Rhenium-catalyzed Amidation of Heteroaromatic Compounds via C–H Bond Activation

Yoichiro Kuninobu,* Yukimi Tokunaga, and Kazuhiko Takai*
Division of Chemistry and Biochemistry, Okayama University, Tsushima, Okayama 700-8530

(Received May 2, 2007; CL-070482; E-mail: kuninobu@cc.okayama-u.ac.jp, ktakai@cc.okayama-u.ac.jp)

Regioselective insertion of isocyanates into a C–H bond of heteroaromatic compounds took place using a rhenium catalyst, $[ReBr(CO)_3(thf)]_2$.

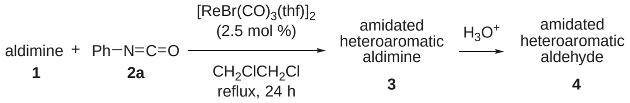
Five-membered heteroaromatics are an important category of compounds because many bioactive molecules and functional materials have them as core structures.[1] Thus, development of the efficient chemical functionalization of heteroaromatic compounds has been desired. There have been many reports on the synthetic methods of heteroaromatic compounds.[2] Recently, chemical transformations via C–H bond activation have received much attention because they are highly efficient and environmentally friendly.[3] Although some functionalizations of heteroaromatic compounds via C–H bond activation have been known, the molecules that insert into a C–H bond have been mostly limited to non-polar unsaturated molecules.[4–6] Only a few reports on the insertion of polar unsaturated molecules have been reported.[7] We have recently succeeded in the insertion of polar unsaturated molecules using a rhenium catalyst.[8] We report herein the rhenium-catalyzed functionalization[9] of heteroaromatic compounds via C–H bond activation followed by the insertion of unsaturated polar molecules, isocyanates, without any additives.

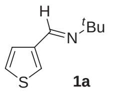
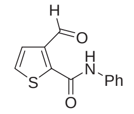
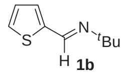
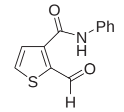
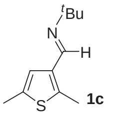
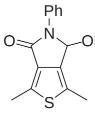
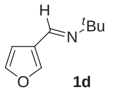
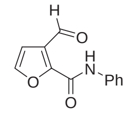
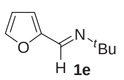
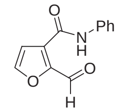
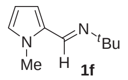
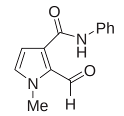
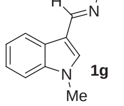
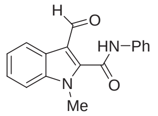
By the treatment of a thiophene bearing an aldimine moiety, **1a**, with phenyl isocyanate **2a** in the presence of a rhenium complex, $[ReBr(CO)_3(thf)]_2$, as a catalyst in 1,2-dichloroethane at 90 °C for 24 h, the insertion of **2a** occurred selectively at only the 2-position of the thiophene ring. This result reflects on the fact that the electron density of a carbon atom at the 2-position is higher than that of a carbon atom at the 4-position. After hydrolysis, thiophene-2-carboxamide **4a** was obtained in 92% yield (Table 1, Entry 1).[10,11] This reaction did not proceed in the absence of the rhenium catalyst or in the presence of transition-metal complexes, which are usually employed as catalysts for C–H bond activation: $Ru_3(CO)_{12}$, $RuH_2(CO)(PPh_3)_3$, $RhCl(PPh_3)_3$, and $Ir_4(CO)_{12}$. The corresponding carboxamide **4a** was not produced with such mild Lewis acids as $SnCl_4$ and $ZnCl_2$, either. The 3-position of thiophene could also be functionalized by using aldimine **1b**, and the corresponding amidated derivative **4b** was formed in 77% yield (Table 1, Entry 2). When a thiophenyl aldimine bearing substituents at the 2- and 5-positions, **1c**, was employed, phenyl isocyanate (**2a**) inserted into a C–H bond at the 4-position of the thiophene ring, and the corresponding thiophenyl amide **3c** was formed in 71% yield (Table 1, Entry 3).[12,13] Cyclic product **5c** was obtained in 57% yield after acidic treatment (Table 1, Entry 3). The reactions between furyl aldimines **1d** and **1e**, and isocyanate **2a**, gave furan-2-carboxamide **4d** and **4e** in 63 and 36% yields, respectively (Table 1, Entries 4 and 5). Heteroaromatic compounds bearing a nitrogen atom on the ring skeleton afforded the corresponding carboxamides **4f** and **4g** in 80 and 92% yields, respectively (Table 1, Entries 6 and 7).

Isocyanates having an electron-withdrawing or electron-donating group, **2b** and **2c**, provided thiophene-2-carboxamide **4h** and **4i** in 72 and 81% yields, respectively (Table 2, Entries 1 and 2). By using an isocyanate bearing a substituent at the ortho-position, amide **4j** was formed in 61% yield (Table 2, Entry 3). Alkyl isocyanates **2e** and **2f** produced the corresponding thiophene-2-carboxamide **4k** and **4l** in 64 and 70% yields, respectively (Table 2, Entries 4 and 5). In Entry 4, cyclic compound **5k** was also formed in 19% yield. Although the insertion of alkyl isocyanates into a C–H bond of aromatic imines did not proceed,[8a] alkyl isocyanates inserted into a C–H bond of heteroaromatic compounds in this reaction.

The proposed mechanism is described as follows (Scheme 1):[14] (1) oxidative addition of a C–H bond of an

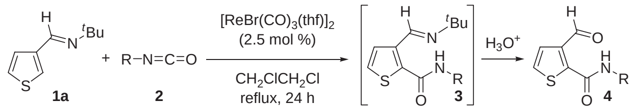
Table 1. Reactions between heteroaromatic aldimines **1** and phenyl isocyanate **2a**[a]

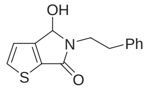
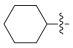


Entry	Aldimine	Yield/%[b]	Product	Yield/%[c]
1	 **1a**	**3a** 94		**4a** 92
2	 **1b**	**3b** 80		**4b** 77
3	 **1c**	**3c** 71		**5c** 57
4	 **1d**	**3d** 72		**4d** 63
5[d]	 **1e**	**3e** 53		**4e** 36
6	 **1f**	**3f** 87		**4f** 80
7[c]	 **1g**	**3g** >99		**4g** 92

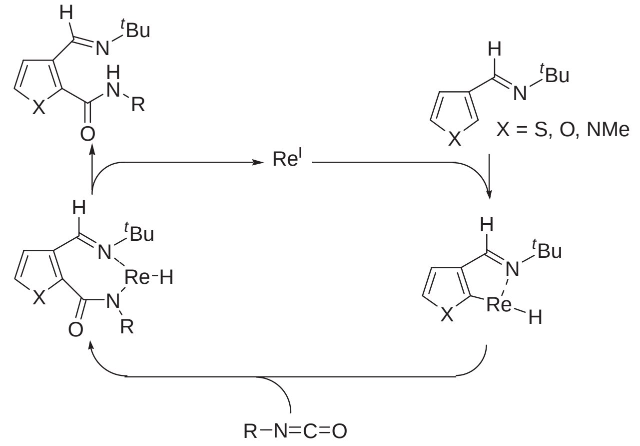
[a] **1** (1.0 equiv); **2a** (1.0 equiv). [b] ^1H NMR yield. [c] Isolated yield. [d] 135 °C.

Table 2. Reactions of thiophenyl aldimine **1a** with several isocyanates **2**[a]



Entry	R	Yield/%[b]	Yield/%[c]	
1	(p-CF$_3$)C$_6$H$_4$ (**2b**)	**3h** 94	**4h** 72	
2	(p-MeO)C$_6$H$_4$ (**2c**)	**3i** 94	**4i** 81	
3	(o-MeO)C$_6$H$_4$ (**2d**)	**3j** 76	**4j** 61	
4	PhCH$_2$CH$_2$ (**2e**)	**3k** 95	**4k** 64	 **5k** 19
5[d]	 (**2f**)	**3l** 80	**4l** 70	

[a]**1a** (1.0 equiv); **2** (1.0 equiv). [b]^{1}H NMR yield. [c]Isolated yield. [d]135 °C.



Scheme 1. Proposed mechanism of the formation of heteroaromatic carboxamides.

aldimine to a rhenium center (C–H bond activation); (2) insertion of an isocyanate into a rhenium–carbon bond; (3) reductive elimination. As a result, an amide derivative is formed and the rhenium catalyst is regenerated.

In summary, we have succeeded in the rhenium-catalyzed insertion of polar unsaturated molecules, isocyanates, into a C–H bond of heteroaromatic compounds. This reaction is the first example of rhenium-catalyzed amidation of heteroaromatic compounds via C–H bond activation. In these reactions, both the 2- and 3-position of heteroaromatic compounds could be functionalized, selectively. In addition, amidation proceeded even at the 4-position where it is usually difficult to be functionalized. The chemical transformations of heteroaromatic compounds via C–H bond activation are now under investigation.

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10 Results for other solvents are as follows: hexane, 85% (80 °C); toluene, 59% (115 °C); THF, 89% (80 °C).
11 The reaction did not proceed using thiophene or thiophene-2-carbaldehyde instead of the aldimine **1a**.
12 There has been a report on whether an olefin inserts into a C–H bond at the 4-position of heteroaromatic compounds; however, the insertion reaction did not proceed. See: F. Kakiuchi, S. Sekine, Y. Tanaka, A. Kamatani, M. Sonoda, N. Chatani, S. Murai, *Bull. Chem. Soc. Jpn.* **1995**, *68*, 62.
13 There has been a report on the insertion of an alkynoate into a C–H bond at the 4-position of pyrroles. See: J. Oyamada, W. Lu, C. Jia, T. Kitamura, Y. Fujiwara, *Chem. Lett.* **2002**, 20.
14 Another possible mechanism is an electrophilic pathway (the Friedel–Crafts type mechanism). In this pathway, a heteroaryl–rhenium complex and H$^+$ are formed as intermediates. We examined the rhenium-catalyzed reaction by adding of a base (tributylamine) and noticed that the reaction with the base proceeded without decreasing the yield. Thus, we are tempted to assume that this reaction proceeds via C–H bond activation.
15 Supporting Information is also available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.