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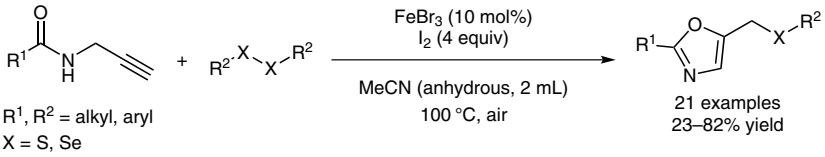
$FeBr_3$-Catalyzed Tandem Reaction of *N*-Propargylamides with Disulfides or Diselenides for the Synthesis of Oxazole Derivatives

Xu-Hong Gao
Peng-Cheng Qian
Xing-Guo Zhang
Chen-Liang Deng*

College of Chemistry and Materials Engineering,
Wenzhou University, Wenzhou 325035,
P. R. of China
dcl78@wzu.edu.cn



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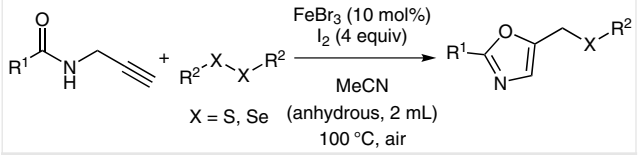
Abstract A methodology of $FeBr_3$-catalyzed tandem reaction of *N*-propargylamides with disulfides or diselenides for the formation of oxazole derivatives has been developed. The strategy includes several steps in one pot. Series of *N*-propargylamides and disulfides were suitable as substrates in this transformation for synthesizing the corresponding oxazole derivatives in moderate to good yields.

Key words $FeBr_3$, tandem, *N*-propargylamides, disulfides, oxazole

Oxazole are widely used N,O-containing heterocyclic compounds,[1] which represent an important structural skeleton found in numerous natural products with biological and pharmaceutical activities such as antitumor, antibacterial, antiviral, and antifungal agents.[2] Methods for the direct synthesis of oxazole rings with different starting materials have been fully developed because of this widespread presence.[3] Among these, transition-metal-catalyzed tandem reaction of *N*-(propargyl)benzamide to oxazoles emerged as an alternative strategy and has attracted much attention. For example, gold-,[4] palladium-,[5] tin-,[6] zinc-,[7] tungsten-,[8] and ruthenium[9]-catalyzed cyclization of propargylamides for the formation of oxazoles has been reported. However, some of the above-mentioned protocols suffer from one or more limitations such as expensive catalysts, hazardous reagents, prolonged reaction time, or harsh reaction conditions. The development of a mild, environmentally benign, and cheaper method is still an immense work. Over the past decades, the use of iron-based catalysts to promote a range of organic reactions have widely been described for their abundance, cheaper costs, and environmentally benign characteristics.[7a,10] However, iron-catalyzed transformation for the synthesis of oxazoles is rarely explored.[7a] Herein, we report our research regarding the iron-catalyzed reaction of *N*-(propargyl)benzamide with disulfides to produce oxazoles. It is worth noting that the protocol is suitable for the construction of selenium-containing oxazoles (Scheme 1).

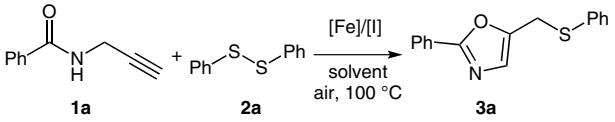


Scheme 1 $FeBr_3$-Catalyzed tandem reaction for the synthesis of oxazole derivatives

The reaction of *N*-(prop-2-yn-1-yl)benzamide (**1a**) with 1,2-diphenyldisulfane (**2a**) was selected as a model reaction to optimize reaction conditions, and the results are summarized in Table 1. We initiated our studies of the treatment of **1a** with **2a** in the presence of $FeCl_3$ (10 mol%) and I_2 (2 equiv) in MeCN (2 mL) at 80 °C for 12 hours under an N_2 atmosphere. A 24% yield of 2-phenyl-5-[(phenylthio)methyl]oxazole (**3a**) was isolated (Table 1, entry 1). In the absence of I_2, only a trace amount of **3a** was detected by GC–MS analysis evidencing that I_2 played a critical role in the transformation (Table 1, entry 2). Consequently, several iodine sources such as NIS, Bu_4NI, and IPy_2BF_4 were tested; however, they were inferior to I_2 in terms of yield (Table 1, entries 3–5). Subsequently, a series of iron salts, including FeF_3, $FeBr_3$, $Fe(acac)_3$, and $Fe(OTf)_3$, were examined. Screening revealed that all of the iron salts had reactivity for the tandem reaction, and $FeBr_3$ was more efficient than the others (Table 1, entries 1 vs. 6–9). For example, the reaction was carried out successfully when FeF_3, $FeBr_3$, $Fe(acac)_3$, and $Fe(OTf)_3$ were used as catalysts, furnishing the target product **3a** in 39%, 50%, 49%, and 26% yield, respectively. Various reaction solvents were also investigated (dioxane, DMSO, toluene, EtOAc, and THF), with MeCN to determine

which provided the best result (Table 1, entries 10–14). Interestingly, increasing the temperature and loading of I_2 enhanced the yield of **3a**. The reaction performed under three equivalents of I_2 increased the yield of **3a** to 60% yield (Table 1, entry 15). The optimum conditions were determined to be four equivalents of I_2 at 100 °C (Table 1, entries 16–18).

Table 1 Optimization of Reaction Conditions[a]



1a **2a** **3a**

Entry	[Fe] (10 mol%)	[I] (2 equiv)	Solvent (2 mL)	Temp (°C)	Yield (%)[b]
1	$FeCl_3$	I_2	MeCN	80	24
2	$FeCl_3$	–	MeCN	80	trace
3	$FeCl_3$	NIS	MeCN	80	20
4	$FeCl_3$	Bu_4NI	MeCN	80	nr
5	$FeCl_3$	IPy_2BF_4	MeCN	80	trace
6	FeF_3	I_2	MeCN	80	39
7	$FeBr_3$	I_2	MeCN	80	50
8	$Fe(acac)_3$	I_2	MeCN	80	49
9	$Fe(OTf)_3$	I_2	MeCN	80	26
10	$FeBr_3$	I_2	dioxane	80	nr
11	$FeBr_3$	I_2	DMSO	80	nr
12	$FeBr_3$	I_2	toluene	80	9
13	$FeBr_3$	I_2	EtOAc	80	29
14	$FeBr_3$	I_2	THF	80	41
15[c]	$FeBr_3$	I_2	MeCN	80	60
16[d]	$FeBr_3$	I_2	MeCN	80	68
17[d]	$FeBr_3$	I_2	MeCN	100	75
18[d]	$FeBr_3$	I_2	MeCN	120	57

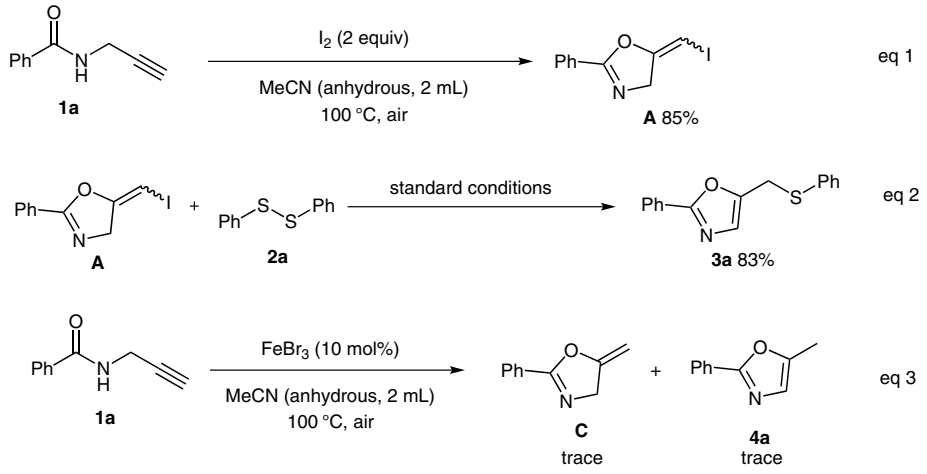
[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), [Fe] (10 mol%), [I] (2 equiv), solvent (anhydrous, 2 mL), stirring at 100 °C for 12 h.
[b] Isolated yield.
[c] I_2 (3 equiv) was added.
[d] I_2 (4 equiv) was added.

With the optimized reaction conditions in hand, the scope of substrates **1** and **2** was explored, and the results are illustrated in Table 2. Generally, propargylamides **1a**–**k**, which contain electron-donating groups or electron-withdrawing groups, proceeded quickly in this cyclization to give moderate to good yields of products. For example, treatment of **1b** with **2a** under standard conditions led to a 78% yield of **3b** (Table 2, entry 1). Substrates **1c**–**e**, with electron-withdrawing groups 4-F, 4-Br, and 4-CN on their aromatic rings, performed well in the reaction to furnish corresponding products in 78%, 71%, and 72% yield, respectively (Table 2, entries 2–4). The bulky substrates **1f** and **1g** reacted well with **2a** to form target products in good yield (Table 2, entries 5 and 6). The heterocyclic substrate **1h** was also suitable for the transformation, achieving the cyclization product **3h** in 61% yield (Table 2, entry 7). It is noteworthy that alkyl-substituted substrates **1i**–**k** could also be employed to produce the corresponding products in moderate yields (Table 2, entries 8–10). The effects of disulfides **2b**–**h** were also evaluated under standard conditions, and they were all suitable substrates for the transformation. For example, disulfide **2b**, with the 2-chlorophenyl group providing steric hindrance, performed successfully to afford product **3l** in 75% yield (Table 2, entry 11). In addition to **2b**, disulfides **2c**–**e**, which bearing electron-withdrawing groups (Cl and F) on their phenyl rings, successfully reacted with **1a** to provide the desired product in 77%, 68%, and 62% yield, respectively (Table 2, entries 12–14). In the case of disulfide **2f**, cyclization product **3p** was separated in 68% yield (Table 2, entry 15). Aliphatic disulfides **2g** and **2h** were also good substrates for the reaction, leading to target products in moderate yield (Table 2, entries 16 and 17). Interestingly, 1,2-diphenyldiselane **2i** was also compatible with the optimized conditions and reacted with **1a** to yield product **3s** in 40% yield (Table 2, entry 18). Another two diselenides **2j**,**k** reacted with **1a** also successfully, albeit in lower yield (Table 2, entries 19 and 20).

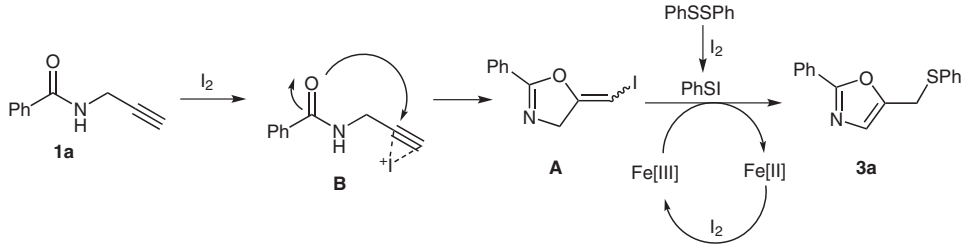
To probe the mechanism of this transformation, a series of control experiments was performed. First, the treatment of **1a** in the presence of I_2 (2 equiv) in MeCN for two hours was executed. An 85% yield of intermediate **A** was isolated (Scheme 2, eq. 1), followed by a reaction with disulfide **2a** under standard reaction conditions to furnish the desired product **3a** in 83% yield (Scheme 2, eq. 2). Subsequently, we conducted the reaction without the assistance of I_2, but only a trace amount of **B** was separated (Scheme 2, eq. 3).

Based on the above results and aforementioned literature,[10,11] we proposed a mechanism for the reaction, as outlined in Scheme 3. First, iodine combined with the terminal alkyne of substrate **1a** to form complex **B**, followed by intramolecular keto–enol tautomerism. The hydroxyl group attacked the iodinium ion to furnish intermediate **A**, which reacted with PhSSPh to produce the target product **3a**.

In summary, we have developed a $FeBr_3$-catalyzed tandem reaction of propargylamides with disulfides for the synthesis of oxazoles.[12] Various substrates proceeded well under optimal reaction conditions to afford the desired products in moderate to good yields. It is noteworthy that the protocol successfully converted diselenides into the corresponding cyclization product, albeit in lower yield. Further studies aimed at expanding the scope of this reaction are currently under way in our lab.

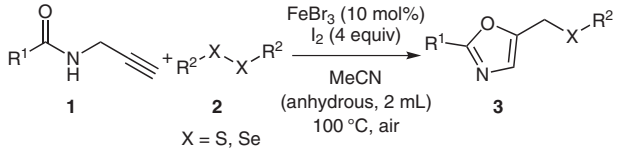


Scheme 2 Control experiments



Scheme 3 Proposed mechanism

Table 2 $FeBr_3$-Catalyzed Tandem Reaction of **1** with **2**[a]



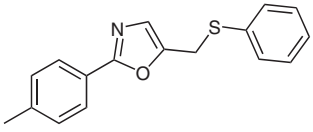
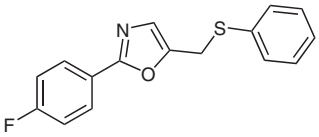
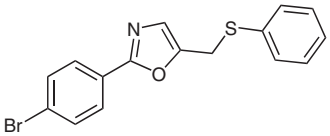
Entry	R^1	R^2	X	Product	Yield (%)[b]
1	**1b** 4-MeC_6H_4	**2a** Ph	S		**3b** 78
2	**1c** 4-FC_6H_4	**2a** Ph	S		**3c** 78
3	**1d** 4-BrC_6H_4	**2a** Ph	S		**3d** 71

Table 2 (continued)

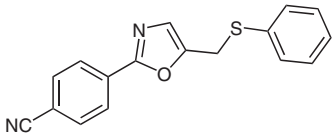
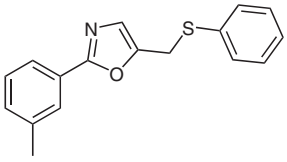
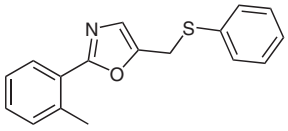
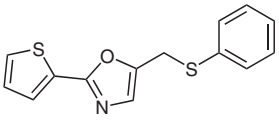
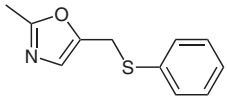
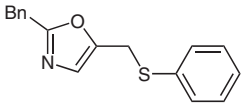
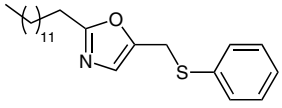
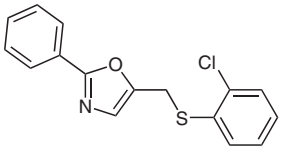
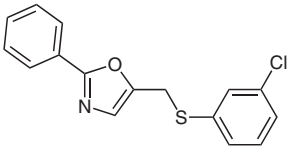
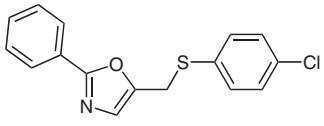
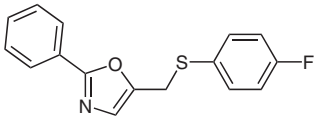
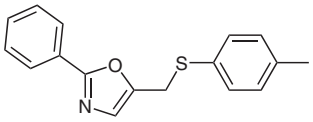
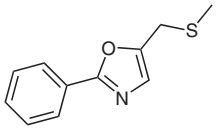
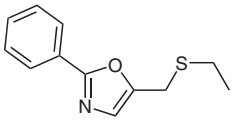
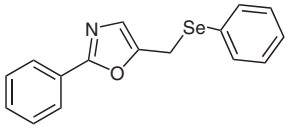
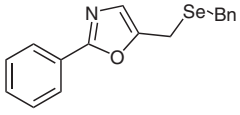
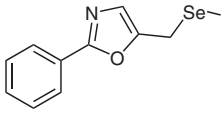
Entry	R^1	R^2	X	Product	Yield (%)[b]
4	**1e** 4-NCC_6H_4	**2a** Ph	S		**3e** 72
5	**1f** 3-MeC_6H_4	**2a** Ph	S		**3f** 82
6	**1g** 2-MeC_6H_4	**2a** Ph	S		**3g** 81
7	**1h** 2-thiophene	**2a** Ph	S		**3h** 61
8	**1i** Me	**2a** Ph	S		**3i** 36
9	**1j** Bn	**2a** Ph	S		**3j** 43
10	**1k** $Me(CH_2)_{12}$	**2a** Ph	S		**3k** 48
11	**1a** Ph	**2b** 2-ClC_6H_4	S		**3l** 75
12	**1a** Ph	**2c** 3-ClC_6H_4	S		**3m** 77
13	**1a** Ph	**2d** 4-ClC_6H_4	S		**3n** 68

Table 2 (continued)

Entry	R^1	R^2	X	Product	Yield (%)[b]
14	**1a** Ph	**2e** 4-FC_6H_4	S		**3o** 62
15	**1a** Ph	**2f** 4-MeC_6H_4	S		**3p** 68
16	**1a** Ph	**2g** Me	S		**3q** 52
17	**1a** Ph	**2h** Et	S		**3r** 64
18	**1a** Ph	**2i** Ph	Se		**3s** 40
19	**1a** Ph	**2j** Bn	Se		**3t** 23
20	**1a** Ph	**2k** Me	Se		**3u** 29

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), $FeBr_3$ (10 mol%), I_2 (4 equiv), MeCN (anhydrous, 2 mL), stirring at 100 °C for 12 h under air atmosphere.
[b] Isolated yield.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1561202.

References

(1) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079.
(2) (a) Lindquist, N.; Fenical, W. *J. Am. Chem. Soc.* **1991**, *113*, 2303. (b) Garfunkle, J.; Ezzili, C.; Rayl, T. J.; Hochstatter, D. G.; Hwang, I.; Boger, D. L. *J. Med. Chem.* **2008**, *51*, 4392.
(3) (a) Zheng, M.; Huang, L.; Huang, H.; Li, X.; Wu, W.; Jiang, H. *Org. Lett.* **2014**, *16*, 5906. (b) Yu, J.; Yang, H.; Fu, H. *Adv. Synth. Catal.* **2014**, *356*, 3669. (c) Yu, X.; Xin, X.; Wan, B.; Li, X. *J. Org. Chem.* **2013**, *78*, 4895. (d) Hu, Y.; Yi, R.; Wang, C.; Xin, X.; Wu, F.; Wan, B. *J. Org. Chem.* **2014**, *79*, 3052. (e) Bartoli, G.; Cimarelli, C.; Cipolletti, R.; Diomedi, S.; Giovannini, R.; Mari, M.; Marsili, L.; Marcantoni, E. *Eur. J. Org. Chem.* **2012**, 630. (f) Kreisberg, J. D.; Magnus, P.; Shinde, S. *Tetrahedron Lett.* **2002**, *43*, 7393.
(4) (a) Weyrauch, J. P.; Hashmi, A. S. K.; Schuster, A.; Hengst, T.; Schetter, S.; Littmann, A.; Rudolph, M.; Hamzic, M.; Visus, J.; Rominger, F.; Frey, W.; Bats, J. W. *Chem. Eur. J.* **2010**, *16*, 956. (b) Hashmi, A. S. K.; Weyrauch, J. P.; Frey, W.; Bats, J. W. *Org. Lett.* **2004**, *6*, 4391. (c) Egorova, O. A.; Seo, H.; Kim, Y.; Moon, D.; Rhee, Y. M.; Ahn, K. H. *Angew. Chem. Int. Ed.* **2011**, *50*, 11446.

(5) (a) Arcadi, A.; Cacchi, S.; Cascia, L.; Fabrizi, G.; Marinelli, F. *Org. Lett.* **2001**, *3*, 2501. (b) Beccalli, E. M.; Borsini, E.; Broggini, G.; Palmisano, G.; Sottocornola, S. *J. Org. Chem.* **2008**, *73*, 4746. (c) Merkul, E.; Müller, T. J. J. *Chem. Commun.* **2006**, 4817.
(6) Kreisberg, J. D.; Magnus, P.; Shinde, S. *Tetrahedron Lett.* **2002**, *43*, 7393.
(7) (a) Senadi, G. C.; Hu, W.-P.; Hsiao, J. S.; Vandavasi, J. K.; Chen, C.-Y.; Wang, J.-J. *Org. Lett.* **2012**, *14*, 4478. (b) Malosh, C. F.; Ready, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 10240. (c) Patil, N. T.; Singh, V. *Chem. Commun.* **2011**, *47*, 11116.
(8) (a) Meng, X.; Kim, S. *Org. Biomol. Chem.* **2011**, *9*, 4429. (b) Onizawa, Y.; Kusama, H.; Iwasawa, N. *J. Am. Chem. Soc.* **2008**, *130*, 802. (c) Kusama, H.; Yamabe, H.; Onizawa, Y.; Hoshino, T.; Iwasawa, N. *Angew. Chem. Int. Ed.* **2005**, *44*, 468.
(9) Milton, M. D.; Inada, Y.; Nishibayashi, Y.; Uemura, S. *Chem. Commun.* **2004**, 2712.
(10) (a) Bolm, C.; Legros, J.; Le Paih, J.; Zani, L. *Chem. Rev.* **2008**, *37*, 1108. (b) Bolm, C.; Legros, J.; Le Paih, J.; Zani, L. *Chem. Rev.* **2004**, *104*, 2617.
(11) (a) Du, H. A.; Tang, R. Y.; Deng, C. L.; Liu, Y.; Li, J. H.; Zhang, X. G. *Adv. Synth. Catal.* **2011**, *353*, 2739. (b) Correa, A.; Carril, M.; Bolm, C. *Angew. Chem. Int. Ed.* **2008**, *47*, 2880. (c) Correa, A.; Elmore, S.; Bolm, C. *Chem. Eur. J.* **2008**, *14*, 3527.

(12) **Typical Procedure**

Under air atmosphere, a reaction tube was charged with *N*-(prop-2-yn-1-yl)benzamide (**1a**, 0.2 mmol), diphenyldisulfane (**2a**, 0.4 mmol), $FeBr_3$ (10 mol%), I_2 (0.8 mmol), and MeCN (2 mL). The vessel was sealed and heated at 100 °C (oil bath temperature) for 12 h and then cooled to room temperature. The reaction mixture was washed with sat. $Na_2S_2O_3$ (2 × 15 mL) and then brine (1 × 15 mL). After the aqueous layer was extracted with EtOAc, the combined organic layers were dried over anhydrous Na_2SO_4, and evaporated under vacuum. The residue was purified by flash column chromatography (hexane–EtOAc) to afford the desired product **3a**.

2-Phenyl-5-[(phenylthio)methyl]oxazole (3a)

Yellow solid (40.1 mg, 75% yield); mp 43–44 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.87 (dd, *J* = 5.9, 2.3 Hz, 2 H), 7.33–7.32 (m, 3 H), 7.30–7.28 (m, 2 H), 7.21–7.18 (m, 2 H), 7.16–7.13 (m, 1 H), 6.76 (s, 1 H), 4.03 (s, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.5, 148.4, 134.5, 131.3, 130.2, 129.0, 128.6, 127.3, 127.3, 126.1, 125.9, 29.7. LRMS (EI, 70 eV): *m/z* (%) = 267 (5) [M^+], 158 (100), 130 (15), 104 (14), 77 (8). ESI-HRMS: *m/z* calcd for $C_{16}H_{14}NOS^+$ [M + H]$^+$: 268.0791; found: 286.0794.