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Communication

An unexpected iron(II)-promoted reaction of *N*-arylprop-2-yn-1-imines with water: Facile assembly of multi-substituted pyrroles

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ABSTRACT

Generation of multi-substituted pyrroles is accomplished through an unexpected iron(II)-promoted reaction of *N*-arylprop-2-yn-1-imines with water. This transformation proceeds smoothly with excellent chemoselectivity and regioselectivity. A stoichiometric amount of $Fe(OTf)_2$ is necessary for the successful conversion. A Lewis acid-promoted tandem reaction pathway is proposed.

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Due to the importance of sulfonyl-containing pharmaceuticals and natural products, we have continuously focused on the methodology development for the generation of sulfonyl compounds from sulfur dioxide [1]. Recently, we designed a reaction with the insertion of sulfur dioxide by using *N*-arylprop-2-yn-1-imines as the substrates. The studies were initially performed for the reaction of *N*-arylprop-2-yn-1-imine **1a**, 4-methylphenyldiazonium tetrafluoroborate and DABCO·$(SO_2)_2$ (Scheme 1). We anticipated that a tandem radical reaction would take place, leading to sulfonyl-containing *N*-heterocyclic product. However, no desired product was observed for the substrate of *N*-arylprop-2-yn-1-imine **1a** when the reaction was performed in 1,2-dichloroethane (DCE) at room temperature. We reasoned that the presence of Lewis acid might coordinate the nitrogen atom, thus facilitating the transformation. Therefore, a stoichiometric amount of zinc triflate was added in the reaction system. To our delight, a product was obtained and isolated although the yield was low (15%). However, it was found that after structural illustration, sulfur dioxide was not involved during the reaction process. Instead, an unexpected multi-substituted pyrrole **2a** was afforded, and the structure was clarified by X-ray analysis (Scheme 1) [2]. From this outcome, it seemed that only *N*-arylprop-2-yn-1-imine **1a** and water were participated in the transformation *via* a tandem process. Additionally, this transformation showed excellent chemoselectivity and regioselectivity, since two molecules of *N*-arylprop-2-yn-1-imine **1a** were involved.

Tandem reaction is well-recognized as a powerful tool towards "molecular skeleton-privileged" architectures [3]. Among these established achievements, alkyne-based regioselective addition combined with various annulation has attracted ever-growing interest of chemist due to its high reaction efficiency and transformation versatility [4]. For example, radical *ipso*-cyclization already represented an elegant alternative for the synthesis of heterocyclic compounds [5]. On the other hand, it is known that pyrrole is the core structure in numerous bioactive natural products [6]. Additionally, there are many pyrrole derivatives showing assorted pharmacological activities such as FPR1 antagonists [7a], antivirals HIV-1 [7b], antitumorals [77c], or anticancer VEGF-R enzyme inhibitors [77d]. Thus, continuous efforts have been given to the preparation of pyrrole derivatives [8]. As part of our program for the generation natural product-like compounds for diverse biological evaluations [9], we are interested in the method development and library construction of pyrrole derivatives. Thus, we started to explored the feasibility for the generation of multi-substituted pyrroles from the above unexpected reaction of *N*-arylprop-2-yn-1-imines.

From the structure of compound **2a**, it seemed that the reaction was initiated by the addition of water to *N*-arylprop-2-yn-1-imine **1a**. Thus, to verify the practicality of the above transformation, we

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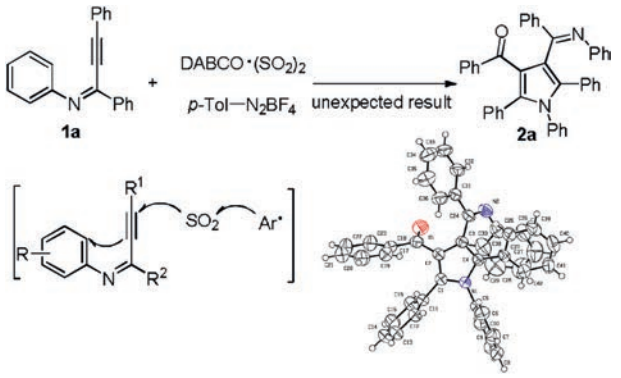
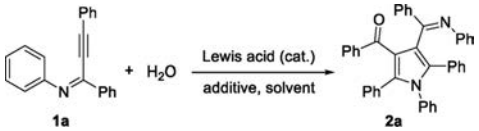


Scheme 1. An unexpected reaction of *N*-arylprop-2-yn-1-imine **1a**.

started to optimize the reaction of *N*-arylprop-2-yn-1-imine **1a** and water. The results are illustrated in Table 1. At the outset, a blank experiment without any additive was carried out. As a result, no formation of desired product **2a** was observed (Table 1, entry 1). In order to facilitate the nucleophilic addition of water to *N*-arylprop-2-yn-1-imine **1a**, several Lewis acids were examined in the reaction. As a consequence, the addition of $Zn(OTf)_2$, $Bi(OTf)_3$, $Dy(OTf)_3$ and $Fe(OTf)_2$ all provided the desired product **2a** (Table 1, entries 2–5). Treated with $Fe(OTf)_2$, the reaction efficiency was improved, leading to the desired product **2a** in 41% yield (Table 1, entry 5). Only a trace amount of product could be obtained when $Fe(OTf)_3$ or HOTf was used (data not shown in Table 1). The solvent effect indicated that 1,2-dichloroethane (DCE) was the best choice. Other solvents such as MeCN, 1,4-dioxane, DCM, and THF provided inferior results (Table 1, entries 6–9). To further increase the reaction efficiency, other additives such as DDQ and TBHP were also screened. The reaction yield was increased to 49% when DDQ was used as an oxidant (Table 1, entry 10). From the results on temperature evaluation, it seemed that the reaction was sensitive for the reaction temperature. The reaction worked better with the formation of desired product **2a** in 56% (Table 1, entry 12) when the reaction was carried out at 50 °C.

Table 1
Initial studies for the reaction of *N*-arylprop-2-yn-1-imine **1a** and water.[a]



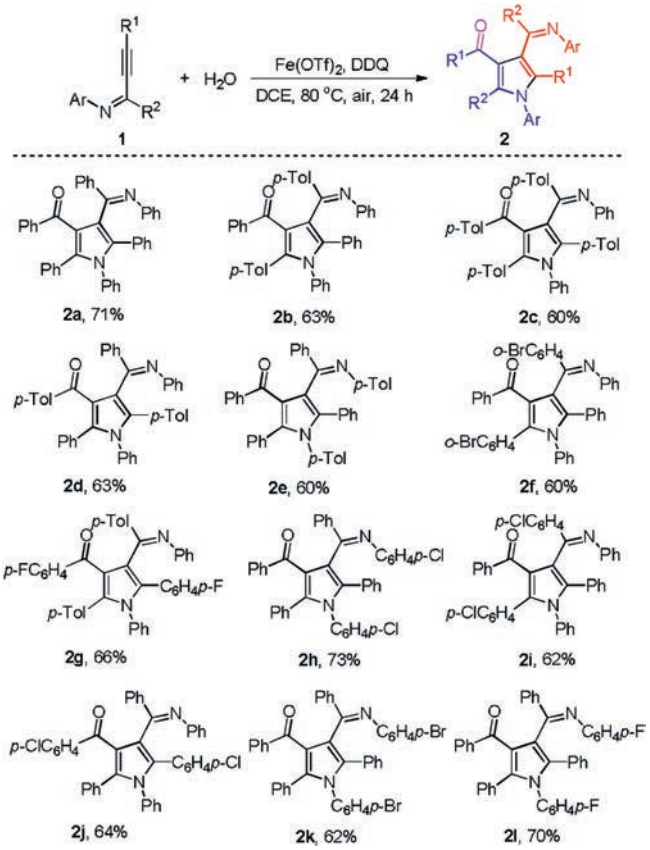
Entry	[M]	Solvent	Additive	T (°C)	Yield (%)[b]
1	–	DCE	–	25	nd
2	$Zn(OTf)_2$	DCE	–	25	15
3	$Bi(OTf)_3$	DCE	–	25	30
4	$Dy(OTf)_3$	DCE	–	25	34
5	$Fe(OTf)_2$	DCE	–	25	41
6	$Fe(OTf)_2$	MeCN	–	25	37
7	$Fe(OTf)_2$	dioxane	–	25	trace
8	$Fe(OTf)_2$	DCM	–	25	37
9	$Fe(OTf)_2$	THF	–	25	trace
10	$Fe(OTf)_2$	DCE	DDQ	25	49
11	$Fe(OTf)_2$	DCE	TBHP	25	nd
12	$Fe(OTf)_2$	DCE	DDQ	50	56
13	$Fe(OTf)_2$	DCE	DDQ	80	71
14[c]	$Fe(OTf)_2$	DCE	DDQ	80	24

[a] Reaction conditions: *N*-arylprop-2-yn-1-imine **1a** (0.4 mmol), water (0.2 mmol), additive (0.3 mmol), Lewis acid (0.3 mmol), solvent (4.0 mL), 24 h.
[b] Isolated yield based on *N*-arylprop-2-yn-1-imine **1a**.
[c] $Fe(OTf)_2$ (30 mol%) was used.

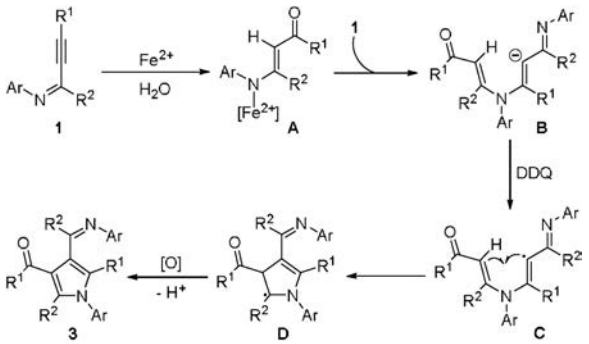
Further examination showed that the desired product **2a** could be produced in 71% yield when the reaction was performed at 80 °C (Table 1, entry 13). Additionally, the loading amount of Lewis acid was evaluated. It was surprised to find that stoichiometric amount of $Fe(OTf)_2$ was requisite. The yield was dramatically reduced when 30 mol% of $Fe(OTf)_2$ was employed (Table 1, entry 14).

With the optimized conditions in hand, we then explored the generality and scope of this iron(II)-promoted reaction of *N*-arylprop-2-yn-1-imines **1** with water. The results are presented in Scheme 2. A range of multi-substituted pyrrole derivatives were generated accordingly in good yields. From the results, it seemed that electronic effect of the substituents R^1 made slight impact on the outcome. Screening on the substituent effect of R^1 and R^2 indicated that the reactions uniquely worked well when both R^1 and R^2 were equal to aryl groups. The reactions of substrates attached with alkyl groups on R^1 or R^2 did not offer the corresponding products (data not shown). Moreover, electronic effect of R^2 did not make significant impact on the reaction yields. For instance, similar yields were observed when 4-methylphenyl-substituted and 4-chlorophenyl-connected substrates were used as the starting materials, leading to the corresponding products **2d** and **2j** in 63% and 64% yields, respectively. Finally, steric effect of the substituent R^2 was explored. It was found that the substrate with steric group was also compatible in this transformation. For example, reaction of the substrate attached with 2-bromophenyl on R^2 position worked well to afford the corresponding product **2f** in 60% yield.

To explore the mechanism of the reaction, we investigated the reaction of *N*-arylprop-2-yn-1-imine **1a** and water in the presence of 2.0 equiv. of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) under the optimized conditions. As expected, the reaction



Scheme 2. Scope exploration for the iron(II)-promoted reaction of *N*-arylprop-2-yn-1-imines **1** with water. Isolated yields based on *N*-arylprop-2-yn-1-imine **1**.



Scheme 3. Plausible mechanism.

was hampered. On the basis of the above results, a plausible mechanism is proposed, which is shown in Scheme 3. We reasoned that assisted with stoichiometric amount of $Fe(OTf)_2$, nucleophilic addition of water to *N*-arylprop-2-yn-1-imine **1** would provide enamine intermediate **A** quickly and efficiently. Sequential aza-Michael-type addition of intermediate **A** to *N*-arylprop-2-yn-1-imine **1** would afford an anion intermediate **B**. In the presence of an oxidant (DDQ), the intermediate **B** would be oxidized into a radical intermediate **C** *via* a single electron transfer (SET). Subsequently, intramolecular radical *ortho*-cyclization would occur giving rise to intermediate **D**, which would undergo deprotonation leading to the desired product pyrrole **2**.

In conclusion, we have described an unexpected iron(II)-promoted reaction of *N*-arylprop-2-yn-1-imines with water, leading to multi-substituted pyrroles in good yields. This transformation proceeds smoothly with excellent chemoselectivity and regioselectivity. A stoichiometric amount of $Fe(OTf)_2$ is necessary for the successful conversion. A Lewis acid-promoted tandem reaction pathway is proposed.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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