

Direct Condensation of Sulfonamide and Formamide: NaI-Catalyzed Synthesis of *N*-Sulfonyl Formamidine Using TBHP as Oxidant

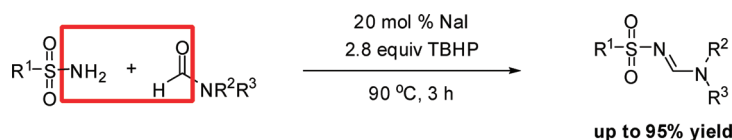
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ABSTRACT



A new *N*-sulfonyl formamidine synthesis was developed via NaI-catalyzed direct condensation of sulfonamide and formamide. The green methodology is featured by high atom economy, easily available starting materials, the lack of need for a transition-metal catalyst, no requirement of hazardous reagent, operational simplicity, and good tolerance with diverse functional groups. Mechanistic studies suggest that the protocol proceeds based upon in situ generated $TsN \cdot NaI$.

N-Sulfonylamidines are unique structural motifs in many bioactive natural products and pharmacophores,¹ and they also serve as useful synthetic intermediates² (Figure 1) and efficient coordinating ligands.³ Conventional methods

known for making *N*-sulfonylamidines involve harsh conditions and corrosive and/or specially designed reagents.⁴ Recently, Chang et al.,^{5a–h} Fokin et al.,^{5e,6a} and others^{5i,j,6b}

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(1) (a) Patai, S.; Rappoport, Z. *The Chemistry of Amidines and Imidates*; Wiley: New York, 1991. (b) Lee, M. Y.; Kim, M. H.; Kim, J.; Kim, S. H.; Kim, B. T.; Jeong, I. H.; Chang, S.; Kim, S. H.; Chang, S.-Y. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 541.

(2) (a) Graham, S. L.; Shepard, K. L.; Anderson, P. S.; Baldwin, J. J.; Best, D. B.; Christy, M. E.; Freedman, M. B.; Gautheron, P.; Habecker, C. N.; Hoffman, J. M.; Lyle, P. A.; Michelson, S. R.; Ponticello, G. S.; Robb, C. M.; Schwam, H.; Smith, A. M.; Smith, R. L.; Sondey, J. M.; Strohmaier, K. M.; Sugrue, M. F.; Varga, S. L. *J. Med. Chem.* **1989**, *32*, 2548. (b) Scholz, T. H.; Sondey, J. M.; Randall, W. C.; Schwam, H.; Thompson, W. J.; Mallorga, P. J.; Sugrue, M. F.; Graham, S. L. *J. Med. Chem.* **1993**, *36*, 2134. (c) Deprez, P.; Heckmann, B.; Corbier, A.; Vever, J.-P.; Fortin, M.; Guillaume, J. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2605. (d) Heitsch, H.; Becker, R. H. A.; Kleemann, H.-W.; Wagner, A. *Bioorg. Med. Chem.* **1997**, *5*, 673. (e) Bekhit, A. A.; Ashour, H. M. A.; Abdel Ghany, Y. S.; Bekhit, A. E.-D. A.; Baraka, A. *Eur. J. Med. Chem.* **2008**, *43*, 456. (f) Vernier, W.; Chong, W.; Rewolinski, D.; Greasley, S.; Pauly, T.; Shaw, M.; Dinh, D.; Ferre, R. A.; Nukui, S.; Ornelas, M.; Reyner, E. *Bioorg. Med. Chem.* **2010**, *18*, 3307. (g) Andersen, N. K.; Chandak, N.; Brulíková, L.; Kumar, P.; Jensen, M. D.; Jensen, F.; Sharma, P. K.; Nielsen, P. *Bioorg. Med. Chem.* **2010**, *18*, 4702.

(3) Barker, J.; Kilner, M. *Coord. Chem. Rev.* **1994**, *133*, 219.

(4) (a) King, C. *J. Org. Chem.* **1960**, *25*, 352. (b) Pettit, G. R.; Kadunce, R. E. *J. Org. Chem.* **1962**, *27*, 4566. (c) Arnswald, M.; Neumann, W. P. *J. Org. Chem.* **1993**, *58*, 7022. (d) Silva, A. L.; Covarrubias-Zúñiga, A.; Maldonado, L. A. *OPPI* **2002**, *34*, 545.

(5) (a) Bae, I.; Han, H.; Chang, S. *J. Am. Chem. Soc.* **2005**, *127*, 2038. (b) Yoo, E. J.; Bae, I.; Cho, S. H.; Han, H.; Chang, S. *Org. Lett.* **2006**, *8*, 1347. (c) Chang, S.; Lee, M. J.; Jung, D. Y.; Yoo, E. J.; Cho, S. H.; Han, S. K. *J. Am. Soc. Chem.* **2006**, *128*, 12366. (d) Cho, S. H.; Chang, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 2836. (e) Yoo, E. J.; Ahlquist, M.; Bae, I.; Sharpless, K. B.; Fokin, V. V.; Chang, S. *J. Org. Chem.* **2008**, *73*, 5520. (f) Kim, J. Y.; Kim, S. H.; Chang, S. *Tetrahedron Lett.* **2008**, *49*, 1745. (g) Yoo, E. J.; Chang, S. *Org. Lett.* **2008**, *10*, 1163. (h) Reference 1b. (i) Shang, Y.; He, X.; Hu, J.; Wu, J.; Zhang, M.; Yu, S.; Zhang, Q. *Adv. Synth. Catal.* **2009**, *351*, 2709. (j) Mandal, S.; Gauniyal, H. M.; Pramanik, K.; Mukhopadhyay, B. *J. Org. Chem.* **2007**, *72*, 9753.

(6) (a) Whiting, M.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2006**, *45*, 3157. (b) Xu, X.; Cheng, D.; Li, J.; Guo, H.; Yan, J. *Org. Lett.* **2007**, *9*, 1585.

(7) (a) Xu, X.; Li, X.; Ma, L.; Ye, N.; Weng, B. *J. Am. Chem. Soc.* **2008**, *130*, 14048. (b) Wang, S.; Wang, Z.; Zheng, X. *Chem. Commun.* **2009**, *45*, 7372. (c) Liu, N.; Tang, B.-Y.; Chen, Y.; He, L. *Eur. J. Org. Chem.* **2009**, 2059. (d) Xu, X.; Ge, Z.; Cheng, D.; Ma, L.; Lu, C.; Zhang, Q.; Yao, N.; Li, X. *Org. Lett.* **2010**, *12*, 897. (e) Zhang, L.; Su, J.-H.; Wang, S.; Wan, C.; Zha, Z.; Du, J.; Wang, Z. *Chem. Commun.* **2011**, *47*, 5488.

have reported pioneering Cu-catalyzed three-component reactions to construct *N*-sulfonylamidine. In addition, dehydrogenation of tertiary amine and a tandem reaction with sulfonyl azide offer another elegant alternative for the *N*-sulfonylamidine synthesis.⁷ These achievements were distinguished by a wide substrate scope, mild conditions, and potential synthetic utility. Herein, we described a fundamentally different strategy to *N*-sulfonyl formamide based on the direct condensation of sulfonamide and formamide. Remarkably, the methodology is free of a transition-metal catalyst, has high atom economy, and does not involve potentially explosive sulfonyl azide.

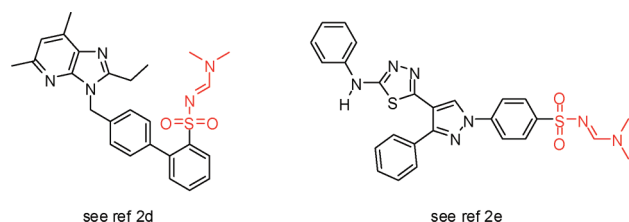
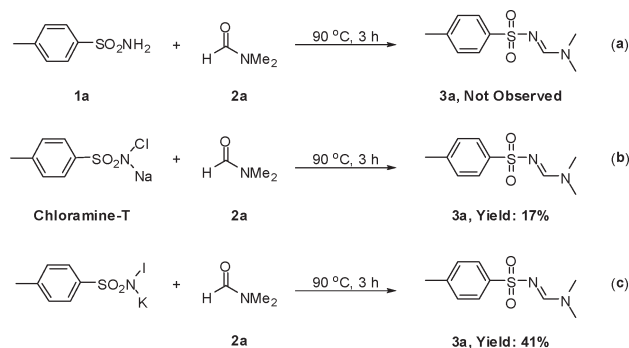


Figure 1. Selected examples of *N*-sulfonyl formamidines.

In theory, direct condensation of sulfonamide and formamide represents the most straightforward and atom economic method for the synthesis of *N*-sulfonyl formamidines. While the condensation of amine and a carbonyl compound is the most popular method for the synthesis of imine, the analogous version of sulfonamide and formamide remains a challenge (Scheme 1a), which can be attributed to the low reactivity of sulfonamide and formamide.⁸ We envisioned that prefunctionalization of sulfonamide would lead to the desired result. Chloramine-T was used as a reaction partner, and the corresponding *N*-sulfonyl formamide **3a** was obtained, albeit in low yield (Scheme 1b). Next, TsN·KI, a stronger nucleophile than chloramine-T, was prepared⁹ and subjected to the reaction in the presence of *N,N*-dimethylformamide (DMF). As expected, a significant increase in yield of *N*-sulfonyl formamide **3a** was observed (Scheme 1c).

Scheme 1. Preliminary Test for *N*-Sulfonyl Formamide Synthesis



Hypervalent iodine reagents have gained wide interest as mild oxidants in organic synthetic chemistry.¹⁰ Recently, a novel C–H oxidation, based upon in situ generation of (hypo)iodite by the action of iodide and H₂O₂/TBHP, was developed by Ishihara and co-workers.¹¹ Inspired by this seminal work, we speculated that in situ generation of TsN·KI from the reaction of iodide with TsNH₂¹² and subsequent condensation with DMF would provide the *N*-sulfonyl formamide **3a** in higher yield (compared to Scheme 1c). In support of this hypothesis, we treated a mixture of TsNH₂ and DMF in the presence of 20 mol % KI and 2.8 equiv of TBHP at 90 °C for 3 h, and the desired *N*-sulfonyl formamide **3a** was obtained in high yield (Table 1, entry 12).

Notably, the reaction was not sensitive to moisture and air and could be performed in an open flask. The optimization of reaction conditions is illustrated in Table 1. The use of NaI as a catalyst provided the best result for this transformation (Table 1, entry 1). When other iodide catalysts were used, the desired product **3a** was generated in moderate to high yield (Table 1, entries 11, 13–15). Interestingly, the use of Bu₄NI as a catalyst,¹³ which was successfully employed in our previous studies,^{13a,d} resulted in a comparable product yield (Table 1, entry 14). Considering the economic aspect and availability, NaI was identified as a catalyst for all the reactions performed thereafter. In the absence of catalyst or oxidant there was no conversion to *N*-sulfonylamidine **3a** (Table 1, entries 9–10). It was noteworthy that the nature of the oxidant plays an important role in the observed yield, and negligible *N*-sulfonylamidine **3a** was obtained when other common oxidants were used (Table 1, entries 2–6). Catalytic NaBr or NaCl was unsuccessful, which indicated that the use of iodide was essential for this transformation (Table 1, entries 7–8). It is noteworthy that no transition-metal catalyst was required for the transformation. When the reaction was performed in the presence of Pd or Cu salts, only a trace amount of *N*-sulfonylamidine **3a** was detected (Table 1, entries 16–17).

(8) In the presence of hazardous POCl₃, sulfonylamidine **3a** was obtained in low 26% yield through condensation of sulfonamide and formamide; see ref 4a.

(9) Jain, S. L.; Sain, B. *Tetrahedron Lett.* **2003**, *44*, 575.

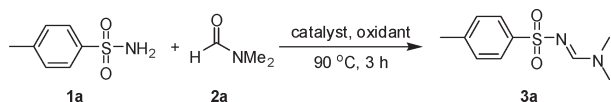
(10) For reviews, see: (a) Wirth, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 3656. (b) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, *108*, 5299. (c) Ochiai, M.; Miyamoto, K. *Eur. J. Org. Chem.* **2008**, 4229. (d) Merritt, E. A.; Olofsson, B. *Angew. Chem., Int. Ed.* **2009**, *48*, 9052. (e) Pouysegue, L.; Deffieux, D.; Quideau, S. *Tetrahedron* **2010**, *66*, 2235. (f) Duschek, A.; Kirsch, S. F. *Angew. Chem., Int. Ed.* **2011**, *50*, 1524. (g) Merritt, E. A.; Olofsson, B. *Synthesis* **2011**, 517.

(11) Uyanik, M.; Okamoto, H.; Yasui, T.; Ishihara, K. *Science* **2010**, *328*, 1376.

(12) Based upon in situ generated KOI, TsN·KI could be obtained in the presence of KOH and iodine. See ref 9.

(13) Recently, we and others reported Bu₄NI-catalyzed C–H activation using TBHP; see: (a) Chen, L.; Shi, E.; Liu, Z.; Chen, S.; Wei, W.; Li, H.; Xu, K.; Wan, X. *Chem.–Eur. J.* **2011**, *17*, 4085. (b) Uyanik, M.; Suzuki, D.; Yasui, T.; Ishihara, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 5331. (c) Froehr, T.; Sindlinger, C. P.; Kloeckner, U.; Finkbeiner, P.; Nachtsheim, B. J. *Org. Lett.* **2011**, *13*, 3754. (d) Wei, W.; Zhang, C.; Xu, Y.; Wan, X. *Chem. Commun.* **2011**, 47, 10827. (e) Ma, L.; Wang, X.; Yu, W.; Han, B. *Chem. Commun.* **2011**, 47, 11333. (f) Jiang, H.; Huang, H.; Cao, H.; Qi, C. *Org. Lett.* **2010**, *12*, 5561. (g) Zhang, J.; Zhu, D.; Yu, C.; Wan, C.; Wang, Z. *Org. Lett.* **2010**, *12*, 2841. (h) He, T.; Yu, L.; Zhang, L.; Wang, L.; Wang, M. *Org. Lett.* **2011**, *13*, 5016.

Table 1. Optimization of Reaction Conditions^a



entry	catalyst	oxidant	yield ^b
1	NaI	TBHP	90%
2	NaI	Oxone	N.D.
3	NaI	NaClO	N.D.
4	NaI	H ₂ O ₂	N.D.
5	NaI	O ₂	N.D.
6	NaI	benzoquinone	N.D.
7	NaBr	TBHP	N.D.
8	NaCl	TBHP	N.D.
9	—	TBHP	N.D.
10	NaI	—	N.D.
11	Lil	TBHP	67%
12	KI	TBHP	88%
13	I ₂	TBHP	49%
14	Bu ₄ NI	TBHP	90%
15	CuI	TBHP	63%
16	PdCl ₂	TBHP	<5%
17	CuCl	TBHP	<5%
18	NaI	TBHP	80% ^d

^a Reaction conditions: 0.5 mmol of TsNH₂ (**1a**), 20 mol % catalyst, 1.4 mmol of TBHP (70% aqueous solution) in 2.0 mL of DMF (**2a**) at 90 °C for 3 h. ^b Isolated yield. ^c Not Detected. ^d 100 mmol of TsNH₂ (**1a**) were used.

To evaluate the generality of the NaI-catalyzed condensation reactions, we next applied this process to a range of sulfonamides and formamides as shown in Figure 2. In general, introduction of an electron-withdrawing or -donating group on the sulfonamides did not play a significant role in the reaction efficiency, leading to the corresponding *N*-sulfonyl formamidines in good to excellent yields. Halides were left untouched under the optimized conditions, in which the products could be further functionalized via transition-metal-catalyzed cross-coupling (Figure 2, products **3e–3g**). The reaction proceeded smoothly even in the presence of sensitive functional groups including aldehyde, ester, benzyl, nitro, and amide. It is noteworthy that sulfonamide bearing removable functional group BocNH– was readily reacted with DMF, leading to *N*-sulfonylamidine **3n** in high efficiency. In addition, a heterocycle such as thiophene also participated in the reaction under the optimized conditions (Figure 2, product **3f**). Butane-1-sulfonamide, an alkyl sulfonamide, worked for this reaction, and the *N*-sulfonylamidine **3q** was obtained in 71% yield. To our satisfaction, an array of formamides including *N,N*-diethylformamide, 4-formylmorpholine, 1-formylpiperidine, and 1-formylpyrrolidine were suitable reaction partners, furnishing the corresponding *N*-sulfonylamidines **3s–3v** in moderate to excellent yields.

Remarkably, the reaction could be readily scaled up to 100 mmol, and the desired *N*-sulfonyl formamidine **3a** was achieved in 80% yield by simple recrystallization

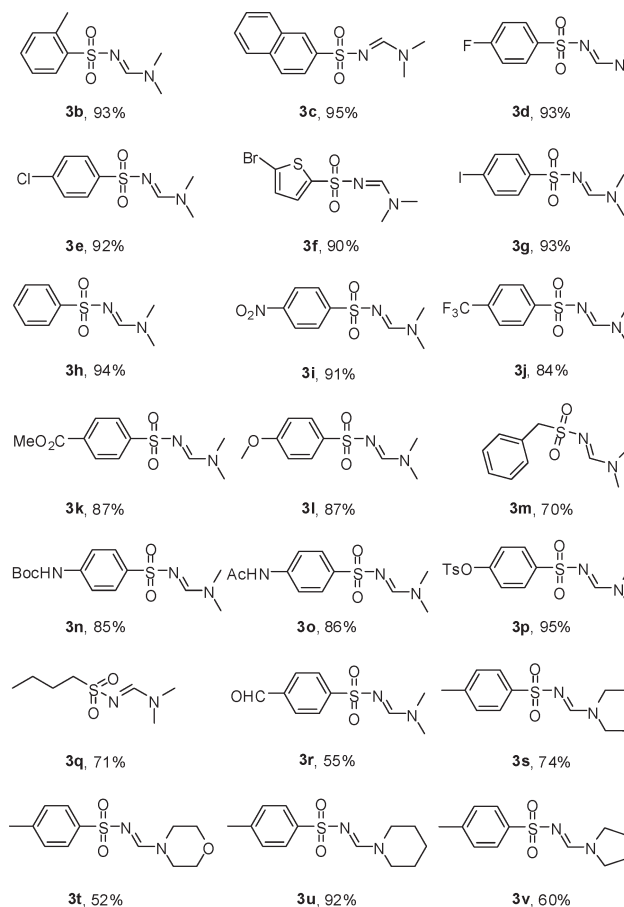
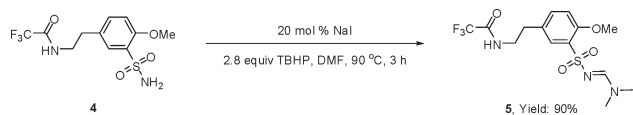


Figure 2. NaI-catalyzed *N*-sulfonylamidines synthesis. Reaction conditions: 0.5 mmol of sulfonamide, 1.4 mmol of TBHP (70% aqueous solution), 20 mol % NaI in 2.0 mL of formamide in 90 °C for 3 h.

(Table 1, entry 18), thus rendering this methodology highly practical. In order to demonstrate further use of

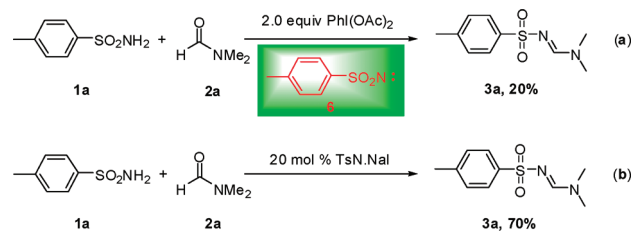
- (14) Englert, H. C.; Gerlach, U.; Goegelein, H.; Hartung, J.; Heitsch, H.; Mania, D.; Scheidler, S. *J. Med. Chem.* **2001**, *44*, 1085.
- (15) For representative examples on in situ generation of nitrene from the reaction of TsNH_2 and $\text{PhI}(\text{OAc})_2$, see: (a) Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726. (b) Evans, D. A.; Faul, M. M.; Bilodeau, M. T. *J. Org. Chem.* **1991**, *56*, 6744. (c) Li, Z.; Conser, K. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1993**, *115*, 5326. (d) Evans, D. A.; Faul, M. M.; Bilodeau, M. T.; Anderson, B. A.; Barnes, D. M. *J. Am. Chem. Soc.* **1993**, *115*, 5328. (e) Li, Z.; Qian, R. W.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1995**, *117*, 5889. (f) Sanders, C. J.; Gillespie, K. M.; Bell, D.; Scott, P. *J. Am. Chem. Soc.* **2000**, *122*, 7132. (g) Yu, X.-Q.; Huang, J.-S.; Zhou, X.-G.; Che C.-M. *Org. Lett.* **2000**, *2*, 2233. (h) Yang, J.; Weinberg, R.; Breslow, R. *Chem. Commun.* **2000**, 531. (i) Gillespie, K. M.; Crust, E. J.; Deeth, R. J.; Scott, P. *Chem. Commun.* **2001**, 785. (j) Espino, C. G.; Du Bois, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 598. (k) Espino, C. G.; Wehn, P. M.; Chow, J.; Du Bois, J. *J. Am. Chem. Soc.* **2001**, *123*, 6935. (l) Diaz-Requejo, M. M.; Belderrain, T. R.; Nicasio, M. C.; Trofimenko, S.; Pérez, P. J. *J. Am. Chem. Soc.* **2003**, *125*, 12078. (m) Dauban, P.; Dodd, R. H. *Synlett* **2003**, 1571. (n) Müller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905. (o) Cui, Y.; He, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 4210. (p) Leung, S. K.-Y.; Tsui, W.-M.; Huang, J. S.; Che, C.-M.; Liang, J.-L.; Zhu, N. *J. Am. Chem. Soc.* **2005**, *127*, 16629. (q) Davies, H. M. L.; Long, M. S. *Angew. Chem., Int. Ed.* **2005**, *44*, 3518. (r) Cho, G. Y.; Bolm, C. *Org. Lett.* **2005**, *7*, 4983. (s) Mohr, F.; Binfield, S. A.; Fettingner, J. C.; Vedernikov, A. N. *J. Org. Chem.* **2005**, *70*, 4833. (t) Mancheño, O. G.; Bolm, C. *Chem.—Eur. J.* **2007**, *13*, 6674. (u) Chang, J. W. W.; Chan, P. W. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 1138.

Scheme 2. Synthetic Application of the Methodology



the methodology, we design a synthetic application for drug discovery. *N*-Sulfonyl formamidine **5** is a precursor to a KATP channel blocker molecule.¹⁴ Under the optimized conditions, **5** was constructed in high 90% yield through direct condensation of sulfonamide **4** and DMF (Scheme 2).

Scheme 3. Investigation on Reaction Mechanism



Further investigation focused on the mechanistic studies of the methodology. When TsNH₂ was treated with PhI(OAc)₂,¹⁵ an in situ generated nitrene **6** was reacted with DMF to provide *N*-sulfonyl formamidine **3a** in low yield (Scheme 3a). Next, TsN·NaI was synthesized¹⁶ and used as a catalyst, and *N*-sulfonylformamidine **3a** was obtained in 70% yield (Scheme 3b). Therefore, we preferred that TsN·NaI, not nitrene **6**, was the reaction intermediate in the transformation.

(16) TsN·NaI was prepared according to ref 9 in the presence of NaOH and iodine.

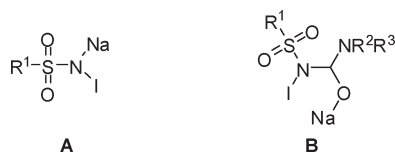


Figure 3. Key intermediates in the transformation.

On the basis of the above experimental studies, we suspected two key intermediates were involved in the transformation as shown in Figure 3. Initially, $R^1SO_2\cdot NaI$ **A** is generated from $R^1SO_2NH_2$ in the presence of NaI and TBHP. Next, the nucleophilic attack of **A** to a formamide forms intermediate **B**. Decomposition of **B** leads to the desired *N*-sulfonyl formamidine.

In summary, we have described an efficient synthetic methodology for C–N bond formation based upon in situ generation of TsN·NaI. This new type of condensation of sulfonamide and formamide for *N*-sulfonyl formamidine is featured by high atom economy, easily available starting materials, the lack of need for a transition-metal catalyst, no requirement of a hazardous reagent, operational simplicity, and good tolerance with diverse functional groups. Further studies on mechanism details and reaction expansion based on TsN·NaI are currently underway in our laboratory.

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Supporting Information Available. Experimental details; ¹H and ¹³C NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.