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1,2-Sulfanyl Group Migration as a Driving Force: New Approach to Pyrroles by Reaction of Allenic Aldehydes with Amines

Lingling Peng, Xiu Zhang, Jie Ma, Zhenzhen Zhong, and Jianbo Wang*

Beijing National Laboratory of Molecular Sciences (BNLMS), Green Chemistry Center (GCC) and Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education, College of Chemistry, Peking University, Beijing 100871, China

wangjb@pku.edu.cn

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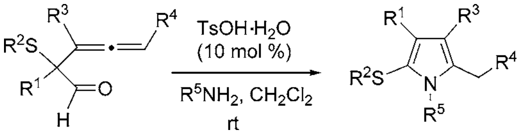
ABSTRACT



Acid-promoted reaction of sulfanyl group substituted allenic aldehyde with amine affords pyrrole derivatives in high yields. The neighboring group participation of the sulfanyl group is the driving force in this transformation.

Pyrroles have attracted attention due to their importance in the fields of natural products, medicinal chemistry, and material sciences.[1−3] Efforts have been directed to the development of efficient methods to synthesize this type of heterocycle.[4] The classic methods for preparing pyrroles include the condensation of α-haloketones with β-keto esters in the presence of amines (Hantzsch procedure),[5] the reaction of 1,4-diketones and amines (Paal−Knorr synthesis),[6] and the condensation of α-amino ketones with β-dicarbonyl compounds (Knorr synthesis).[7] Recently, new approaches based on transition-metal-catalyzed processes have been

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(1) For general reviews on pyrroles, see: (a) Jones, R. A. In *Pyrroles, Part II, The Synthesis, Reactivity and Physical Properties of Substituted Pyrroles*; Wiley: New York, 1992. (b) Gilchrist, T. L. *Heterocyclic Chemistry*, 3rd ed.; Addison-Wesley Longman: Essex, 1997; pp 192−209. (c) *Comprehensive Heterocyclic Chemistry*; Bird, C. W., Ed.; Pergamon Press: Oxford, 1996; Vol. 2. (d) Joule, J. A.; Mills, K. In *Heterocyclic Chemistry*; Blackwell Science: Oxford, 2000; Chapter 13.

(2) For recent reviews of pyrroles in natural products, see: (a) Fürstner, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 3582. (b) Hoffmann, H.; Lindel, T. *Synthesis* **2003**, 1753. For selected recent reports, see: (c) Boger, D. L.; Boyce, C. W.; Labroli, M. A.; Sehon, C. A.; Jin, Q. *J. Am. Chem. Soc.* **1999**, *121*, 54. (d) Fürstner, A.; Weintritt, H. *J. Am. Chem. Soc.* **1998**, *120*, 2817. (e) Sayah, B.; Pelloux-Leon, N.; Vallee, Y. *J. Org. Chem.* **2000**, *65*, 2824. (f) Liu, J.-H.; Yang, Q.-C.; Mak, T. C. W.; Wong, H. N. C. *J. Org. Chem.* **2000**, *65*, 3587. (g) Brower, J. O.; Lightner, D. A.; McDonagh, A. F. *Tetrahedron* **2001**, *57*, 7813.

(3) For reviews of the pyrrole structure in materials, see: (a) *Electronic Materials: The Oligomer Approach*; Müllen, K., Wegner, G., Eds.; Wiley-VCH: Weinheim, 1997. (b) Deronzier, A.; Moutet, J.-C. *Curr. Top. Electrochem.* **1994**, *3*, 159−200. (c) Higgins, S. *Chem. Soc. Rev.* **1997**, *26*, 247. For recent reports, see: (d) Yamaguchi, S.; Tamao, K. *J. Organomet. Chem.* **2002**, *653*, 223. (e) Domingo, V. M.; Aleman, C.; Brillas, E.; Julia, L. *J. Org. Chem.* **2001**, *66*, 4058.

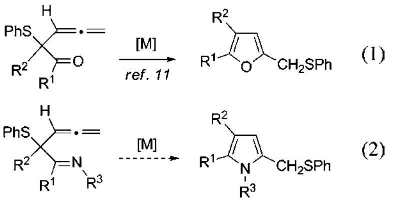
(4) For reviews on pyrrole synthesis, see: (a) Sundberg, R. J. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996; Vol. 2, p 119. (b) Gilchrist, T. L. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2849. (c) Balme, G. *Angew. Chem., Int. Ed.* **2004**, *43*, 6238. For selected recent references, see: (d) Dhawan, R.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2004**, *126*, 468. (e) Wurz, R. P.; Charette, A. B. *Org. Lett.* **2005**, *7*, 2313. (f) Kamijo, S.; Kanazawa, C.; Yamamoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 9260. (g) Gorin, D. J.; Davis, N. R.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 11260. (h) Larionov, O. V.; de Meijere, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 5664. (i) Shimizu, M.; Takahashi, A.; Kawai, S. *Org. Lett.* **2006**, *8*, 3585. (j) Winkler, J. D.; Ragains, J. R. *Org. Lett.* **2006**, *8*, 4031. (k) Crawley, M. L.; Goljer, I.; Jenkins, D. J.; Mehlmann, J. F.; Nogle, L.; Dooley, R.; Mahaney, P. E. *Org. Lett.* **2006**, *8*, 5837. (l) Dong, C.; Deng, G.; Wang, J. *J. Org. Chem.* **2006**, *71*, 5560. (m) Crawley, M. L.; Goljer, I.; Jenkins, D. J.; Mehlmann, J. F.; Nogle, L.; Dooley, R.; Mahaney, P. E. *Org. Lett.* **2006**, *8*, 5837. (n) St. Cyr, D. J.; Martin, N.; Arndtsen, B. A. *Org. Lett.* **2007**, *9*, 449. (o) Huang, X.; Shen, R.; Zhang, T. *J. Org. Chem.* **2007**, *72*, 1534. (p) Bélanger, G.; April, M.; Dauphin, É.; Roy, S. *J. Org. Chem.* **2007**, *72*, 1104.

(5) For recent examples of Hantzsch synthesis of pyrroles, see: (a) Kameswaran, V.; Jiang, B. *Synthesis* **1997**, *5*, 530. (b) Trautwein, A. W.; Sussmuth, R. D.; Jung, G. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2381. Palacios, F.; Aparico, D.; de los Santos, J. M.; Vicario, J. *Tetrahedron* **2001**, *57*, 1961. (c) Matiychuk, V. S.; Martyak, R. L.; Obushak, N. D.; Ostapiuk, Y. V.; Pidlypnyi, N. I. *Chem. Heterocycl. Comp.* **2004**, *40*, 1218.

10.1021/ol070205d CCC: $37.00

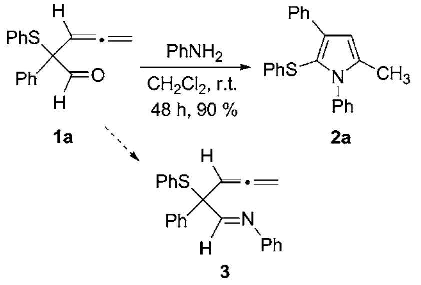
reported.[8−10] In those approaches, the transition-metal catalysts usually activate unsaturated bonds of alkynes[8] or allenes,[9] which then accept intramolecular nucleophilic attack by nitrogen. Herein, we report a novel cyclization reaction leading to multisubstituted pyrrole products by acid-promoted reaction of allenic aldehydes with amines. The cyclization procedure, which can be accelerated by acids, does not need a transition metal to activate the allene moiety. The 1,2-thio group migration is the driving force in this cyclization.

We have recently reported transition-metal-catalyzed reaction of allenic sulfides, which gives furan derivatives through 1,4-sulfanyl group migrations (eq 1).[11] Naturally, we expected to observe a similar reaction for imines, which would give pyrrole derivatives with 1,4-migration of the thio group (eq 2).



For this purpose, we tried to prepare the allenic imine substrate **3** by the reaction of allenic aldehyde **1a** with aniline at room temperature. Surprisingly, the expected allenic imine sulfide **3** was not isolated. Instead, 2-thio-substituted pyrrole derivative **2a** was obtained in high yield (Scheme 1).

Scheme 1



Further experiments indicated that raising the temperature could shorten the reaction time for the formation of **2a** (Table 1). Lewis acids, such as $BF_3{\cdot}Et_2O$, AuCl, and AgOTf, all can accelerate the reaction. Protonic acids, such as $TsOH{\cdot}H_2O$ and HCl, also promote this reaction. Thus, with 10 mol % of $TsOH{\cdot}H_2O$, the reaction of **1a** with aniline in CH_2Cl_2 at room temperature afforded the pyrrole product in 98% yield.

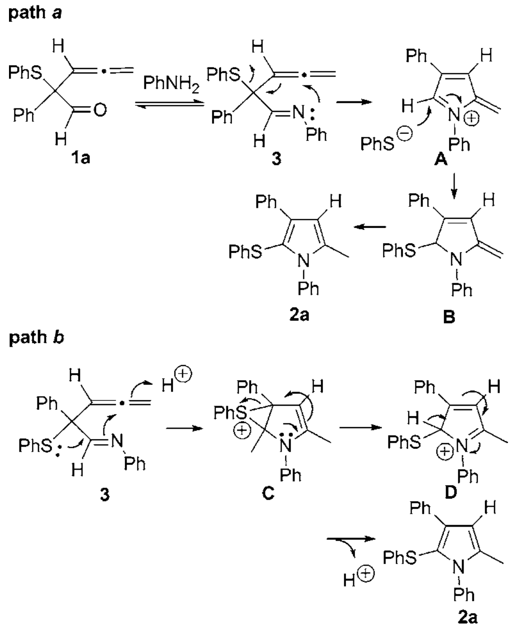
Table 1. Reaction of **1a** and Aniline under Various Conditions

entry	catalyst[a]	solvent	temp (°C)	time (h)	**2a**, yield (%)[b]
1	none	CH_2Cl_2	25	48	90
2	none	neat	25	30	97
3	none	DCE	60	24	84
4	$TsOH{\cdot}H_2O$	CH_2Cl_2	25	24	98
5	$TsOH{\cdot}H_2O$	DCE	60	3	97
6	HCl	CH_2Cl_2	25	24	92
7	$BF_3{\cdot}Et_2O$	CH_2Cl_2	25	5	53
8	AuCl	CH_2Cl_2	25	24	95
9	AgOTf	CH_2Cl_2	25	12	87
10	AuCl	DCE	60	3	83

[a] For entries 4−7, 10 mol % of catalyst was used; for entries 8−10, 5 mol % of catalyst was used. [b] Isolated yield after column chromatography.

This unexpected pyrrole formation can be explained by two pathways, path a and path b, as shown in Scheme 2. In both cases, the reaction of **1a** with aniline first generates imine intermediate **3**. In path a, intramolecular nucleophilic attack of the nitrogen atom to the middle carbon of the allene

Scheme 2



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(6) For recent examples of Paal−Knorr reactions, see: (a) Minetto, G.; Raveglia, L. F.; Sega, A.; Taddei, M. *Eur. J. Org. Chem.* **2005**, 5277. (b) Banik, B. K.; Banik, I.; Renteria, M.; Dasgupta, S. K. *Tetrahedron Lett.* **2005**, *46*, 2643. (c) Bharadwaj, A. R.; Scheidt, K. A. *Org. Lett.* **2004**, *6*, 2465. (d) Minetto, G.; Raveglia, L. F.; Taddei, M. *Org. Lett.* **2004**, *6*, 389. (e) Banik, B. K.; Samajdar, S.; Banik, I. *J. Org. Chem.* **2004**, *69*, 213. (f) Wang, B.; Gu, Y.; Luo, C.; Yang, T.; Yang, L.; Suo, J. *Tetrahedron Lett.* **2004**, *45*, 3417. (g) Banik, B. K.; Samajdar, S.; Banik, I. *J. Org. Chem.* **2004**, *69*, 213.

(7) For an example of Knorr pyrrole synthesis, see: Alberola, A.; Ortega, A. G.; Sadaba, M. L.; Sanudo, C. *Tetrahedron* **1999**, *55*, 6555.

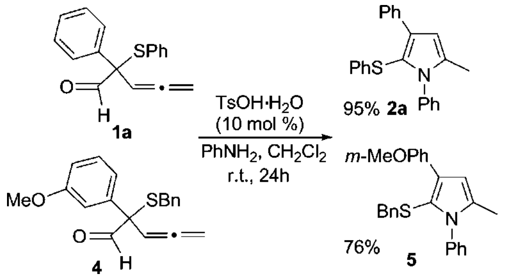
(8) (a) Harrison, T. J.; Kozak, J. A.; Corbella-Pané, M.; Dake, G. R. *J. Org. Chem.* **2006**, *71*, 4525. (b) Ishikawa, T.; Aikawa, T.; Watanabe, S.; Saito, S. *Org. Lett.* **2006**, *8*, 3881. (c) Ramanathan, B.; Keith, A. J.; Armstrong, D.; Odom, A. L. *Org. Lett.* **2004**, *6*, 2957. (d) Hiroya, K.; Matsumoto, S.; Ashikawa, M.; Ogiwara, K.; Sakamoto, T. *Org. Lett.* **2006**, *8*, 5349. (e) Gorin, D. J.; Davis, N. R.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 11260. (f) Gabriele, B.; Salerno, G.; Fazio, A. *J. Org. Chem.* **2003**, *68*, 7853.

(9) (a) Binder, J. T.; Kirsch, S. F. *Org. Lett.* **2006**, *8*, 2151. (b) Kel'in, A. V.; Sromek, A. W.; Gevorgyan, V. *J. Am. Chem. Soc.* **2001**, *123*, 2074. (c) Yu, H.-Y.; Dieter, R. K. *Org. Lett.* **2001**, *3*, 3855. (d) Kim, J. T.; Kel'in, A. V.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2003**, *42*, 98. (e) Lee, C. -F.; Yang, L.-M.; Hwu, T.-Y.; Feng, A.-S.; Tseng, J.-C.; Luh, T.-Y. *J. Am. Chem. Soc.* **2000**, *122*, 4992.

moiety and the simultaneous elimination of the thiophenyl anion generate a five-membered iminium intermediate **A**. Then, the thiophenyl anion attacks the iminium carbon to afford **B**, which isomerizes to **2a**. Alternatively, the reaction may follow path b. From imine **3**, the thiophenyl group assists the nucleophilic attack of imine nitrogen to generate intermediate **C**, which contains a three-centered thiirenium ring. Opening of the thiirenium ring leads to **D**, which is deprotonated to afford **2a**. The difference between path a and b is that in path a the 1,2-thio group migration[12,13] is intermolecular whereas in path b it is intramolecular.

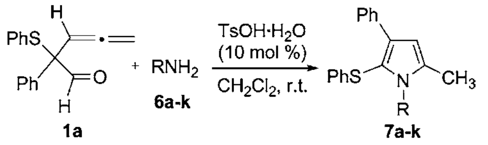
To differentiate the two pathways, a crossover experiment was carried out (Scheme 3). A 1:1 mixture of **1a** and **4** with aniline was treated with 10 mol % of TsOH·H_2O at room temperature. It gave pyrrole derivatives **2a** and **5** in 95% and 76% yield, respectively. No crossover products could be detected. This result demonstrated that the 1,2-sulfur migration was intramolecular, thus supporting path b as the more likely reaction mechanism.

Scheme 3



It is worthwhile to note that only unreacted starting materials and the pyrrole product could be isolated if the reaction was stopped before completion. No intermediate allenic imine **3** could be identified. This observation indicates that in allenic imine **3** intramolecular imine nitrogen attack to the allene is highly facile. The long reaction time when the reaction was carried out in the absence of acid was due to the slow reaction of the imine formation step. The role of acid in accelerating the overall transformation is obviously to promote the imine formation. It is also noted that under the same reaction conditions allenic aldehyde **1a** did not undergo a similar reaction to afford the corresponding furan products. This result indicates that the strong nucleophilicity of the imine nitrogen is also critical in this process.

Table 2. TsOH-Catalyzed Reaction of **1a** and Amines **6a**−**k**

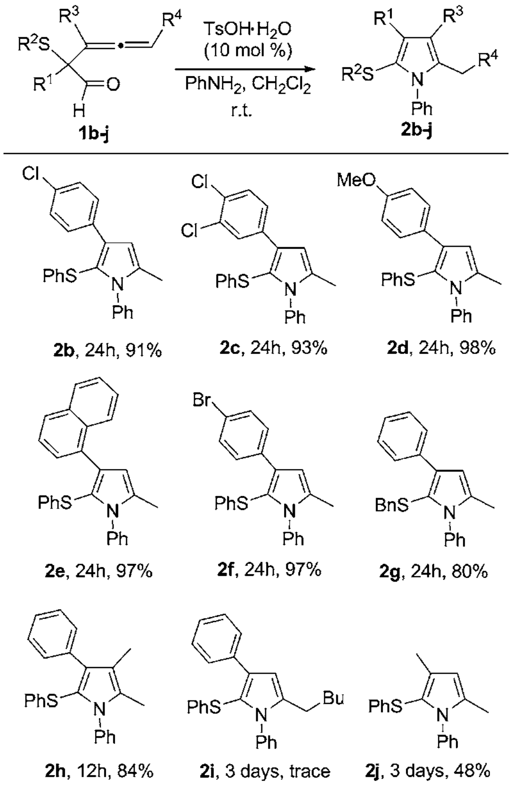


entry	amine **6** (R)	time (h)	**7**, yield (%)[a]
1	**6a**, *p*-MeC_6H_4	12	**7a**, 92
2	**6b**, *p*-BrC_6H_4	24	**7b**, 86
3	**6c**, *p*-ClC_6H_4	24	**7c**, 98
4	**6d**, *m*-MeC_6H_4	24	**7d**, 97
5	**6e**, *p*-$NO_2C_6H_4$	120	**7e**, trace
6	**6f**, Ac	120	nr[b]
7	**6g**, Ms	120	nr
8	**6h**, Bn	12	**7h**, 81
9[c]	**6h**, Bn	48	**7h**, 96
10	**6i**, Bu	12	—[d]
11	**6j**, allyl	12	**7j**, 41
12	**6k**, *tert*-Bu	12	**7k**, trace

[a] Isolated yield after column chromatography. [b] Starting material was recovered. [c] Reaction was carried out without TsOH·H_2O. [d] Reaction gave a complex mixture.

Because this reaction provides a straightforward way to form multisubstituted pyrrole derivatives from readily available starting material, this transformation may find utilities in organic synthesis. Thus, with cheap TsOH·H_2O as the catalyst, we proceeded to expand the substrate scope (Table

Scheme 4



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(10) (a) Takaya, H.; Kojima, S.; Murahashi, S. -I. *Org. Lett.* **2001**, *3*, 421. (b) Shen, H.-C.; Li, C.-W.; Liu, R.-S. *Tetrahedron Lett.* **2004**, *45*, 9245. (c) Wurz, R. P.; Charette, A. B. *Org. Lett.* **2005**, *7*, 2313. (d) Kamijo, S.; Kanazawa, C.; Yamamoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 9260. (e) Larionov, O. V.; de Meijere, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 5664. (f) Lu, L.-h.; Chen, G.-f.; Ma, S.-M. *Org. Lett.* **2006**, *8*, 835.

(11) Peng, L.; Zhang, X.; Ma, M.; Wang, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 1905.

(12) For a review on thio group migration, see: Fox, D. J.; House, D.; Warren, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 2462.

(13) 1,2-Thio group migration to the sp^2 carbon of iminium has been known. See: (a) Plate, R.; Nivard, R. J. F.; Ottenheijm, H. C. J. *Tetrahedron* **1986**, *42*, 4503. (b) Hamel, P. *J. Org. Chem.* **2002**, *67*, 2854.

2). The reactions of **1a** with a series of amines were examined. With aromatic amines, the reaction gave high yields of the corresponding pyrrole derivatives. The exception is for the amine **6e**, in which the aromatic group of amine is *p*-nitrophenyl. This low yield is likely due to the unfavorable formation of the imine intermediate. Similarly, no reaction occurred with $AcNH_2$ and $MsNH_2$ even after stirring for 5 days (entries 6 and 7). The reaction with benzylamine gave a little lower yield when catalyzed with $TsOH{\cdot}H_2O$ (entry 8). When the reaction with benzylamine was carried out in the absence of $TsOH{\cdot}H_2O$, it gave a high yield of the pyrrole product, although the reaction took longer. The reaction with allyl amine afforded the pyrrole product in 41% yield (entry 11). However, the reaction with *n*-butyl amine was found to give only a complex mixture, whereas the reaction with *tert*-butyl amine proceeded very slowly (entries 10 and 12).

Then, the scope and limitations of this reaction were further demonstrated by the reaction of a series of allenic aldehydes with aniline, as summarized in Scheme 4. Pyrrole products were isolated in high yields, except in the case of **1i**, which might be due to the steric and electronic effects of the terminal alkyl group in the allene moiety. It was noteworthy that the allenic substrate **1h**, in which R^3 was the methyl group, also worked well to give **2h** in good yield. Finally, the reaction of allenic aldehyde **1j**, in which the aromatic substituent was replaced with a methyl group, also gave the corresponding pyrrole products, although the yield was diminished.

In conclusion, we have developed an acid-promoted cyclization reaction of allenic aldehydes with amines, which gives various 2-thio-substituted pyrrole[14] products in good to excellent yields. This reaction provides a new entry to this type of substituted pyrroles.

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Supporting Information Available: Experimental procedure, characterization data, and ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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[14] (a) Katritzky, A. R.; Wang, X. J.; Denisenko, A. *J. Org. Chem.* **2001**, *66*, 2850. (b) Nedolya, N. A.; Brandsma, L.; Verkruijsse, H. D.; Trofimov, B. A. *Tetrahedron Lett.* **1997**, *38*, 7247.