Synthesis of 1-amino-3-aryl naphthalenes from bis(trifluoromethanesulfonyl)imide with diyne

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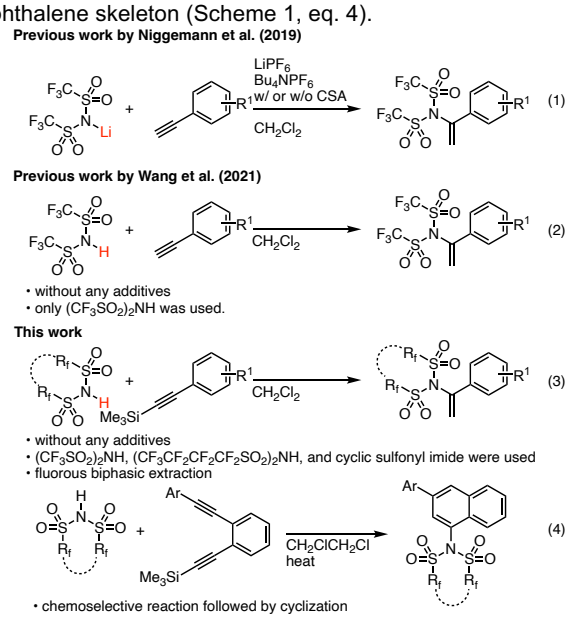
Abstract: Although the synthesis of vinyl triflates has a long history, the synthesis of vinyl bis(perfluoroalkanesulfonyl)imides has not been reported until recently. Herein, we report a simple reaction method that does not require any additives. The stereoselectivity originates from the steric hindrance between the aryl group and the imide. The reaction proceeds chemoselectively, and subsequent acid cyclization provides the 1-amino-3-aryl naphthalene skeleton.

Introduction

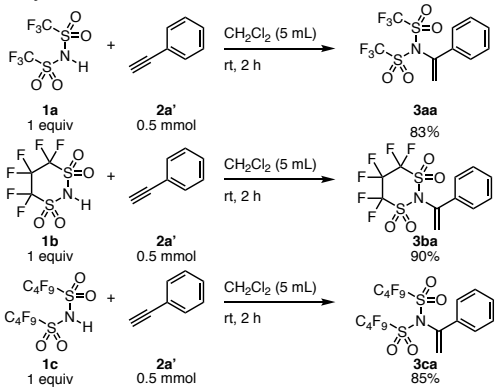
Vinyl cations have a long history as synthetic intermediates.[1–10] The treatment of alkynes with trifluoromethanesulfonic acid (TfOH) is a useful method for the synthesis of vinyl triflates.[1,11–15] Since the pK_a values[16] of sulfonyl imides such as bis(trifluoromethanesulfonyl)imide (Tf_2NH)[17–19] (**1a**) (-11.9 in 1,2-dichloroethane) and 1,1,2,2,3,3-hexafluoropropane-1,3-disulfonimide (*c*-HFSI-H) (**1b**) (-13.1 in 1,2-dichloroethane) comparable to that of TfOH (-11.4 in 1,2-dichloroethane), they have sufficient acidity for reaction with alkynes. Indeed, Tsuchimoto and co-workers reported the hydration of alkynes with Tf_2NH as a catalyst.[20] However, due to their lower nucleophilicity and the non-coordinating nature of their conjugate bases, the synthesis of C(sp^2)-substituted sulfonyl imides has scarcely been reported. For example, in 1993, DesMarteau *et al*. reported the pyrolysis of aryl diazonimides with a sulfone imide counter anion,[21] and Ochiai *et al.* reported substitution reactions of hypervalent bromine compounds, but the oxygen adducts were preferentially obtained.[22] Liégault, Taillefer, and co-workers accomplished the iodine(III)-mediated *para*-selective direct imidation of anilides.[23] Additionally, during our initial study, Niggemann and co-workers reported the synthesis of vinyl triflimides from alkynes and Tf_2NLi in the presence of additives (Scheme 1, eq. 1).[24,25] In their study, the reaction of internal alkynes such as 1-phenyl-1-hexyne gave the corresponding vinyl triflimides with high stereoselectivity. However, in the absence of $LiPF_6$ and Bu_4NPF_6, no product was obtained. They proposed that the stereoselectivity was achieved via a supramolecular framework between the Li cation, H_2O, and the anion Tf_2N. However, we hypothesized that Tf_2NH is initially formed *in situ* from Tf_2NLi and $LiPF_6$ or Bu_4NPF_6, and that Tf_2NH is the real active species. During the preparation of this manuscript, Wang and co-workers reported the same transformation under almost identical conditions (Scheme 1, eq. 2).[26] In the present work, we describe a simple method for accessing vinyl triflimides from alkynes using cyclic sulfonyl imides and Tf_2NH (Scheme 1, eq. 3) from TMS-protected aryl acetylenes. The stereoselectivities toward internal alkynes in our approach are comparable to those of Niggemann's system.[24]Our work also expands the reaction scope beyond the Tf_2N used by Wang et al. to other bis(perfluoroalkanesulfonyl)imides. We reveal that the stereoselectivities toward internal alkynes are caused by steric hindrance between the aryl group and imide.[26] We have also developed a simple purification procedure using a liquid–liquid fluorous–aqueous methanol biphasic extraction. The reaction proceeds with high chemoselectivity for a substrate having both a TMS-protected and an internal alkyne, leading to a 1-amino-naphthalene skeleton (Scheme 1, eq. 4).



Scheme 1. Syntheses of vinyl bis(perfluoroalkanesulfonyl)imides

Results and Discussion

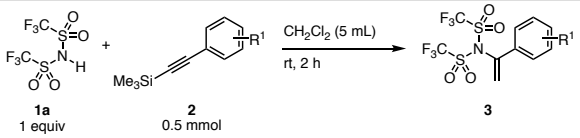
We chose phenylacetylene (**2a′**) as a model substrate for the initial study (Scheme 2). **2a′** was added to a dichloromethane solution of Tf_2NH (**1a**), and the resulting solution was stirred at room temperature for 2 hours. The desired product **3aa** was obtained as the major product, along with a trace amount of acetophenone. The reaction of **2a** with cyclic sulfone imide **1b** or bis(nonafluorobutanesulfonyl)imide (Nf_2NH) **1c** gave the corresponding products **3ba** and **3ca** in 90% and 85% yields, respectively.



Scheme 2. Imidation of ethylbenzene (2a′)

Next, we surveyed the substrate scope (Table 1). The Sonogashira coupling reaction is a common method for the synthesis of terminal alkynes. Since the direct use of acetylene leads to the formation of diarylalkynes, TMS acetylene is often used. To achieve step economy, TMS-protected alkynes were used in this study. The reaction of TMS-protected aryl alkynes **2b**–**2e** with an electron-donating group on the benzene ring produced the corresponding vinyl sulfonyl imides **3ab**, **3ac**, **3ad,** and **3ae** in good yields (entries 1–4). The reaction of ethyl 4-((trimethylsilyl)ethynyl)benzoate (**2f**) gave a lower yield due to the poorer stabilization of the vinyl cation by the ester group (entry 5). Increasing the amount of **1a** improved the yield (entry 6). Substrates **2g**–**2j** with a halogen atom on the benzene ring afforded the corresponding vinyl sulfonyl imides **3ag**–**3aj** in 78%, 79%, 83%, and 63% yield, respectively (entries 7–10).

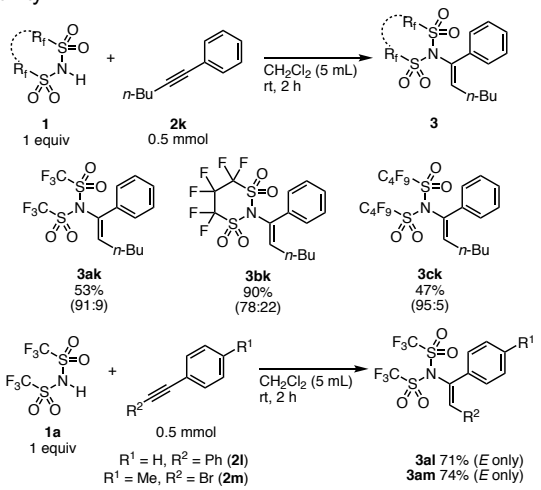
Table 1. Substrate Scope



Entry	2 (R^1)	3	yield [b]
1	4-Me (**2b**)	**3ab**	86%
2	4-*t*-Bu (**2c**)	**3ac**	89%
3	4-Ph (**2d**)	**3ad**	83%
4	4-OMe (**2e**)	**3ae**	83%
5	4-CO_2Et (**2f**)	**3af**	28% [c]
6[d]	4-CO_2Et (**2f**)	**3af**	67%
7[e]	4-F (**2g**)	**3ag**	78%
8	4-Cl (**2h**)	**3ah**	79%
9	4-Br (**2i**)	**3ai**	83%
10	4-I (**2j**)	**3aj**	63%

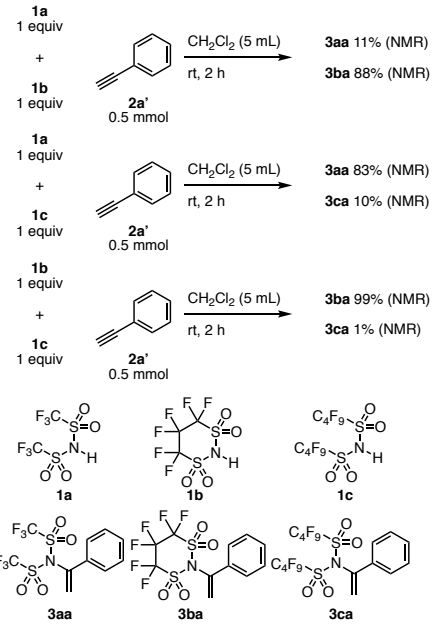
[a] **1a** (1 equiv), **2** (0.5 mmol), CH_2Cl_2 (5 mL), rt, 2 mL. [b] Yield of the product isolated after flash column chromatography on SiO_2. [c] Determined by ^1H NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard. [d] **1a** (1.5 equiv), 16 h. [e] Terminal alkyne **2g′** was used instead of TMS-protected alkyne **2g**.

We then tested the stereoselectivity using internal alkyne **2k** with Tf_2NH **1a**, cyclic sulfonyl imide **1b**, and bis(nonafluorobutanesulfonyl)imide (Nf_2NH, **1c**) (**Scheme 3**). The reaction of **1k** with **2a** gave the corresponding vinyl triflimide **3ka** in 66% yield with 91% selectivity toward the *E* isomer. This selectivity is in close agreement with the value reported by Niggemann et al.[24] The stereoselectivity decreased for the less sterically hindered cyclic sulfonyl imide **2b**. These results suggest that the selectivity does not originate from a supramolecular framework, but instead comes from the steric hindrance of the nucleophile. The reaction using **2c** exhibited higher stereoselectivity, but a low yield. The reactions of diphenyl acetylene (**1l**) and bromoalkyne **1m** with Tf_2NH gave the corresponding imides **3al** and **3am** in good yields with perfect selectivity.[25]



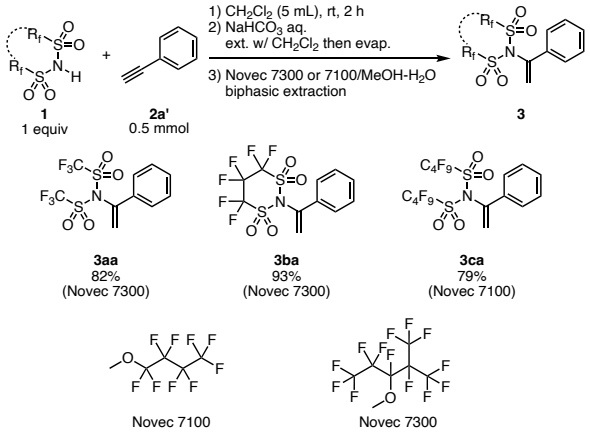
Scheme 3. Stereoselectivity of internal alkynes

Next, we carried out competition reactions to examine the differences in the reactivities of 1a–1c (Scheme 4). Due to the steric hindrance of the sulfonyl imide **1b**, the vinyl cyclic sulfonyl imide **3ba** was obtained as the major product in these reactions.



Scheme 4. Competition reactions

Since the percentage of fluorine atoms in **3aa** is relatively high, we tested the use of aqueous–fluorous biphasic extraction for its isolation (Scheme 5).[27] We found that the combination of Novec-7100 or 7300 with aqueous methanol provided a suitable solvent system. After biphasic extraction, the desired product was obtained in 82% yield. The reactions of cyclic imide **1b** and Nf_2NH (**1c**) gave the corresponding products **3ba** and **3ca** in 93% and 79% yields after biphasic extraction, respectively.



Scheme 5. Aqueous–fluorous biphasic extraction

To obtain mechanistic insight, we carried out DFT calculations using Tf_2NH (**1a**) and 1-phenylpropyne (**2o**) as the bis(sulfonic) imide and alkyne, respectively, at the BHandHLYP/6-311+G(d,p), M06-2X/6-31G(d,p), and M06-2X/6-311+G(d,p) levels of theory and considering the solvent effect. Selected optimized geometries of the complexes and transition states involved in the addition are summarized in Table S1 in the ESI,† and the calculated complexation energies and energy barriers are listed in Table S2 in the ESI.† The reaction profile of the addition of **1a** to **2o** was calculated at the M06-2X/6-311+G(d,p) level with CH_2Cl_2 solvent effects, and is shown in Fig. 1. The addition was not predicted to proceed through a concerted pathway, but instead via two steps: proton transfer from **1a** to **2o**, followed by trapping of the resulting $Tf2N^-$ anion by the vinyl cation generated from **2o**. Substrate complex **A** (formed by the interaction between **1a** and **2o**) was predicted to exist at the reactant side of transition state **B** on the potential energy surface of the reaction. The proton transfer was predicted to be endothermic, and the activation energy of the process was calculated to be 81.5 kJ mol^{-1}. Unsurprisingly, neither transition states nor intermediates were located for the ion trapping step from transition state **B** to product **C**, and a highly exothermic reaction energy of 157.2 kJ mol^{-1} was predicted. Although no transition states were found, the NTf_2 anion would avoid the bulky methyl group in its approach to the vinyl cation, affording *E*-product **C** exclusively.

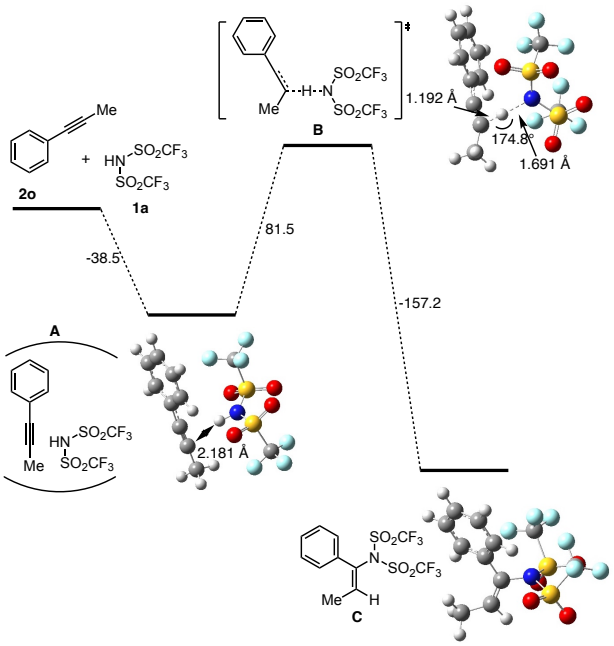
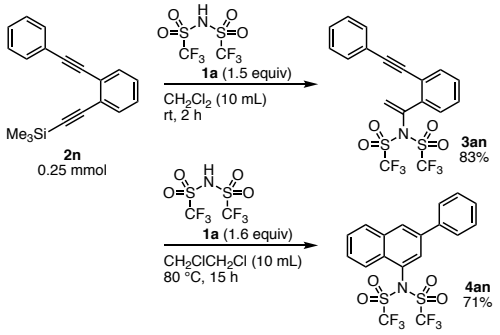
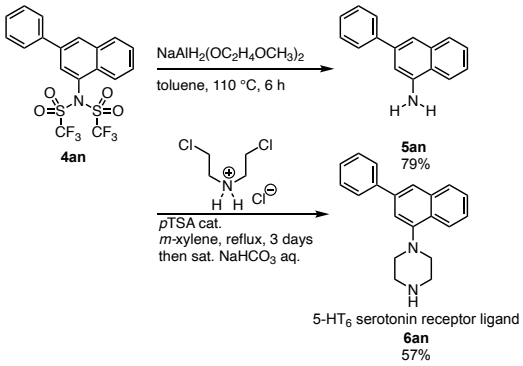


Fig. 1 Reaction profile for the addition of Tf_2NH (1a) to 1-phenylpropyne (2o). Energies (in kJ mol^{-1}) were calculated at the M06-2X/6-311+G(d,p) level of theory with CH_2Cl_2 solvent effects using the PCM method.

We then examined the chemoselectivity with regard to the alkyne moieties in diyne **2n** (**Scheme 6**). A substrate having both TMS-protected and internal alkynes gave the mono-imidation product **2n** in 83% yield. **3an** was easily converted to the naphthalene skeleton **4an** under thermal conditions with acid.

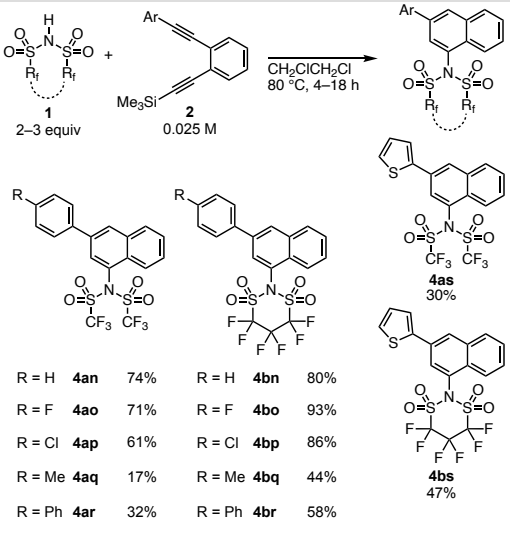




Scheme 6. Chemoselective reaction followed by cyclization

Next, we conducted one-pot syntheses of the naphthalene skeletons (Table 2). The reactions of Tf_2NH (**1a**) and cyclic sulfonyl imide **1b** with alkyne **2n** gave the corresponding naphthalene products **4an** and **4bn** in 74% and 80% yield, respectively. Substrates with a halogen atom produced the respective products **4ao**, **4ap**, **4bo**, and **4bp** in good yields. However, substrates featuring an electron-donating group (*p*-tolyl, *p*-biphenyl, and 2-thienyl) provided the products **4aq**, **4ar**, and **4as** in low yields, due to the formation of 1-chloro-3-arylnaphthalene.[28] Conducting the reactions using cyclic sulfonyl imide **1b** improved the yields.

Table 2. One-pot synthesis of naphthalene skeletons



Next, we demonstrated the synthesis of a bioactive compound from **4an**. The two trifluoromethanesulfonyl groups were removed from **4an** using $NaAlH_2(OC_2H_4OCH_3)_2$[29] to give 1-napthyl amine **5an**, which was then converted to pyridine **6an**, which is a 5-HT_6 serotonin receptor ligand.[30]

Conclusion

In conclusion, we have developed a simple and efficient procedure for the synthesis of vinyl perfluoroalkanesulfonic imides. The reaction proceeds with high stereoselectivity and chemoselectivity. A substrate having both a terminal and an internal alkyne gave the mono-imidation product, which is easily converted to a naphthalene skeleton. The obtained compounds can be easily converted into biologically active compounds. Further molecular transformation reactions are currently under investigation and will be reported in due course.

Supporting Information ((optional))

The authors have cited additional references within the Supporting Information.[[31,32]]

Acknowledgements

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Keywords: strong acids • sulfonylimidation • cyclization • naphthalene • chemoselective reaction

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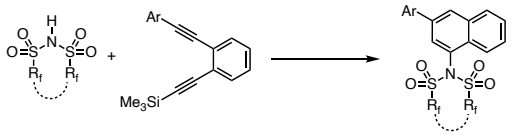

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