring opening to afford their 1-azadiene analogues; as such, there are few examples of stable 2-azetines in the literature and those reported require electron-withdrawing substituents, for example, carbonyl, carboxyl, sulfonyl, or nitro groups, attached to the nitrogen atom.[3,4] As a consequence, the chemistry of 2-azetines remains largely unexplored, and has been predominantly focused on their potential as a precursor to azadienes. Moreover, there are no general synthetic routes to 2-azetines.[5] Although, the [2+2] cycloaddition of alkynes and imines appears to be a convenient route to this type of heterocyclic framework, only a few specific examples have been reported; in these cases, electron-rich alkynes, as ynamines,[6] alkynyl selenides,[7] or alkynyl sulphides,[8] are able to form the expected 2-azetine skeleton, which is not isolated but rapidly opens to the azadiene system. The [2+2] cycloaddition of electron-poor alkynes and imines has only previously been suggested as an intermediate in the cyclization reaction between an alkynyl(ethoxy)carbene of tungsten and imine fluorenones to afford pyrroline derivatives.[9]

As part of our interest in Fischer-type metal carbenes, we have recently considered more-electrophilic metal carbenes, the so-called non-heteroatom-stabilized carbenes.[10] These compounds are particularly useful in organic synthesis, and our preliminary results have revealed significant differences in the reactivity of both heteroatom-[11] and non-heteroatom-stabilized systems.

Herein, we report the [2+2] cycloaddition reaction of alkynyl-substituted (pentacarbonyl)chromium or -tungsten carbene complexes with imines as a suitable procedure for accessing stable 2-azetine derivatives. Moreover, the conjugation of the resulting azetine unit with the metal carbene allows for a facile synthesis of novel cyclopenta[*e*]-[1,3]oxazines involving treatment with alkynes. This three-component process (azetine, alkyne, and CO ligand) features cleavage of the azetine C3–C4 bond, rather than the expected N–C4 bond, and the formation of three C–C bonds and one C–O bond (Scheme 1).



Scheme 1. The formation of cyclopenta[*e*][1,3]oxazines from non-heteroatom stabilized carbene complexes by bond cleavage of azetinyl-carbenes. Bond cleavage and formation is shown by arrows.

Stable, easy-to-handle methoxycarbenes **1** are used as in situ precursors of alkynylcarbenes **3** using the methoxy-acetylide **2** exchange reaction (Table 1). The resultant solution of **3** in tetrahydrofuran was treated at −80 °C with 1.3–5.0 equivalents of imine **4** (see the Supporting Information) and the mixture was allowed to warm to 0 °C. Removal of the solvent followed by chromatographic purification afforded the 2-azetine metal carbenes **5a–i** in 50–75 % overall yield from the Fischer carbenes **1**. The structure of azetines **5a–i** was determined by NMR spectroscopy and HRMS data. The structure of compound **5b** was unambiguously confirmed by single-crystal X-ray diffraction analysis. It is noteworthy that the strongly electron-accepting metal–carbene functionality at the C3 atom confers a much improved stability on these *N*-alkyl-2-azetines.[12]

We also used this procedure to regioselectively synthesize 2-azetines bearing an alkyne functionality (**5e,f**).[13] Furthermore, the furfural imine (R^3 = Fu = furfural) underwent heterocyclization with β-ferrocenylethynylcarbenes (R^2 = Fc = ferrocene; see cycloadduct **5d**).[14] Interestingly, azetine **5f** was formed with complete chemoselectivity from a cycloaddition through the more electrophilic alkyne unit of

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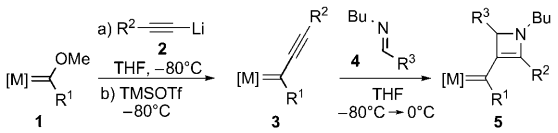
Table 1: Synthesis of azetinylcarbenes **5**.[a]



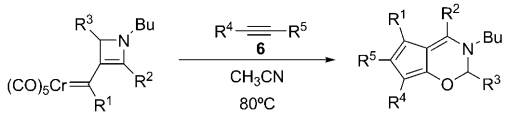
	[M] = Cr(CO)$_5$					[M] = W(CO)$_5$			
	R^1	R^2	R^3	yield[b] [%]		R^1	R^2	R^3	yield[b] [%]
5a	Ph	Ph	Ph	62	**5g**	Ph	Ph	Ph	74
5b	Ph	Fc	Ph	75	**5h**	Ph	Fc	Ph	73
5c	Ph	Ph	*p*-Tol	56	**5h**	Ph	Ph	*c*-C_6H_{11}	63
5d	Ph	Fc	Fu	64					
5e	Ph−C≡C	Ph	Ph	50					
5f	Fc−C≡C	Ph	Ph	72					

[a] The diynylcarbene precursor for **5e** was synthesized from **3** (R^1 = Ph−C≡C, R^2 = Fc). Fc = ferrocenyl; Fu = 2-furyl. [b] Overall yield from Fischer carbenes **1**.

the carbene **3** (Ph-C≡C versus Fc-C≡C). Therefore, the nonstabilized (alkynyl)carbene system, unlike the traditional heteroatom-stabilized analogues, readily undergoes a [2+2] heterocyclization reaction with imines to afford stable 2-azetines. This procedure also suggests that the C3 metal–carbene functionality is an efficient stabilizing motif for the 2-azetine ring.

We then examined the reactivity of the chromium azetinyl carbene towards neutral and activated alkyne substrates (Table 2). Therefore, the treatment of an acetonitrile solution

Table 2: Three-component synthesis of bicyclic [1,3]oxazines **7**.

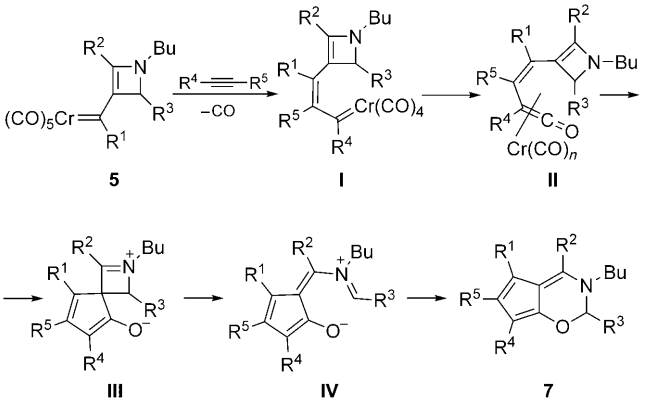


	R^1	R^2	R^3	R^4	R^5	Yield [%]
7a	Ph	Ph	Ph	Fc	H	64
7b	Ph	Ph	Ph	*p*-Tol	H	65
7c	Ph	Ph	Ph	*c*-C_6H_{11}	H	32
7d	Ph	Fc	Ph	*p*-Tol	H	69
7e	Ph	Ph	*p*-Tol	Fc	H	57
7f	Ph−C≡C	Ph	Ph	*p*-Tol	H	36
7g	Ph	Ph	Ph	CO_2Me	H	82
7h	Ph	Ph	*p*-Tol	CO_2Me	H	78
7i	Ph	Ph	Ph	CO_2Me	CO_2Me	62

of chromium carbene **5a–c,e** with terminal alkynes **6** at 80 °C resulted in the formation of substituted 2,3-dihydrocyclopenta[*e*]oxazines **7a–f** in moderate to good yields after chromatographic purification. Higher yields were obtained for the electron-poor alkyne methyl propiolate (**7g,h**). Although the non-activated internal alkyne 4-octyne reacted poorly (<15% yield, not shown), dimethyl acetylenedicarboxylate afforded the expected cycloadduct **7i** in 62% yield.[15] NMR spectroscopy (^{1}H/^{13}C, and 1D/2D experiments) was used to determine the structures **7a–i**. Moreover, the structures of compounds **7a** and **7d** were unambiguously confirmed by X-ray crystallography.

From a synthetic standpoint, some features are noticeable: 1) hexasubstituted cyclopentaoxazines were obtained as a single isomer; 2) the three components, the azetine-3-yl carbene, the alkyne, and carbon monoxide, assembled regioselectively; and 3) one C–O and three C–C bonds were formed. Moreover, the C3–C4 bond of the azetine unit was cleaved, in sharp contrast with the C4–N cleavage-initiated reactivity pattern of simple azetines (electrocyclic ring opening).

We proposed a mechanism on the basis of the reactivities of Group 6 metal–carbenes, and azetines (Scheme 2). In this mechanism, the reaction is initiated by the regioselective



Scheme 2. Proposed mechanism for the formation of cyclopentadiene-fused oxazines **7**.

insertion of an alkyne into the Cr=C bond to form intermediate **I**. A carbon monoxide ligand inserts into the newly formed metal–carbene to generate metal–ketene complex **II**. Subsequent intramolecular nucleophilic attack affords azetinium species **III**, which would advance through electrocyclic ring opening (intermediate **IV**) and cyclization to give product **7**. Whilst the insertion reaction of alkynes and carbon monoxide into the related metal alkoxycarbenes is well documented,[16] to the best of our knowledge the postulated electrocyclic ring opening of 1-azetinium species (**III**→**IV**) has not been reported.[17]

In conclusion, we have developed a two-step, regioselective route to the 2,3-dihydrocyclopenta[*e*][1,3]oxazine skeleton **7** from readily available acyclic adducts. This route enables the synthesis of a heterocyclic motif with very high structural complexity from five units: an aryl(methoxy)carbene, acetylide, imine, alkyne, and carbon monoxide, in an ordered and selective sequence. The first step of the process is an efficient and simple procedure to access the *N*-alkyl-2-azetine skeleton **5**. A preliminary study of the reactivity of this system towards alkynes shows that the reactivity of the azetine unit is controlled by the conjugated metal–carbene moiety, which is responsible for the unexpected C3–C4 bond-cleavage via an azetinium ion. Furthermore, this synthesis is tolerant of valuable functional groups, such as alkyne and ester groups. We believe that the intrinsic

reactivity of both carbene and azetine moieties makes **5** a valuable intermediate in the preparation of nitrogen-containing polycyclic arrays.

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Keywords: alkynes · azetines · carbenes · heterocycles · regioselectivity

[1] For a recent review on the synthesis of azetidines and azetidinones, see: A. Brandi, S. Cicchi, F. M. Cordero, *Chem. Rev.* **2008**, *108*, 3988 – 4035.
[2] S. Mangelinckx, V. Van Speybroeck, P. Vansteenkiste, M. Waroquier, N. De Kimpe, *J. Org. Chem.* **2008**, *73*, 5481 – 5488.
[3] a) R. N. Warrener, G. Kretschmer, M. N. Paddon-Row, *J. Chem. Soc. Chem. Commun.* **1977**, 806 – 807; b) M. E. Jung, Y. M. Choi, *J. Org. Chem.* **1991**, *56*, 6729 – 6730; c) A. P. Marchand, D. Rajagopal, S. G. Bott, T. G. Archibald, *J. Org. Chem.* **1994**, *59*, 1608 – 1612; d) P. R. Dave, R. Duddu, J. Li, R. Surapaneni, R. Gilardi, *Tetrahedron Lett.* **1998**, *39*, 5481 – 5484; e) A. C. B. Burtoloso, C. R. D. Correia, *Tetrahedron Lett.* **2006**, *47*, 6377 – 6380.
[4] a) The isolation of dimethyl 1-ethyl-4-methyl-2-azetine-2,3-dicarboxylate in 9% yield has been reported; see: E. Winterfeldt, W. Krohn, *Chem. Ber.* **1969**, *102*, 2336 – 2345; b) for an example of fluorinated 3-acyl-2-amino-2-azetine derivatives, see: P. L. Coe, I. R. Owen, S. J. Till, *J. Chem. Soc. Perkin Trans. 1* **2000**, 1529 – 1535.
[5] Typical procedure involves the multistep synthesis of a suitable azetidine precursor, followed by elimination; a) see Ref. [2, 3b, d, e]; b) Y. Dejaegher, S. Mangelinckx, N. De Kimpe, *J. Org. Chem.* **2002**, *67*, 2075 – 2081.
[6] M. E. Kuehne, P. J. Sheeran, *J. Org. Chem.* **1968**, *33*, 4406 – 4413.
[7] Y. Ma, C. Qian, *Tetrahedron Lett.* **2000**, *41*, 945 – 947.
[8] H. Ishitani, S. Nagayama, S. Kobayashi, *J. Org. Chem.* **1996**, *61*, 1902 – 1903.
[9] R. Aumann, Z. Yu, R. Froehlich, F. Zippel, *Eur. J. Inorg. Chem.* **1998**, 1623 – 1629.
[10] For recent results from our research group involving non-heteroatom-stabilized alkynylcarbene complexes, see: a) J. Barluenga, P. García-García, D. de Sáa, M. A. Fernández-Rodríguez, R. Bernardo de La Rúa, A. Ballesteros, E. Aguilar, M. Tomás, *Angew. Chem.* **2007**, *119*, 2664 – 2666; *Angew. Chem. Int. Ed.* **2007**, *46*, 2610 – 2612; b) J. Barluenga, D. de Sáa, A. Gómez, A. Ballesteros, J. Santamaría, A. de Prado, M. Tomás, A. L. Suarez-Sobrino, *Angew. Chem.* **2008**, *120*, 6321 – 6324; *Angew. Chem. Int. Ed.* **2008**, *47*, 6225 – 6228; c) J. Barluenga, A. Gómez, J. Santamaría, M. Tomás, *J. Am. Chem. Soc.* **2009**, *131*, 14628 – 14629.
[11] For recent reviews, see: a) A. de Meijere, H. Schirmer, M. Duetsch, *Angew. Chem.* **2000**, *112*, 4124 – 4162; *Angew. Chem. Int. Ed.* **2000**, *39*, 3964 – 4002; b) J. W. Herndon, *Tetrahedron* **2000**, *56*, 1257 – 1280; c) M. A. Sierra, *Chem. Rev.* **2000**, *100*, 3591 – 3637; d) K. H. Dötz, *Metal Carbenes in Organic Synthesis (Topics in Organometallic Chemistry)*, *Vol. 13*, Springer, New York, **2004**; e) J. Barluenga, J. Santamaría, M. Tomás, *Chem. Rev.* **2004**, *104*, 2259 – 2283; f) J. Barluenga, M. A. Fernández-Rodríguez, E. Aguilar, *J. Organomet. Chem.* **2005**, *690*, 539 – 587; g) J. Santamaría, *Curr. Org. Chem.* **2009**, *13*, 31 – 46; h) K. H. Dötz, J. Stendel, *Chem. Rev.* **2009**, *109*, 3227 – 3274.
[12] The azetines **5** are stable when stored under nitrogen at 0–20 °C.
[13] When an alkyl acetilyde ($R^2 = Bu$; $R^1 = R^3 = Ph$) is employed, the expected azetine was not formed, but a [4+3] cyclization was observed wherein the phenylimine behaves as the 1-azadiene unit.
[14] The reaction of furfural imines with carbenes **3,** where R^2 groups other than a ferrocenyl group ($R^2 \neq Fc$) are used, undergo a [3+3] cyclization reaction to afford benzofurans; see Ref. [10c].
[15] The reaction of the tungsten azetine complex **5g** with *para*-tolylacetylene formed a complex mixture rather than the expected cycloadduct **7b**.
[16] For a sequence involving initial insertion of two alkyne units and carbon monoxide into a Fischer alkenyl carbene, followed by nucleophilic cyclization, see: F. Stein, M. Duetsch, R. Lackmann, M. Noltemeyer, A. de Meijere, *Angew. Chem.* **1991**, *103*, 1669 – 1671; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1658 – 1660.
[17] a) For a rare example of the formation of a 1-azetinium salt from the [2+2] cycloadditon of a nitrilium salt and methyleneadamantane, see: A. H. Moustafa, W. Wirschun, C. C. Freyhardt, J. C. Jochims, R. Abu-El-Halawa, *J. Prakt. Chem.* **1997**, *339*, 615 – 622; b) it is well established that vinyl or allylammonium salts undergo the [3,3] rearrangement faster than their uncharged parent allylenamines; see: K. C. Majumdar, T. Bhattacharyya, B. Chattopadhyay, B. Sinha, *Synthesis* **2009**, 2117 – 2142.

