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Preparation of imidazolinium salts by the Pd-catalyzed reduction of thioureas with triethylsilane and trialkylsilyl triflate

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ABSTRACT

A Pd-catalyzed method for the preparation of imidazolinium salts from the corresponding thioureas that could then be used for the synthesis of imidazolium and amidinium salts is described. This method has great potential because all the required reagents are readily available and thioureas are safely converted to their corresponding precursors of NHCs under mild conditions.

Since the first isolation of a stable *N*-heterocyclic carbene (NHC) by Arduengo at al. in 1991,[1] the use of NHCs as ligands[2] and catalysts[3] has been increasing steadily. The synthesis of NHCs mainly depends on the conversion of the corresponding imidazolium and imidazolinium salts; therefore, the preparation of imidazolium and imidazolinium salts is important.

Many imidazolium and imidazolinium salts have been reported, and the most widely used methods for their preparation, as summarized in Scheme 1,[2n] are as follows: (i) N-alkylation of an imidazole or imidazoline (method A),[4] (ii) reaction of the corresponding diamine with an orthoformate and a source of HX (method B),[5] and (iii) reaction of a formamidine with an ethyl dication equivalent (method C).[6]

Although several methods are available for the synthesis of imidazolium and imidazolinium salts, including those in Scheme 1, the methods suffer from a limited substrate scope. Therefore, a new preparation method for imidazolium and imidazolinium salts is required to expand the substrate scope.

Recently, we have developed the Pd-catalyzed reductive cleavage of alkyl aryl sulfides using triethylsilane (TESH) that increased both the reaction rate and the functional group selectivity in the presence of trimethylsilyl chloride (TMSCl) (Scheme 2).[7,8] This ligand-free approach has many advantages such as mild conditions, ease of operation, use of readily available reagents, and high functional group selectivity. In this study, we found that thioureas can be converted to the corresponding imidazolium, imidazolinium, and amidinium salts using TESH and trialkylsilyl triflate in the presence of a catalytic amount of Pd catalyst.

NHCs have also been directly generated by the corresponding thioureas with potassium (Scheme 1). This method has advantage in that a variety of thioureas are available but also has drawbacks arising from the nature of potassium. That is, the strong reducing ability of potassium limits the scope of substrates and a risk of accidental fire accompanies during operation owing to the pyrophoric nature of potassium.

Because the reaction of thioureas with electrophiles usually takes place at the S atom owing to the electron-donating nature of the N atoms, the reaction of thioureas with silylation reagents was expected to afford the corresponding imidazolium and imidazolinium salts. The resulting trialkylsilylthio group at the sp^2-hybridized carbon atom of these heterocycles was intended to be removed by the Pd-catalyzed reaction with trialkylsilanes.

Thus, the reaction of thiourea **1a** was attempted using a catalytic amount of $PdCl_2$ (5 mol %), TESH (3.0 equiv), and TMSCl (1.2 equiv) in THF (Scheme 3), which are the optimized conditions for the reductive cleavage of alkyl aryl sulfides developed by us.[7] The reaction did not proceed; however, the same reaction using trimethylsilyl trifluoromethanesulfonate (TMSOTf) in toluene at 80 °C afforded imidazolinium salt **2a** in 35% yield. The reaction in the absence of $PdCl_2$ did not afford any products.

Table 1 (entries 1–12) shows the results of further optimization of reaction conditions using thiourea **1a** as the substrate. The use of $Pd(OAc)_2$ (5 mol %), as the catalyst, improved the yield to 96% (entry 1). When 10 mol % of $Pd(OAc)_2$ was used, the reaction was completed within 2 h to afford **2a** in 99% yield (entry 2) while

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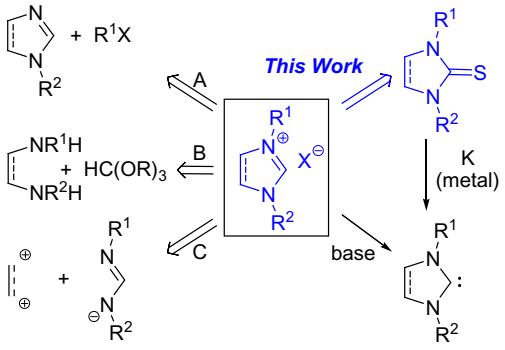
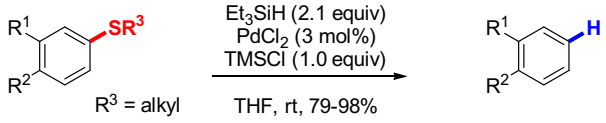
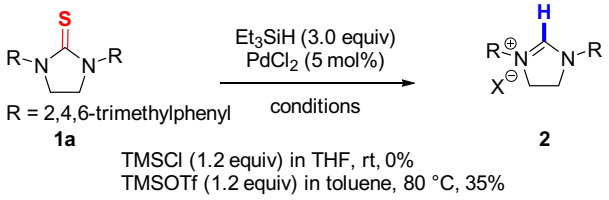


Scheme 1. Preparation methods of imidazolinium salt and imidazolium salt.



Scheme 2. Pd-Catalyzed reductive cleavage of alkyl aryl sulfides with triethylsilane reported by us.[7]



Scheme 3. Preliminary experimental results of Pd-catalyzed transformations of **1a** (R = 2,4,6-trimethylphenyl) to **2**.

the reaction using 3 mol % $Pd(OAc)_2$ did not proceed to completion even after 24 h, and the final yield was 69% (entry 3). The yield of the reaction was improved to 98% when an excess amount (5.0 equiv) of TESH was used (entry 4), too; however, the yield decreased to 80% when a lesser amount (2.2 equiv) of TESH was used (entry 5). When less amount (0.6 equiv) of TMSOTf was used, the yield decreased to 56% and the unreacted starting material remained (entry 6), indicating that TMSOTf can be used to activate thiourea **1a**. Thus, the use of TMSOTf is important in the Pd-catalyzed reaction because the reaction in the presence of TMSCl (enrty 7) or in the absence of TMSOTf (enrty 8) did not afford the desired products.

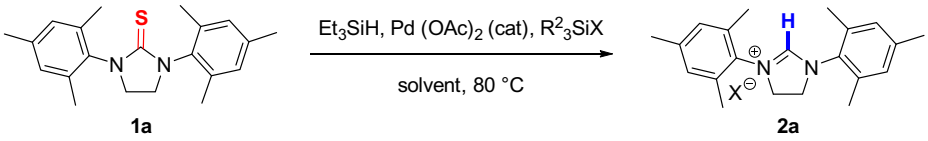
When $(TfOSiMe_2CH_2)_2$[9] (0.6 equiv) was used instead of TMSOTf (1.2 equiv), the reaction also proceeded, though the yield was 79% (entry 9). The reaction with $(TfOSiMe_2CH_2)_2$ (0.6 equiv) and TESH (5.0 equiv) afforded **2a** in 92% yield (entry 10). The use of 10 mol % of $Pd(OAc)_2$ afforded **2a** in 97% yield (entry 11), while the use of 3 mol % of $Pd(OAc)_2$ afforded **2a** in 77% yield (entry 12).

Although the reactions employing Pd/C and $Pd_2(dba)_3$ as the catalyst afforded the product, the starting material remained, resulting in a low yield of the desired product in both the cases. The reactions with triphenylphosphine-ligated Pd catalysts resulted in a complex mixture of products, while the desired product was not formed. Other organosilanes except TESH, for example, Ph_3SiH or $(EtO)_3SiH$ did not improve the yield. The reaction in THF and 1,4-dioxane resulted in S-alkylation of **1a** with the solvents owing to their activation by TMSOTf, and the reaction in 1,2-dichloroethane was slow.

With the optimized reaction conditions in hand, the scope of this reaction was studied using thioureas **1b**–**k** under the optimized reaction conditions A and B (Table 2). The reaction of 1-adamantyl derivative **1b** was completed within 3 h to afford **2b** in 98% (entry 1, reaction conditions A) and 97% yields (reaction conditions B). The reaction of 2-methylphenyl derivative **1c** was fast and afforded **2c** in 92% yield (entry 2, reaction conditions A). The reaction of **1c** under the reaction conditions B resulted in over-reduction to afford the cyclic aminal that was converted to the acyclic formamide after workup. The reactions of 2,6-dimethylphenyl derivative **1d** and 2,6-diethylphenyl derivative **1e** successfully afforded the corresponding products **2d** and **2e** in 99% yield (entry 3, reaction conditions B) and 96% yield (entry 4, reaction conditions A), respectively.

The reaction of 2,6-diisopropylphenyl derivative **1f** was sluggish owing to the steric hindrance and **2f** was obtained in 58% yield (entry 5, reaction conditions B). The reactions of 2,4,6-trimethylphenyl derivative **1g**, a six-membered thiourea, and 4-methoxy-2,6-dimethylphenyl derivative **1h** afforded the corresponding

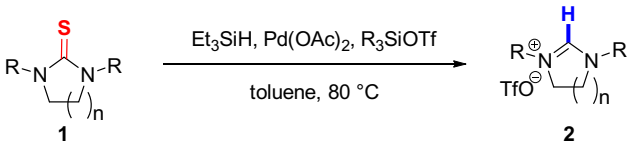
Table 1
Preparation of imidazolinium salt **2a**



Entry	$Pd(OAc)_2$ (mol %)	Et_3SiH (equiv)	R^2_3SiX (equiv)	Time (h)	Yield[a] (%)
1	5	3.0	TMSOTf (1.2)	24	96
2	**10**	**3.0**	**TMSOTf (1.2)**	**2**	**99**
3	3	3.0	TMSOTf (1.2)	24	69[b]
4	**5**	**5.0**	**TMSOTf (1.2)**	**24**	**98**
5	5	2.2	TMSOTf (1.2)	24	80
6	5	5.0	TMSOTf (0.6)	24	56[b]
7	5	3.0	TMSCl (1.2)	24	NR[c]
8	5	3.0	—	24	NR[c]
9	10	3.0	$(TfOSiMe_2CH_2)_2$ (0.6)	3.5	79[b]
10	5	5.0	$(TfOSiMe_2CH_2)_2$ (0.6)	2	92
11	**10**	**5.0**	**$(TfOSiMe_2CH_2)_2$ (0.6)**	**1.5**	**97**
12	3	5.0	$(TfOSiMe_2CH_2)_2$ (0.6)	18	77[b]

[a] Isolated yields.
[b] Starting material remained.
[c] NR: no reaction.

Table 2
Preparation of imidazolinium salts **2b-j** from thiourea **1b-j**

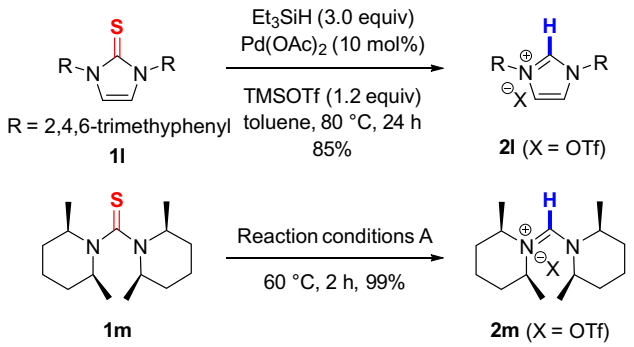


Entry	Thiourea (R)	Reaction conditions A[a]		Reaction conditions B[b]	
		Time (h)	Yield[c] (%)	Time (h)	Yield[c] (%)
1	1-Adamantyl-(n = 1) (**1b**)	3	98	2	97
2	2-Methylphenyl-(n = 1) (**1c**)	1	92	1	0[d]
3	2,6-Dimethylphenyl-(n = 1) (**1d**)	37	85	3	99
4	2,6-Diethylphenyl-(n = 1) (**1e**)	24	96	2	94
5	2,6-Diisopropylphenyl-(n = 1) (**1f**)	35	44	24	58
6	2,4,6-Trimethylphenyl-(n = 2) (**1g**)	24	92	3	94
7	4-Methoxy-2,6-dimethylphenyl-(n = 1) (**1h**)	22	96	3	93
8	4-Methoxycarbonyl-2,6-dimethylphenyl-(n = 1) (**1i**)	24	28	10	32
9	4-Carboxy-2,6-dimethylphenyl-(n = 1) (**1j**)	24	38 (73)[e]	2	19
10	4-Fluoro-2,6-dimethylphenyl-(n = 1) (**1k**)	12	91	1	98

[a] Reaction conditions A: Et_3SiH (3.0 equiv), TMSOTf (1.2 equiv), $Pd(OAc)_2$ (5 mol %).
[b] Reaction conditions B: Et_3SiH (5.0 equiv), $(TfOSiMe_2CH_2)_2$ (0.6 equiv), $Pd(OAc)_2$ (10 mol %).
[c] Isolated yields.
[d] No desired products were obtained owing to overreduction.
[e] Et_3SiH (10.0 equiv), $Pd(OAc)_2$ (10 mol %), and TMSOTf (4.0 equiv) were used.

imidazolinium salts **2g** and **2h** in 94% yield (entry 6, reaction conditions B) and 96% yield (entry 7, reaction conditions A), respectively. However, 4-methoxycarbonyl-2,6-dimethylphenyl derivative **1i** underwent hydrolysis of the methyl ester under all the reaction conditions probably owing to the formation of conjugated system with the formed electron-withdrawing imidazolinium salt, affording **2i** in low yields (entry 8). The reaction of 4-carboxy-2,6-dimethylphenyl derivative **1j** required an excess amount of TESH and TMSOTf because TESH and TMSOTf were consumed in the reaction with the carboxy group of **1j**. Thus, the yield of **2j** was 38% yield (entry 9); however, the yield was improved to 73% when Et_3SiH (10.0 equiv), $Pd(OAc)_2$ (10 mol %), and TMSOTf (4.0 equiv) were used. The reaction of 4-fluoro-2,6-dimethylphenyl derivative **1k** afforded **2k** in 98% yield (entry 10, reaction conditions B). As summarized in Table 2, although TMSOTf has advantage in commercial availability, the reactions using $(TfOSiMe_2CH_2)_2$ are generally faster than those using TMSOTf and the yields are higher in some cases.

Imidazolium salts were successfully prepared by the developed method, too. for example, the imidazolinium salt **2l** was formed from **1l** in 85% yield (Scheme 4). Moreover, amidinium salts were successfully synthesized by the reaction of acyclic thioureas, for example, the amidinium salt **2m** was obtained from **1m** in 99% yield.



Scheme 4. Preparation of **2l** and **2m**.

The ^1H NMR spectrum of a $CDCl_3$ solution of thiourea **1a** and TMSOTf indicated the formation of imidazolinium salt **3a** (Fig. 1), which was confirmed to be converted to **2a** under the reaction conditions A. Therefore, the Pd-catalyzed reaction of **1a** is proposed to proceed via **3a**, that is, the reaction of **3a** with TESH is proposed to afford **2a**. Another possible product of the reaction would be volatile TES-S-TMS. Hence, in this preparation method, imidazolinium, imidazolium, and amidinium salts could be easily obtained by filtration of the Pd catalyst by removal of volatile materials after the completion of the reaction.

Interestingly, the Pd-catalyzed reaction of **4a** (Fig. 1) afforded thiourea **1a**, which was assumed to be formed by the cleavage of the S-Me bond by attack of the iodide on the methyl group during the reaction. The Pd-catalyzed reaction of **5a** (Scheme 5), which was prepared by the corresponding thiourea with methyl triflate in 75% yield, expectedly afforded **2a** in 83% yield; however, the use of TMSOTf is advantageous because the yield is higher and in addition, methyl triflate causes alkylation of heteroatoms in substrates owing to its high reactivity, limiting the substrate scope.

In summary, we have developed a Pd-catalyzed method for the preparation of imidazolinium salts from the corresponding

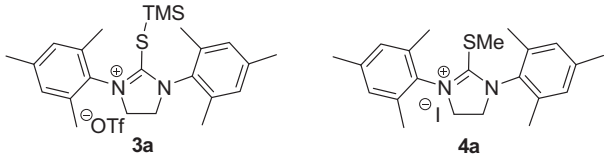
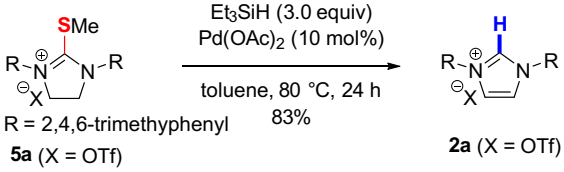


Figure 1. Structures of **3a** and **4a**.



Scheme 5. Preparation of **2a** from **5a**.

thioureas that could then be used for the synthesis of imidazolium and amidinium salts. This method has great potential because all the required reagents are readily available and thioureas are safely converted to their corresponding salts, precursors of NHCs, under mild reaction conditions. Moreover, this method has the merit of applying for the substrate unsuitable for the reaction with potassium which causes reduction. Further studies on the substrate scope are now underway.

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Supplementary data

Supplementary data (full characterization of new compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.01.022.

References and notes

1. Arduengo, A. J., III; Harlow, R. L.; Kline, M. *J. Am. Chem. Soc.* **1991**, *113*, 361–363.
2. (a) Bourissou, D.; Guerret, O.; Gabbaï, F. P.; Bertrand, G. *Chem. Rev.* **2000**, *100*, 39–91; (b) César, V.; Bellemin-Laponnaz, S.; Gade, L. H. *Chem. Soc. Rev.* **2004**, *33*, 619–636; (c) Cavell, K. *Dalton Trans.* **2008**, 6676–6685; (d) Díez-González, S.; Nolan, S. P. *Acc. Chem. Res.* **2008**, *41*, 349–358; (e) Hahn, F. E.; Jahnke, M. C. *Angew. Chem., Int. Ed.* **2008**, *47*, 3122–3172; (f) Jacobsen, H.; Correa, A.; Poater, A.; Costabile, C.; Cavallo, L. *Coord. Chem. Rev.* **2009**, *253*, 687–703; (g) Lin, J. C. Y.; Huang, R. T. W.; Lee, C. S.; Bhattacharyya, A.; Hwang, W. S.; Lin, I. J. B. *Chem. Rev.* **2009**, *109*, 3561–3598; (h) Poyatos, M.; Mata, J. A.; Peris, E. *Chem. Rev.* **2009**, *109*, 3677–3707; (i) Samojłowicz, C.; Bieniek, M.; Grela, K. *Chem. Rev.* **2009**, *109*, 3708–3742; (j) Dıéz-González, S.; Marion, N.; Nolan, S. P. *Chem. Rev.* **2009**, *109*, 3612–3676; (k) Mercs, L.; Albrecht, M. *Chem. Soc. Rev.* **2010**, *39*, 1903–1912; (l) Clavier, H.; Nolan, S. P. *Chem. Commun.* **2010**, *46*, 841–861; (m) Dröge, T.; Glorius, F. *Angew. Chem., Int. Ed.* **2010**, *49*, 6940–6952; (n) Melaimi, M.; Soleilhavoup, M.; Bertrand, G. *Angew. Chem., Int. Ed.* **2010**, *49*, 8810–8849; (o) Benhamou, L.; Chardon, E.; Lavigne, G.; Bellemin-Laponnaz, S.; César, V. *Chem. Rev.* **2011**, *111*, 2705–2733; (p) Valente, C.; Çalimsiz, S.; Hoi, K. H.; Mallik, D.; Sayah, M.; Organ, M. G. *Angew. Chem., Int. Ed.* **2012**, *51*, 3314–3332.
3. Reviews on NHC organocatalysis: (a) Marion, N.; Diez-Gonzalez, S.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 2988–3000; (b) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606–5655; (c) Nair, V.; Vellalath, S.; Babu, B. P. *Chem. Soc. Rev.* **2008**, *37*, 2691–2698; (d) Moore, J. L.; Rovis, T. *Top. Curr. Chem.* **2009**, *290*, 77–144; (e) Biju, A. T.; Kuhl, N.; Glorius, F. *Acc. Chem. Res.* **2011**, *44*, 1182–1195; (f) Rong, Z.-Q.; Zhang, W.; Yang, G.-Q.; You, S.-L. *Curr. Org. Chem.* **2011**, *15*, 3077–3090; (g) Grossmann, A.; Enders, D. *Angew. Chem., Int. Ed.* **2012**, *51*, 314–325; (h) Vora, H. U.; Wheeler, P.; Rovis, T. *Adv. Synth. Catal.* **2012**, *354*, 1617–1639; (i) Bugaut, X.; Glorius, F. *Chem. Soc. Rev.* **2012**, *41*, 3511–3522; (j) Fèvre, M.; Pinaud, J.; Gnanou, Y.; Vignolle, J.; Taton, D. *Chem. Soc. Rev.* **2013**, *42*, 2142–2172.
4. Paczal, A.; Bényei, A. C.; Kotschy, A. *J. Org. Chem.* **2006**, *71*, 5969–5979.
5. Selected recent examples: (a) Waltman, A. W.; Grubbs, R. H. *Organometallics* **2004**, *23*, 3105–3107; (b) Xu, G.; Gilbertson, S. R. *Org. Lett.* **2005**, *7*, 4605–4608; (c) Clavier, H.; Coutable, L.; Toupet, L.; Guillemin, J.-C.; Mauduit, M. *J. Organomet. Chem.* **2005**, *690*, 5237–5254; (d) Vougioukalakis, G. C.; Grubbs, R. H. *Organometallics* **2007**, *26*, 2469–2472; (e) Stylianides, N.; Danopoulos, A. A.; Pugh, D.; Hancock, F.; Zanotti-Gerosa, A. *Organometallics* **2007**, *26*, 5627–5635; (f) Aidouni, A.; Bendahou, S.; Demonceau, A.; Delaude, L. *J. Comb. Chem.* **2008**, *10*, 886–892; (g) Leuthäusser, S.; Schmidts, V.; Thiele, C. M.; Plenio, H. *Chem. Eur. J.* **2008**, *14*, 5465–5481; (h) Bhanu Prasad, B. A.; Gilbertson, S. R. *Org. Lett.* **2009**, *11*, 3710–3713.
6. Selected recent examples: (a) McGarrigle, E. M.; Fritz, S. P.; Favereau, L.; Yar, M.; Aggarwal, V. K. *Org. Lett.* **2011**, *13*, 3060–3063; (b) Zhang, J.; Su, X.; Fu, J.; Shi, M. *Chem. Commun.* **2011**, *47*, 12541–12543; (c) Zhang, J.; Su, X.; Fu, J.; Qin, X.; Zhao, M.; Shi, M. *Chem. Commun.* **2012**, *48*, 9192–9194; (d) Opalka, S. M.; Park, J. K.; Longstreet, A. R.; McQuade, D. T. *Org. Lett.* **2013**, *15*, 996–999; (e) Kolychev, E. L.; Asachenko, A. F.; Dzhevakov, P. B.; Bush, A. A.; Shuntikov, V. V.; Khrustalev, V. N.; Nechaev, M. S. *Dalton Trans.* **2013**, *42*, 6859–6866; (f) Zhukhovitskiy, A. V.; Mavros, M. G.; Van, V. T.; Johnson, J. A. *J. Am. Chem. Soc.* **2013**, *135*, 7418–7421.
7. Matsumura, T.; Niwa, T.; Nakada, M. *Tetrahedron Lett.* **2012**, *53*, 4313–4316.
8. Metal-catayzed reductive cleavage of a carbon-sulfur bond using organosilane: (a) Graham, T. H.; Liu, W.; Shen, D.-M. *Org. Lett.* **2011**, *13*, 6232–6235; (b) Barbero, N.; Martin, R. *Org. Lett.* **2012**, *14*, 796–799.
9. Baker, T.; Lewis, S. E. *Synth. Commun.* **2010**, *40*, 2747–2752.