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Copper(I)-Catalyzed [3+1] Cycloaddition of Alkenyldiazoacetates and Iminoiodinanes: Easy Access to Substituted 2-Azetines

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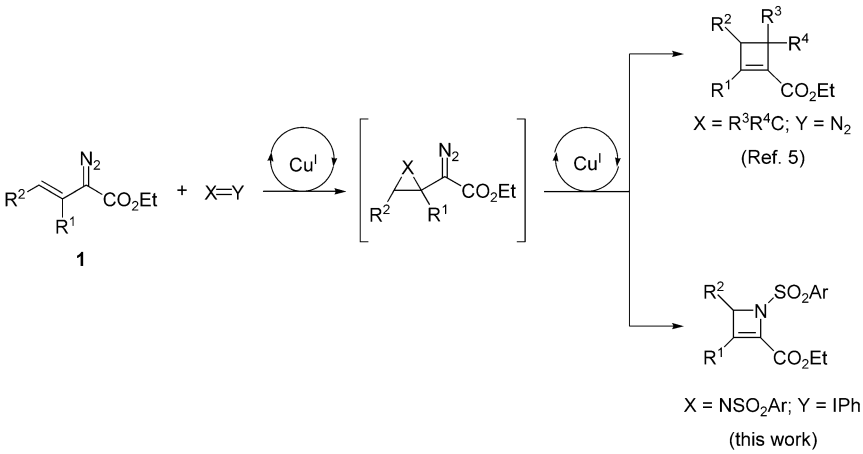
Dedicated to Prof. Julio Delgado Martín on the occasion of his 70th birthday

Four-membered nitrogen heterocycles are an important class of compounds, exhibiting a wide range of biological activities. In contrast to the well-studied chemistry of 2-azetidinones (β-lactmas) and azetidines,[1] 2-azetines represent a virtually unexplored class of azaheterocycles. Both stability considerations and the absence of efficient routes to the preparation of this heterocyclic core have led to a lack of studies involving azetine derivatives. The [2+2] cycloaddition of imines and electron-rich alkynes (e.g., ynamines, alkynyl selenides/sulfides) could be considered a convenient method to generate this heterocyclic framework, however, the resulting azetine ring is not isolated and rapidly undergoes electrocyclic ring opening to the corresponding azadiene derivatives.[2,3] In fact, only one report on the preparation of azetine derivatives by [2+2] cycloaddition of imines to electron-poor alkynes has been published to date.[4] On the other hand, we recently found that vinyldiazo acetates readily undergo copper(I)-catalyzed cyclopropanation and ring expansion to cyclobutenes.[5] Based on the ability of iminoiodinanes to transfer a nitrene function to olefins,[6] we now report a direct and regioselective route to substituted 2-azetines **3** from stabilized alkenyldiazo derivatives **1**[7] and (*N*-arylimino)phenyliodinanes **2** using a copper(I) catalyst (Scheme 1).[8]



Scheme 1. Vinyldiazo compounds as precursors for the synthesis of four-membered carbo- and heterocycles.

In accordance with our previous research, $[Cu(MeCN)_4][BF_4]$ in dichloromethane was initially selected as the catalytic system. Stirring a solution of vinyldiazoacetate **1a** ($R^1=R^2=H$), (*N*-(*p*-toluenesulfonyl)imino)phenyliodinane (PhI=NTs) **2a**, and $[Cu(MeCN)_4][BF_4]$ (5 mol%) in dichloromethane at room temperature for 4 h resulted in the formation of 2-azetine **3aa** in 33% yield after chromatographic purification. While other copper(I)-based catalysts did not improve the efficiency of the process, replacing dichloromethane with acetonitrile as the solvent increased the yield to 56% (Table 1). Importantly, this formal [3+1] heterocyclization reaction takes place with complete regioselectivity. The structure of azetine **3aa** was elucidated by NMR spectroscopy ($^1H/^{13}C$ and 1D/2D experiments) and high-resolution mass spectrometry (HRMS) data.

Further studies performed to determine the scope of the process are given in Table 1. In relation to the structure of the diazo substrate **1**, some points should be noted: 1) the reaction works well for substrates with alkyl/aryl substitution at C-α (**1b**,**c**) and C-β (**1d**), while diazo compound **1e** bearing a β-alkoxycarbonyl substituent does not react under these conditions; 2) using *tert*-butyl vinyldiazoacetate (**1f**) does not appreciably decrease the yield; 3) keto-stabilized diazo compounds, for example, **1g** where the electon-withdrawing group (EWG) is an acetyl, are also amenable to

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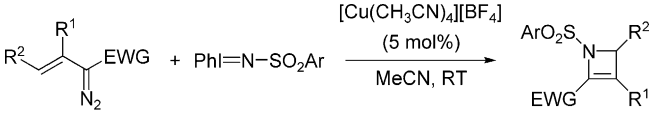
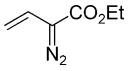
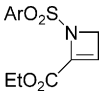
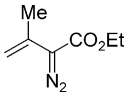
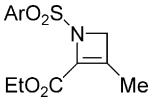
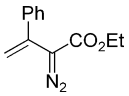
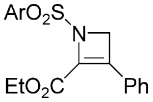
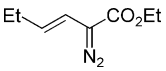
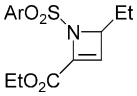
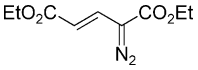
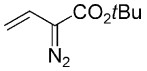
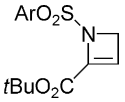
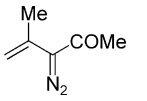
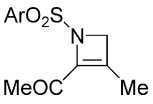
Table 1. Copper (I)-catalyzed synthesis of azetine derivatives **3** from vinyldiazo compounds **1** and iminoiodinanes **2**.



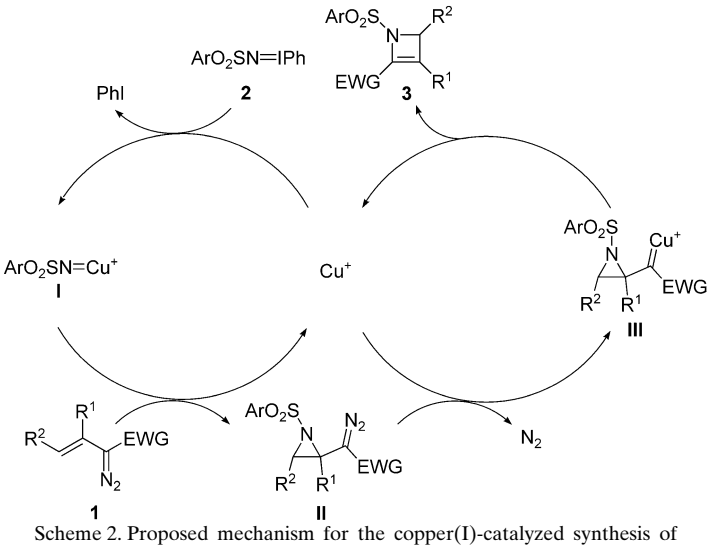
1 **2** **3**

Substrate **1**		Ar (**2**)	Product **3**		Yield[a] [%]
	**1a**	*p*-MeC_6H_4 (**2a**)		**3aa**	56
		p-$NO_2C_6H_4$ (**2d**)		**3ad**	54
	**1b**	*p*-MeC_6H_4 (**2a**)		**3ba**	62
		C_6H_5 (**2b**)		**3bb**	66
		p-$MeOC_6H_4$ (**2c**)		**3bc**	53
		p-$NO_2C_6H_4$ (**2d**)		**3bd**	57
	**1c**	*p*-MeC_6H_4 (**2a**)		**3ca**	58
	**1d**	*p*-MeC_6H_4 (**2a**)		**3da**	44
	**1e**	*p*-MeC_6H_4 (**2a**)	no reaction	–	–
	**1f**	*p*-MeC_6H_4 (**2a**)		**3fa**	52
	**1g**	*p*-MeC_6H_4 (**2a**)		**3ga**	46

[a] Yield of isolated product after column chromatography.

this cyclization. On the other hand, the nature of substituents on the aromatic ring (Ar) in the iminoiodane **2** (*p*-Me, **2a**; H, **2b**; *p*-OMe, **2c**; *p*-NO_2, **2e**) appear to exert little influence on the reaction. With the exception of 4-substituted azetine **3da**, all of the compounds prepared are stable and can be stored in pure form or in solution without noticeable decomposition for a number of days at 0–20 °C.[9]

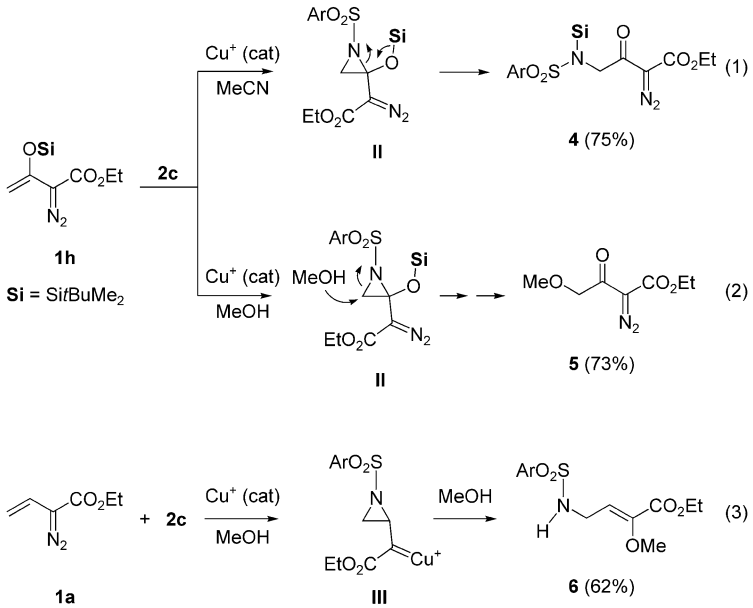
In accordance with our previous work,[5] the mechanism outlined in Scheme 2 is proposed for the formation of compounds **3**. The process would be initiated by the aziridination of the



Scheme 2. Proposed mechanism for the copper(I)-catalyzed synthesis of azetine derivatives **3** from vinyldiazo compounds **1** and iminoiodinanes **2**.

C=C functionality of **1** by metal-bound nitrene intermediate **I** to form key aziridinyldiazoacetate intermediate **II**.[10] Formation of the 2-azetine structure (**3**) would imply the copper-catalyzed decomposition of **II** to copper–aziridinylcarbene **III** followed by selective [1,2]-amino rearrangement.[11,12]

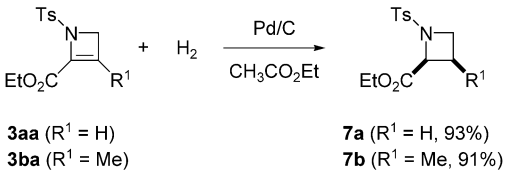
Further studies were directed toward finding evidence for the presence of key intermediates **II**/**III** (Scheme 3). The reaction of silyloxy-substituted vinyl diazoacetate **1h** (R^1 = $OSiMe_2tBu$) with iodinane **2c** (Ar = *p*-$MeOC_6H_4$) did not lead to the expected 2-azetine derivative. Instead, a novel functionalized diazocompound (**4**) was obtained in 75% yield by ring opening of the corresponding silyloxy-substituted aziridine **II** [Eq. (1), Scheme 3].[13] Moreover, the ring opening of this hypothetical aziridine **II** could be selectively



Scheme 3. Experimental evidence for the participation of aziridinyl intermediates **II** and **III** (Ar = *p*-$MeOC_6H_4$).

effected by an external nucleophile such as methanol. Thus, diazo compound **1h** led directly to stabilized β-methoxydiazo derivative **5** (73% yield) when the reaction was carried out in methanol [Eq. (2), Scheme 3]. Finally, support for the participation of metal carbene intermediate **III** arose from the reaction of vinyldiazoacetate **1a** with **2c** in methanol in the presence of copper(I) [Eq. (3), Scheme 3]. In this case, ethyl 2-methoxy-4-aminoalkenoate **6** was produced, probably by MeO–H insertion into the metal carbene of **III** followed by ring opening of the resulting aziridine intermediate.[14,15]

Finally, we have undertaken preliminary studies focused on the synthetic potential of the new azetine framework (**3**). This core structure can be seen as a precursor for the azetidine-2-carboxylic acid scaffold, an important moiety due to its presence in conformationally restricted α-amino acids.[16] In this context, *cis*-hydrogenation was accomplished by simply subjecting compounds **3aa** and **3ba** in ethyl acetate to hydrogen gas (1 atm) in the presence of palladium on carbon to afford azetidines **7a,b** in near quantitative yield (Scheme 4).



3aa (R^1 = H) **7a** (R^1 = H, 93%)
3ba (R^1 = Me) **7b** (R^1 = Me, 91%)

Scheme 4. Synthesis of azetidine derivatives **7a**,**b** from azetines **3aa** and **3ba**.

In conclusion, we have developed a simple and regioselective copper(I)-catalyzed synthesis of functionalized 2-azetine derivatives by the formal [3+1] cycloaddition of vinyldiazo derivatives and iminoiodinanes. Such a process is explained by a copper(I)-catalyzed aziridination of the alkenyl functionality followed by a regioselective copper(I)-catalyzed ring expansion of the resulting aziridinyldiazo intermediate. It is noteworthy that the implications of the copper catalyst are multiple, sequentially producing aziridination through metal nitrene species and 1,2-amino migration through metal carbene species. The resulting azetine structure (α-dehydro amino acid) is a direct precursor of a relevant type of conformationally restricted α-amino acid.

Experimental Section

$[Cu(MeCN)_4][BF_4]$ (7.9 mg, 0.025 mmol) was added to a solution of vinyldiazo **1** (0.5 mmol) and iminoiodane **2** (0.5 mmol) in CH_3CN (5 mL). The mixture was stirred at RT until consumption of **1** (monitored by TLC; 2–3 h). The solvent was removed in vacuo, and the residue was purified by flash chromatography (SiO_2; hexane/EtOAc, 5:1) to give 2-azetine derivative **3**.

Full synthetic protocols, characterization data, and NMR spectra for products **3**–**7** are given in the Supporting Information.

Acknowledgements

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Keywords: 2-azetines · carbenes · copper catalysts · cycloaddition · diazo compounds · iminoiodinanes

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[15] An alternative mechanism for the formation of compound **6** could involve nucleophilic attack of methanol at the carbenoid carbon of intermediate **III**, followed by metal elimination and ring opening of the aziridine.
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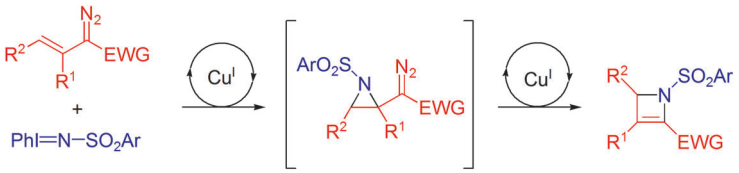

The copper(I)-catalyzed reaction of alkenyldiazoacetates and iminoiodinanes affords functionalized azetine derivatives. This process is consistent with the formation of an aziridinyldiazoacetate intermediate, which gives rise to the four-membered heterocycles by metal-catalyzed ring expansion. The resulting azetine structure is a direct precursor of azeditine-2-carboxylic acid derivatives.

Synthetic Methods

J. Barluenga, L. Riesgo, G. Lonzi, M. Tomás, L. A. López** .... ▮▮▮▮–▮▮▮▮

Copper(I)-Catalyzed [3+1] Cycloaddition of Alkenyldiazoacetates and Iminoiodinanes: Easy Access to Substituted 2-Azetines