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Insertion of Arynes into Thioureas: A New Amidine Synthesis

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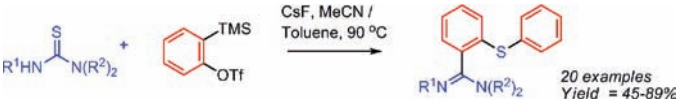
ABSTRACT

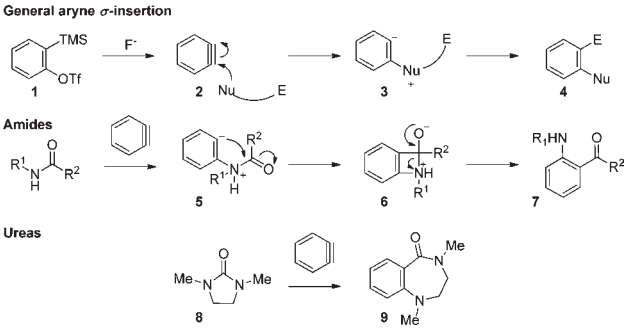


Arynes, generated from trimethylsilyl phenyltriflate precursors, have been found to react with thioureas via a formal π-insertion into the C═S bond. The reaction contrasts with that of ureas, which proceeds via benzyne σ-insertion into the C–N bond, and represents a new, operationally simple route to functionalized amidines.

The introduction of 2-(trimethylsilyl) phenyltriflates, **1**, as aryne precursors,[1] activated by fluoride under mild conditions, has fueled the discovery of new transformations that exploit the strained triple bond of the benzyne molecule (Scheme 1). A rich area of research concerns σ-insertion reactions; addition of a nucleophile to benzyne, **2**, forms the zwitterionic intermediate **3**.[2] If the nucleophilic component has a suitable electrophilic site, rearrangement is possible to form a double functionalized arene product **4**. Such transformations often proceed under mild conditions in the absence of transition metal or Lewis acid reagents and encompass a wide range of nucleophiles (N, C, S, etc.) to afford useful aromatic products.[3]

We[4] and Larock[5] have demonstrated that amides are good substrates for aryne insertion to afford versatile amino ketones, **7**. Similarly, Hiyama and co-workers have

Scheme 1. Aryne σ-Insertion Processes



shown that cyclic ureas **8** can produce the biologically active benzodiazepine motif **9** when treated with benzyne.[6] Both transformations can be understood in terms of initial

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(2) Reviews: (a) Yoshida, H.; Ohshita, J.; Kunai, A. *Bull. Chem. Soc. Jpn.* **2010**, *83*, 199–219. (b) Peña, D.; Pérez, D.; Guitián, E. *Angew. Chem., Int. Ed.* **2006**, *45*, 3579–3581.

(3) Recent examples: (a) McAusland, D.; Seo, S.; Pintori, D. G.; Finlayson, J.; Greaney, M. F. *Org. Lett.* **2011**, *13*, 3667–3669. (b) Li, P.; Zhao, J.; Wu, C.; Larock, R. C.; Shi, F. *Org. Lett.* **2011**, *13*, 3340–3343. (c) Rogness, D. C.; Larock, R. C. *J. Org. Chem.* **2011**, *76*, 4980–4986. (d) Okuma, K.; Matsunaga, N.; Nagahora, N.; Shioji, K.; Yokomori, Y. *Chem. Commun.* **2011**, *47*, 5822–5824. (e) Allan, K. M.; Gilmore, C. D.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 4488–4491. (f) Laczkowski, K. Z.; Garcia, D.; Pena, D.; Cobas, A.; Perez, D.; Guitian, E. *Org. Lett.* **2011**, *13*, 960–963. (g) Biju, A. T.; Glorius, F. *Angew. Chem., Int. Ed.* **2010**, *49*, 9761. (h) Okuma, K.; Fukuzaki, Y.; Nojima, A.; Sou, A.; Hino, H.; Matsunaga, N.; Nagahora, N.; Shioji, K.; Yokomori, Y. *Bull. Chem. Soc. Jpn.* **2010**, *83*, 1238–1247. (i) Hong, D.; Chen, Z.; Lin, X.; Wang, Y. *Org. Lett.* **2010**, *12*, 4608–4611. (j) Dubrovskiy, A. V.; Larock, R. C. *Org. Lett.* **2010**, *12*, 3117. (k) Yoshida, H.; Morishita, T.; Ohshita, J. *Chem. Lett.* **2010**, *39*, 508–509. (l) Jeganmohan, M.; Bhuvaneswari, S.; Cheng, C.-H. *Chem.—Asian J.* **2009**, *5*, 153–159.

(4) Pintori, D. G.; Greaney, M. F. *Org. Lett.* **2010**, *12*, 168–171.

(5) Liu, Z.; Larock, R. C. *J. Am. Chem. Soc.* **2005**, *127*, 13112–13113.

(6) Yoshida, H.; Shirakawa, E.; Honda, Y.; Hiyama, T. *Angew. Chem., Int. Ed.* **2002**, *41*, 3247–3249.

(7) (a) Cant, A. A.; Roberts, L.; Greaney, M. F. *Chem. Commun.* **2010**, 8671–8673. (b) Cant, A. A.; Bertrand, G. H. V.; Henderson, J. L.; Roberts, L.; Greaney, M. F. *Angew. Chem., Int. Ed.* **2009**, *48*, 5199–5202. (c) Henderson, J. L.; Edwards, A. S.; Greaney, M. F. *Org. Lett.* **2007**, *9*, 5589–5592.

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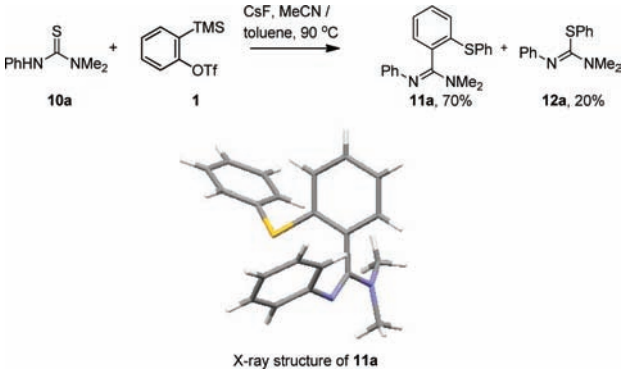
N-arylation followed by incipient azetidinium (**6**) formation and then cleavage of the C−N bond to give the products. As part of our efforts to define new, synthetically useful pathways in aryne chemistry,[3a,4,7] we chose to investigate thioureas as substrates in an analogous process. The more nucleophilic sulfur atom would be expected to out-compete the N-arylation pathway, setting up an alternative insertion pathway resulting in cleavage of the C−S π-bond rather than the acyl C−N σ-bond. To test the idea we heated thiourea **10a** (1 equiv) with benzyne precursor **1** (2.1 equiv) in the presence of cesium fluoride (Scheme 2). Somewhat surprisingly, we observed the formation of two separate compounds containing one and two additional benzene rings, respectively. NMR and X-ray analysis characterized the structures as the insertion/arylation amidine product **11a** (70%, major) and the simple S-arylated compound **12a** (20%, minor). As expected, the sulfur atom preferentially adds to benzyne to give the formal π-insertion product, which in the presence of excess aryne undergoes a second S-arylation to afford **11a** as the major product.

Scheme 2. Insertion of Benzyne into Thioureas



Amidines are useful heterocyclic building blocks, as well as important motifs in medicinal chemistry in their own right.[8] Classical methods of amidine synthesis usually involve nucleophilic addition to nitriles (Pinner reaction for primary and secondary amidines) or desulfurizing thioamides with stoichiometric mercury in the presence of amine nucleophiles.[9] The reaction at hand offers a new approach that requires no transition metals, as well as accessing an interesting motif whereby the sulfur atom in the starting material is transposed in the amidine product, offering possibilities for further functionalization.

To explore the scope of this amidine synthesis we first prepared a series of *N*,*N*-dimethyl-*N*-arylthioureas and examined the affect of varying the aryl substituents (Table 1). The combined yields of **11** and **12** were generally excellent, with the selectivity between the two products correlating with the electronic properties of the aryl substituent. Electron-releasing groups in the *para* position (Me, Et, t-Bu and OMe, entries 1−4) were noticeably selective for the insertion product **11**. The most electron-rich substrate **10e** gave a 9:1 selectivity for **11e** in an excellent 89% isolated yield. Electron-withdrawing groups in the *para* position tended to increase the amount of simple arylation product **12**, with F, CN, NO_2, OCF_3, and CO_2Me substituents (entries 5, 7−10) all producing **11** and **12** in ratios from 0.9:1 (NO_2, entry 8) to 1.4:1 (F, entry 5). The reaction was successful for *ortho* (entry 11) and *meta* (Supporting Information) MeO groups, with product ratios being close to 1:1. Finally, we were pleased to see that the pyridyl derivative **10m** underwent successful insertion (entry 12), with no problems of side reactions[3k] from the nucleophilic azine nitrogen.

We extended the scope of the thiourea substrates to encompass alternative alkyl groups on either thiourea nitrogen atom. The sterically hindered iPr and cyclohexyl derivatives were productive, producing the insertion products **11o** and **11p** in moderate yields (Table 1, entries 14 and 15). Replacing the aryl group and using an all alkyl-substituted thiourea was likewise successful, with the cyclohexyl and benzyl derivatives **10r** and **10s** undergoing insertion in good yield (entries 17 and 18). Cyclic thiourea **10t** is directly analogous to Hiyama's urea substrate that undergoes C−N σ-insertion.[6] Here, we see the expected C−S insertion to form the novel amidine **11t** in 75% yield and with >4:1 selectivity relative to simple arylation. Finally, 3-methoxybenzyne proved equally effective as simple benzyne, affording the functionalized amidine **11u** in high yield as a single diastereoisomer (entry 20).

To clarify the relationship between the two products **11** and **12** in the mechanistic pathway of the reaction, we re-exposed arylation products **12a** and **12k** to the reaction conditions. Interestingly, no reaction was observed in either case, with both substrates undergoing slow decomposition over prolonged heating. It appears, therefore, that **12** is not a precursor to **11** in the reaction. A possible mechanism taking account of this observation is presented in Scheme 3.

Following initial reaction with benzyne, zwitterionic intermediate **13** may undergo quenching via intermolecular proton transfer from the acetonitrile co-solvent and subsequent proton loss from the iminium ion. The resulting *S*-phenyl isothioureas **12** are then much less reactive substrates for a second aryne insertion.

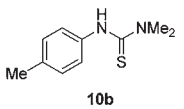
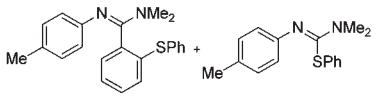
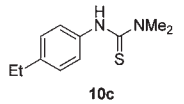
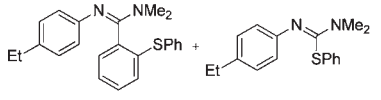
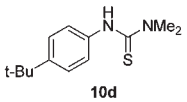
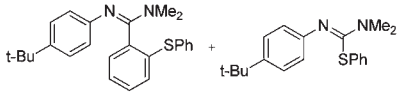
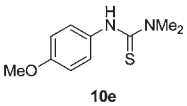
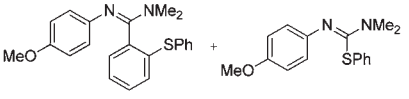
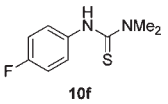
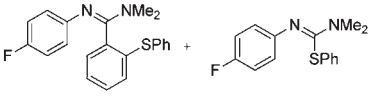
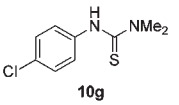
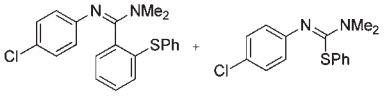
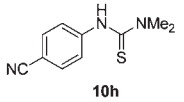
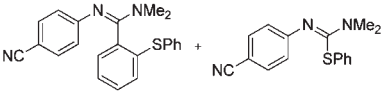
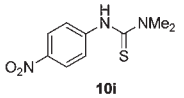
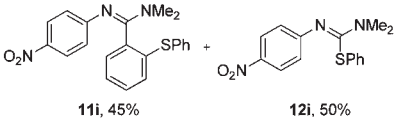
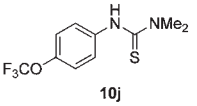
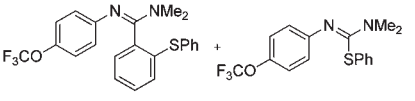
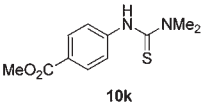
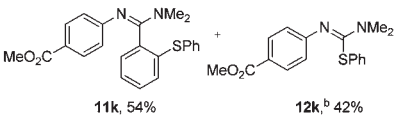
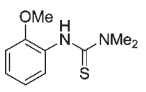
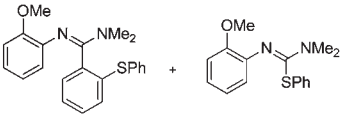
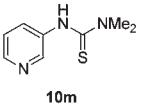
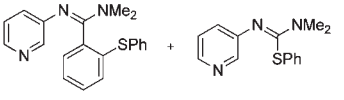
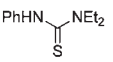
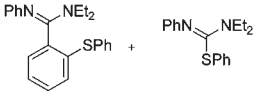
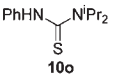
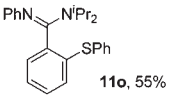
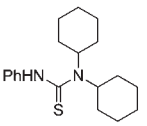
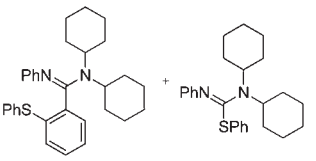
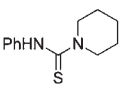
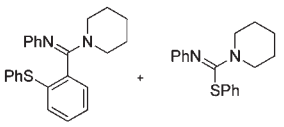
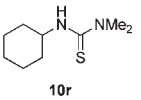
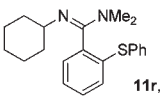
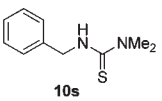
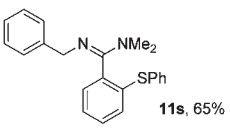
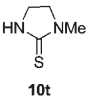
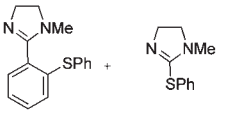
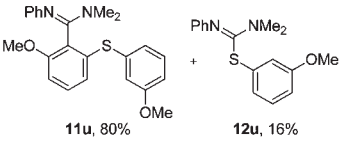
The insertion products **11** presumably arise from intermediate **13** in the usual fashion for aryne insertion chemistry, formation of a four-membered intermediate **14**,

(8) (a) DeKorver, K. A.; Johnson, W. L.; Zhang, Y.; Hsung, R. P.; Dai, H.; Deng, J.; Lohse, A. G.; Zhang, Y.-S. *J. Org. Chem.* **2011**, *76*, 5092–5103 and references therein. (b) Zhang, Y.; DeKorver, K. A.; Lohse, A. G.; Zhang, Y.-S.; Huang, J.; Hsung, R. P. *Org. Lett.* **2009**, *11*, 899–902.

(9) Dunn, P. J. Amidines and *N*-Substituted Amidines. In *Comprehensive Organic Functional Group Transformations II*; Katritzky, A. R., Taylor, R. J. K., Eds.; Elsevier: New York, 2005; Vol. 5, pp 655−699.

(10) S-Arylation of thiols with benzyne: (a) Scardiglia, F.; Roberts, J. D. *Tetrahedron* **1958**, *3*, 197–208. (b) Bunnett, J. F.; Brotherton, T. K. *J. Org. Chem.* **1958**, *23*, 904–906. (c) Bates, R. B.; Janda, K. D. *J. Org. Chem.* **1982**, *47*, 4374–4376. (d) Lin, W.; Sapountzis, I.; Knochel, P. *Angew. Chem., Int. Ed.* **2005**, *44*, 4258–4261. (e) Cano, R.; Ramon, D. J.; Yus, M. *J. Org. Chem.* **2011**, *76*, 654–660.

Table 1. Insertion Products from Thioureas[e]

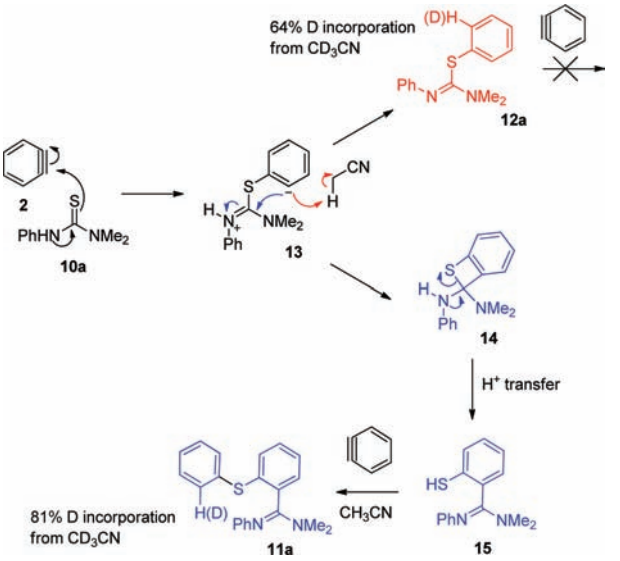
entry	thiourea	products[a]
1	 **10b**	 **11b**, 80% **12b**, 16%
2	 **10c**	 **11c**, 75% **12c**, 20%
3	 **10d**	 **11d**, 68% **12d**, 26%
4	 **10e**	 **11e**, 89% **12e**, 9%
5	 **10f**	 **11f**, 55% **12f**, 38%
6	 **10g**	 **11g**, 70% **12g**, 24%
7	 **10h**	 **11h**, 52% **12h**, 42%
8	 **10i**	 **11i**, 45% **12i**, 50%
9	 **10j**	 **11j**, 50% **12j**, 45%
10	 **10k**	 **11k**, 54% **12k**,[b] 42%
11	 **10l**	 **11l**, 45% **12l**, 48%
12	 **10m**	 **11m**, 60% **12m**, 35%
13	 **10n**	 **11n**, 66% **12n**, 25%
14[c]	 **10o**	 **11o**, 55%
15	 **10p**	 **11p**, 50% **12p**, 45%
16	 **10q**	 **11q**, 58% **12q**, 38%
17[c]	 **10r**	 **11r**, 68%
18[c]	 **10s**	 **11s**, 65%
19	 **10t**	 **11t**, 75% **12t**, 18%
20[d]	**10a**	 **11u**, 80% **12u**, 16%

[a] Isolated yields. Compounds **11** and **12** assigned as *E* and *Z* isomers, respectively, around the C=N bond by analogy with X-ray structures of **11a** and **12k**. [b] X-ray structure available. [c] Arylation product **12** could not be purified from the reaction mixture. [d] 3-Methoxybenzyne precursor used instead of **1**, see Supporting Information. [e] Conditions: Thiourea **10** (1 equiv), CsF (6 equiv), and **1** (2.1 equiv) in toluene/acetonitrile (3:1); 90 °C, 6-8 h.

(11) Intramolecular 1,5-H transfer is a possible quenching mechanism for intermediate **13**. A control experiment established no N-H exchange for thiourea **10a** after stirring in CD_3CN in the presence of CsF. Deuterium is thus incorprated into **12** via the intermolecular route, suggesting that intermolecular quenching of the phenyl anion is the dominant pathway for **12** in general.

which collapses via C−S bond cleavage to give thiophenol **15**. This compound was never isolated in the reaction medium, even when using 1 equiv of benzyne, indicating that S-arylation of **15** is fast[10] under the reaction conditions to provide the observed products **11**.

Scheme 3. Mechanistic Pathway



When the insertion reaction was run for substrate **10a** using deuterated acetonitrile as solvent, we observed deuterium incorporation for both **11a** and **12a**, confirming the vulnerability of intermediate **13** to protonation by the solvent.[11] Quenching of the phenyl anion in the aryne addition adduct with acetonitrile has been observed in other systems where rearrangement is relatively slow, such as aryne addition to allylamines[7b] or α-substituted β-ketoesters.[12] Here, the thiourea carbon in intermediate **13** is considerably less electrophilic than in the analogous amide addition adducts (e.g., **5** in Scheme 1),[4,5] resulting in slower rearrangement and competitive protonation for some substrates (e.g., **10f**–**10l**).

In summary, we have developed a new insertion reaction of benzyne using thioureas as substrates to afford useful amidine products. The reaction bifurcates between simple S-arylation and benzyne insertion, with control of either pathway being possible by tuning the electronic properties of the thiourea. The aryne inserts into the thiourea C=S bond, in contrast to C–N insertion for related ureas, demonstrating how small changes to nucleophile structure can afford divergent, synthetically useful reaction pathways in aryne chemistry.

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Supporting Information Available. Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(12) Tambar, U. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2005**, *127*, 5340–5341.