

“On Water”: Efficient Iron-Catalyzed Cycloaddition of Aziridines with Heterocumulenes**

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The use of water as a reaction medium for organic synthesis has attracted much interest in recent years,^[1–3] because water is the most abundant liquid on the planet, cheap, readily available, nontoxic, and nonflammable. The [3+2] cycloaddition reaction of aziridines with heterocumulenes provides a powerful tool to access a wide range of functionalized five-membered heterocycles that exhibit interesting biological and medicinal properties.^[4] Thus, the cycloaddition of aziridines with carbodiimides,^[5] isocyanates,^[5–8] and isothiocyanates^[5,7,9–11] has been studied employing Pd,^[5] Ni,^[6] HBF₄,^[7] Mg–MeOH,^[8] PBu₃,^[9] NaI^[10] or Ph₄SbBr^[11]-based systems as either the catalyst or stoichiometric reagent. These reactions are effective in an organic medium and generally involve an inert atmosphere. In continuation of our studies on heterocycle synthesis,^[13] we wish to herein report the first example of iron(III)-catalyzed cycloaddition of aziridines with heterocumulenes that takes place in aqueous suspension at moderate temperature. The protocol is simple and utilizes environmentally benign nontoxic and cheap iron(III) salt as the catalyst^[14] and water as a reaction medium in air.

Firstly, the optimization of the reaction conditions was carried out by using phenyl isoselenocyanate (**1a**) and 1-isopropyl-2-phenylaziridine (**2a**) as model substrates in the presence of Fe(NO₃)₃·9H₂O (10 mol %) and water as the solvent at various temperatures (Table 1). Gratifyingly, the reaction proceeded to afford selectively the target iminoazo-selenolidine^[12] **3a** after five hours in 80 % conversion at room temperature when the suspension of the soluble Fe(NO₃)₃·9H₂O and the insoluble substrates **1a** and **2a** in water was stirred (Table 1, entry 1). Increase of the reaction temperature to 60 °C led to completion of the process in one hour with 100 % conversion (Table 1, entry 3). In a set of iron(III) salts screened, Fe(NO₃)₃·9H₂O, Fe₂(SO₄)₃·5H₂O, FeCl₃·6H₂O, and [Fe(acac)₃], all were active, and the former afforded the best results (Table 1, entries 5–8). The effect of an organic medium, such as toluene, CH₂Cl₂, and (CH₂Cl)₂, was examined, but no reaction was observed, and the starting material was recovered intact (Table 1, entries 9–11). Lowering the amount of the iron(III) catalyst (5 mol %) or the

Table 1: Optimization of the reaction conditions.^[a]

Entry	Catalyst	Solvent	T [°C]	t [h]	Conversion 3a [%] ^[b]
1	Fe(NO ₃) ₃ ·9H ₂ O	H ₂ O	25	5	80
2	Fe(NO ₃) ₃ ·9H ₂ O	H ₂ O	40	3	87
3	Fe(NO ₃) ₃ ·9H ₂ O	H ₂ O	60	1	100
4	Fe(NO ₃) ₃ ·9H ₂ O	H ₂ O	60	2	82 ^[c]
5	Fe(NO ₃) ₃ ·9H ₂ O	H ₂ O	60	1	91 ^[d]
6	FeCl ₃ ·6H ₂ O	H ₂ O	60	1	87
7	Fe ₂ (SO ₄) ₃ ·5H ₂ O	H ₂ O	60	1	58
8	[Fe(acac) ₃]	H ₂ O	60	1	47
9	Fe(NO ₃) ₃ ·9H ₂ O	toluene	60	1	n.d.
10	Fe(NO ₃) ₃ ·9H ₂ O	CH ₂ Cl ₂	40	1	n.d.
11	Fe(NO ₃) ₃ ·9H ₂ O	(CH ₂ Cl) ₂	60	1	n.d.
12	–	H ₂ O	60	8	12

[a] Isoselenocyanate **1a** (0.5 mmol), aziridine **2a** (0.6 mmol), Fe(NO₃)₃·9H₂O (10 mol %) and solvent (1 mL) were stirred in air. [b] Determined by 400 MHz ¹H NMR spectroscopy. [c] 5 mol % of catalyst used. [d] 1 equiv of aziridine **2a** used. n.d. = not detected; acac = acetylacetonate.

quantity of the aziridine (1 equiv) led to the formation of **3a** in less than 91 % conversion (Table 1, entries 4 and 5). Control experiments confirmed that without the iron(III) catalyst the reaction produced **3a** after eight hours in 12 % conversion (Table 1, entry 12).

Next, the scope of the procedure was studied for the reactions of the substituted isoselenocyanates (Table 2). A series of substrates **1a–l** having both the electron-withdrawing and -donating groups on the phenyl ring readily reacted with aziridine **2a** to give the target products in one hour with good to high yields.^[12] For example, aryl isoselenocyanates containing 2-methoxy, 3-methyl, 4-chloro, 4-iodo, 4-methoxy, 4-methyl, and 4-nitro substituents on the phenyl ring reacted to the target products **3b–h** in 61–90 % yield. Recrystallization of **3b** in hexane gave crystals, the structure of which was confirmed by single-crystal X-ray analysis (Figure 1). Aryl isoselenocyanate bearing 3,4-dimethyl substituents on the phenyl ring proceeded to give **3i** in 93 % yield. Naphthyl **1j** and fluorene **1k** isoselenocyanates underwent reactions to afford **3j** and **3k** in 85 % and 75 % yield, respectively. A similar result was observed with cyclohexyl isoselenocyanate **1l** affording **3l** in 72 % yield.

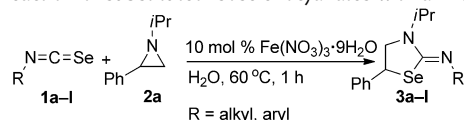
The reactions of a series of aziridines were further studied with phenyl isoselenocyanate (Table 3). As above, the reactions took place efficiently to afford the target molecules in good to high yield. For example, aryl aziridines **2b–o** having

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Table 2: Reaction of substituted isoselenocyanates with aziridine.^[a]



Entry	Isoselenocyanates	R	Product (Yield [%]) ^[b]
1	1a	Ph	3a (88)
2	1b	2-MeOC ₆ H ₄	3b (90)
3	1c	3-MeC ₆ H ₄	3c (85)
4	1d	4-ClC ₆ H ₄	3d (86)
5	1e	4-IC ₆ H ₄	3e (89)
6	1f	4-MeOC ₆ H ₄	3f (82)
7	1g	4-MeC ₆ H ₄	3g (79)
8	1h	4-NO ₂ C ₆ H ₄	3h (61)
9	1i	3,4-Me ₂ C ₆ H ₃	3i (93)
10	1j	1-naphthyl	3j (85)
11	1k	2-fluorene	3k (75)
12	1l	cyclohexyl	3l (72)

[a] Reaction conditions: Isoselenocyanate **1a–l** (0.5 mmol), aziridine **2a** (0.6 mmol), Fe(NO₃)₃·9H₂O (10 mol %) and water (1 mL) were stirred at 60 °C for 1 h in air. [b] Yield of isolated product.

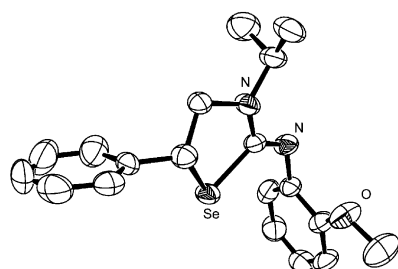
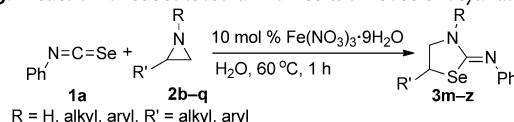


Figure 1. ORTEP diagram of ((Z)-N-(3-isopropyl-5-phenyl-1,3-selenazolidin-2-ylidene)-2-methoxybenzenamine (**3b**). Thermal ellipsoids are drawn at a 40% probability level. Hydrogen atoms have been omitted for clarity.^[15]

unsubstituted, benzyl, *n*-butyl, cyclohexyl, and phenyl substituents on the nitrogen atom gave the target iminoazosele-nolidines **3m–q** in 61–91% yields. Moreover, both the substrates bearing electron-donating and -withdrawing groups on the phenyl ring of the aziridines were compatible, and the cycloaddition products were obtained in high yields. For example, the substrates having 2-chloro, 3-nitro, 4-bromo, 4-chloro, 4-fluoro, 4-methoxy, and 4-methyl substituents on the phenyl ring reacted to the target molecules **3r–x** in 66–88% yields. Aryl aziridine **2n** having 3,4-dimethyl substituents on the phenyl ring underwent reaction with 87% yield. A similar result was observed with aziridine **2o** giving the target molecule **3z** in 71% yield. Under these conditions, *N*-benzoyl-2-phenyl aziridine (**2p**) proceeded in an intramolecular cyclization to afford 4,5-dihydro-2,5-diphenyloxazole (**10**) in 78% yield as sole product (see the Supporting Information), whereas the aziridine **2q** underwent decomposition and no cycloaddition product was obtained.

Finally, to reveal the generality of the protocol, the reactions of aziridines **2** with carbodiimides **4**, isocyanates **5**, and isothiocyanates **6** were studied as representative examples (Table 4). The reactions occurred efficiently at 80 °C to

Table 3: Reaction of substituted aziridines with isoselenocyanate.^[a]



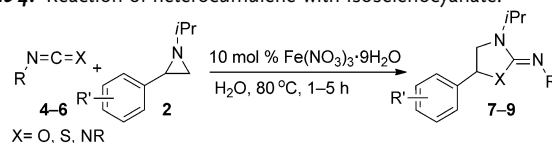
Entry	Aziridine	R	R'	Product (Yield [%]) ^[b]
1	2b	H	Ph	3m (81)
2	2c	Bn	Ph	3n (75)
3	2d	<i>n</i> Bu	Ph	3o (91)
4	2e	cyclohexyl	Ph	3p (79)
5	2f	Ph	Ph	3q (61)
6 ^[c]	2g	<i>i</i> Pr	2-ClC ₆ H ₄	3r (78)
7	2h	<i>i</i> Pr	3-NO ₂ C ₆ H ₄	3s (66)
8	2i	<i>i</i> Pr	4-BrC ₆ H ₄	3t (74)
9	2j	<i>i</i> Pr	4-ClC ₆ H ₄	3u (86)
10	2k	<i>i</i> Pr	4-FC ₆ H ₄	3v (71)
11	2l	<i>i</i> Pr	4-MeOC ₆ H ₄	3w (88)
12	2m	<i>i</i> Pr	4-MeC ₆ H ₄	3x (82)
13	2n	<i>i</i> Pr	3,4-Me ₂ C ₆ H ₃	3y (87)
14	2o	<i>i</i> Pr	(-C ₆ H ₄ -4-CH ₂) ₂ N(<i>i</i> Pr)	3z (71)
15	2p	Bz	Ph	3aa n.d.
16	2q	Boc	Ph	3ab n.d.

[a] Reaction conditions: Aziridine **2b–q**, isoselenocyanate **1a** (0.5 mmol), Fe(NO₃)₃·9H₂O (10 mol %), and water (1 mL) were stirred at 60 °C for one hour in air. [b] Yield of isolated product. [c] Reaction time: 2.5 h. n.d. = not detected.

provide the target molecules **7–9** in 65–79% yields. Isothiocyanates **6** exhibited greater reactivity compared to carbodiimides **4** and isocyanates **5**. These observed results suggest that the procedure affords a general method for the cycloaddition of aziridines with heterocumulenes to give the target heterocycles in good to high yield.

To investigate if the protocol can be applied to a larger scale, the reaction of **1b** with **2a** was examined on gram scale (Scheme 1). As above, the reaction readily proceeded to afford **3b** in 91% yield. This result clearly suggests that the

Table 4: Reaction of heterocumulene with isoselenocyanate.^[a]



Entry	Heterocumulene	X	R	R'	t [h]	Product (Yield [%]) ^[b]
1	4a	N	Ph	H	2	7a (79)
2	4b	N	4-ClC ₆ H ₄	H	3	7b (75)
3	4a	N	Ph	4-Me	1.5	7c (68)
4	5a	O	Ph	H	3.5	8a (65)
5	5b	O	Ph	4-MeO	3	8b (71)
6	5c	O	Ph	4-Me	5	8c (67)
7	6a	S	Ph	4-Cl	1	9a (76)
8	6b	S	Ph	4-MeO	1	9b (78)
9	6c	S	Ph	4-Me	1	9c (71)
10	6d	S	Ph	3,5-Me ₂	1	9d (74)

[a] Reaction condition: Heterocumulene **4–6** (0.5 mmol), aziridine **2** (0.6 mmol), Fe(NO₃)₃·9H₂O (10 mol %) and water (1 mL) were stirred at 80 °C. [b] Yield of isolated product.

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- [15] CCDC-899302 (**3b**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.