Acids

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Synthesis, Characterization, and Applications of Zwitterions Containing a Carbanion Moiety**

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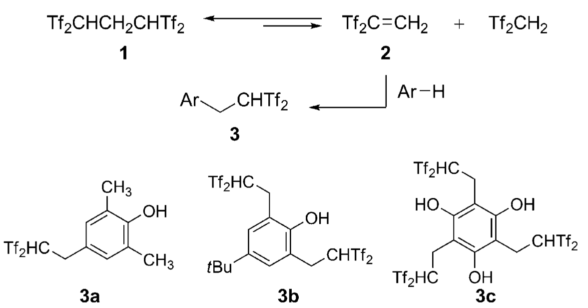
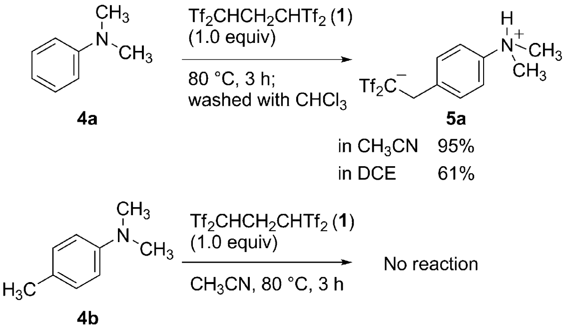
Carbon acids, which have active hydrogen atoms on carbon centers, hold a unique position among organic acids. Since the C–H bond is so nearly homopolar, the dissociation of the C–H bond is less facile than those of O–H and N–H bonds. Therefore, stabilization of the carbanions, which are the conjugate bases, facilitates the ionization of the carbon acids. For example, the bis(triflyl)methyl (Tf_2CH; $Tf = CF_3SO_2$) group is known to be acidic because of *gem*-disubstitution of the carbon atom with two triflyl groups. This type of carbon acid shows notably strong acidity both in the gas[1] and solution phase.[2] For example, the pK_a value of Tf_2CH_2 in DMSO has been measured as 2.1, and this value means that Tf_2CH_2 is a stronger proton donor relative to trifluoroacetic acid (pK_a in DMSO = 3.45). Recently, we developed a methodology to introduce the Tf_2CH group to an arene framework using $Tf_2CHCH_2CHTf_2$ (**1**; Scheme 1).[3] That is, the reaction of electronically rich arenes such as phenols and aryl ethers with highly electrophilic $Tf_2C{=}CH_2$ (**2**), which is generated by the retro-Michael reaction of **1**,[4] results in introduction of 2,2-bis(triflyl)ethyl groups to the benzene ring. As shown in previous work by Yamamoto and co-workers[5] and our group,[6] Tf_2CH-substituted compounds show excellent catalyst activity compared to that of usual organic acids such as TfOH and Tf_2NH. Therefore, our synthetic methodology realized a convenient and practical synthesis of highly active carbon acid catalysts. Herein, we describe the reaction of anilines with **1**. On the basis of this reaction, acidic zwitterions containing a carbanion moiety and an ammonium moiety were successfully obtained. Furthermore, detailed structural studies of the zwitterions and their applications are demonstrated.



Scheme 1. In situ generation of $Tf_2C{=}CH_2$ (**2**).

Considering our previous work,[3] we initially carried out the reaction of *N*,*N*-dimethylaniline (**4a**) with $Tf_2CHCH_2CHTf_2$ (**1**) in various solvents (Scheme 2). By treating **4a** with an equimolar amount of **1** in acetonitrile for 3 hours at 80 °C, the desired product **5a** was quantitatively formed as a white precipitate in the reaction mixture. Pure **5a** was obtained in 95 % yield by washing these precipitates with chloroform. When the reaction was conducted in 1,2-dichloroethane (DCE) under similar reaction conditions, the reaction did not go to completion within 3 hours, but did give **5a** in 61 % yield. Unfortunately, when 4-methyl-substituted *N*,*N*-dimethylaniline (**4b**) was treated with an equimolar amount of **1** in acetonitrile the desired *ortho*-substituted product was not formed.



Scheme 2. Reactions of *N*,*N*-dimethylanilines with $Tf_2CHCH_2CHTf_2$ (**1**).

The zwitterionic structure of **5a** was confirmed by its NMR spectra in both [D_6]acetone and [D_3]acetonitrile solutions. That is, in the ^1H NMR spectrum of the [D_6]acetone solution, the signal for the two hydrogen atoms on the benzylic carbon center were observed as a singlet at $\delta = 3.75$ ppm, and any signals for hydrogen atoms on a methine carbon center were not observed. Simultaneously, a hydrogen on the ammonium nitrogen atom was observed as a broad signal at $\delta = 10.4$ ppm. In addition, in the ^{13}C NMR spectrum

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of **5a** in [D$_6$]acetone, a signal for the anionic carbon atom was observed at $\delta = 65.9$ ppm. Since the methine carbon atom of **3a**, derived from 2,6-dimethylphenol, was observed at $\delta = 81.0$ ppm in [D$_6$]acetone (Scheme 1), the large upfield shift of the methine carbon atom of **5a** also supported its anionic nature. A similar observation was evident in the ^{1}H and ^{13}C NMR spectra of **5a** in [D$_3$]acetonitrile (see the Supporting Information).

Furthermore, X-ray crystallographic analysis of **5a** successfully demonstrated its zwitterionic structure in the solid phase (Figure 1). The important structural details of **5a** are listed in Table 1. Although the hydrogen atom could not be located with the same degree of accuracy as the heavier atoms, it fully supported the sp^2-hybridized nature of anionic C1 because the bond angles around C1 are 120.5° (C2-C1-S1), 120.3° (S1-C1-S2), and 119.2° (S2-C1-C2). At the same time, the bond angles around cationic N1 (114.3° for C6-N1-C9, 110.3° for C9-N1-C10, and 110.4° for C10-N1-C6) suggested a tetrahedral structure. It should be noted that the hydrogen atom on N1 is found from crystallographic data. In addition, the bond lengths of C1-S1 (166.6 pm) and C1-S2 (167.2 pm) were significantly shorter than those of S1-C12 (184.2 pm) and S2-C11 (185.0 pm).[7] This observation can be explained by negative hyperconjugation[8] between the lone electron pair (on C1) which occupies a p orbital (n_{C1}) and σ* orbitals of S1-C12 and S2-C11. These $n_{\mathrm{C1}}/\sigma^*_{\mathrm{S1\text{-}C12}}$ and $n_{\mathrm{C1}}/\sigma^*_{\mathrm{S2\text{-}C11}}$ interactions were also supported by the torsion angles of C2-C1-S1-C12 (−83.5°) and C2-C1-S2-C11 (−98.2°). In contrast, the S=O bond lengths of neurtal sulfones are typically, 143.6 pm, thus the somewhat longer S=O bonds indicate weak delocalization of n_{C1} into sulfonyl oxygen atoms. Interestingly, the planar nature of C1 brings about the chirality in the molecular structure of **5a** in the solid state.[9] This crystal structure was also constructed by a unit cell including a pair of heterochiral two molecules of **5a** ($Z = 4$). To the best of our knowledge, the present crystallographic analysis is the first example of such zwitterions containing a carbanion moiety.

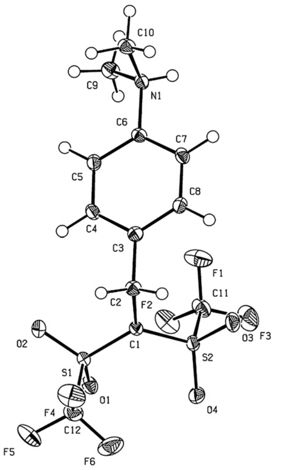
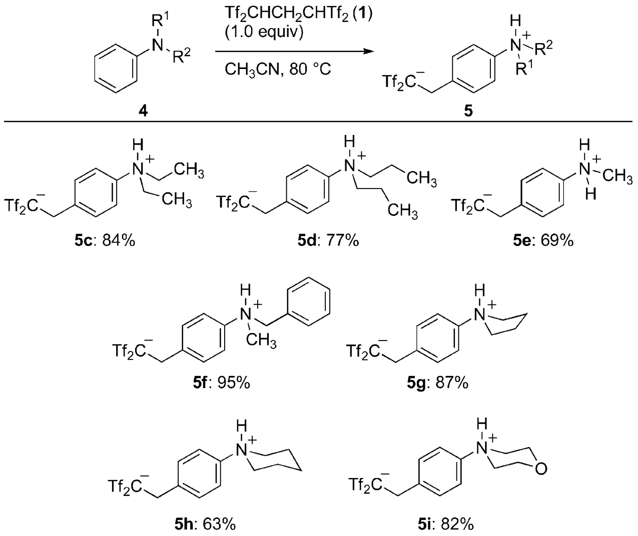


Figure 1. ORTEP drawing of **5a**. The thermal ellipsoids are shown at 50% probability.[16]

Table 1: Selected interatomic distances and angles in **5a**.

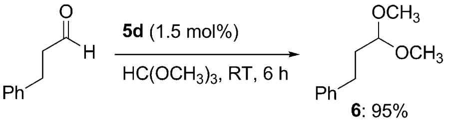
Lengths [pm]		Angles [°]		Torsions [°]	
C1-S1	166.6	C2-C1-S1	120.5	C2-C1-S1-C12	−83.5
C1-S2	167.2	S1-C1-S2	120.3	C2-C1-S2-C11	−98.2
C1-C2	152.8	S2-C1-C2	119.2	C3-C2-C1-S1	−103.5
S1-C12	184.2	C6-N1-C9	114.3	C3-C2-C1-S2	79.9
S1-O1	144.1	C9-N1-C10	110.3	C4-C3-C2-C1	75.9
S1-O2	144.0	C10-N1-C6	110.4	C8-C3-C2-C1	−103.6
S2-C11	185.0			C5-C6-N1-C9	−35.9
S2-O3	143.8			C5-C6-N1-C10	89.2
S2-O4	144.4				
N1-C6	148.3				
N1-C9	149.7				
N1-C10	150.4				

Next, we carried out the reaction of several anilines with **1** in acetonitrile (Scheme 3). Under similar reaction conditions, *N*,*N*-diethyl- and *N*,*N*-dipropyl-substituted anilines were converted into the zwitterions **5c** and **5d**, respectively, in good yields. Although this reaction can be applied to aniline itself, the desired product was obtained in an impure form. In contrast, the reaction of the secondary aniline **4e** gave the pure product **5e** in 69% yield. We also found that several *N*,*N*-disubstituted anilines form the corresponding zwitterions in good to excellent yields. For example, the substitution reaction of *N*-benzyl-*N*-methylaniline (**4f**) selectively proceeded at the electronically rich benzene ring to give the zwitterion **5f** in 95% yield. Likewise, the reactions of *N*-phenylpyrolidine (**4g**), *N*-phenylpiperidine (**4h**), and *N*-phenylmorpholine (**4i**), led to the isolation of the corresponding zwitterions **5g**–**i**.

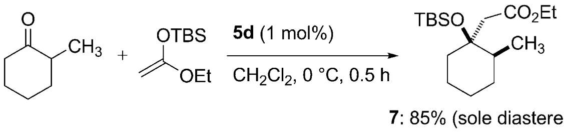


Scheme 3. Preperation of the zwitterions **5**, which contain a carbanion moiety.

The synthesized zwitterions showed somewhat weaker Brønsted acidity compared to those of phenol-based carbon acids such as **3**. The pK_a value of **3a** in DMSO has been reported as 2.3[3] and that of zwitterion **5a**, derived from *N*,*N*-dimethylaniline, was 2.4.[10] This fact suggests that the synthesized zwitterions make up a novel class of Brønsted acid catalysts.[11] For instance, in the presence of catalytic amount of the zwitterion **5d**,[12] the acetal-forming reaction of phenylpropionaldehyde with trimethyl orthoformate, which is a typical reaction catalyzed by Brønsted acids, proceeded to give the dimethyl acetal **6** in 95% yield [Eq. (1)]. In the diastereoselective Mukaiyama aldol reaction of 2-methylcyclohexanone, only 1 mol% of **5d** was enough to complete this reaction and the aldol product **7** was obtained in 85% yield in a highly diastereoselective manner [Eq. (2); TBS = *tert*-butyldimethylsilyl]. Furthermore, the present zwitterion catalysis was applied to the olefination reaction of lactone substrates, which was recently developed by our group.[6a] The reaction of isochroman-1-one required the use of at least 2 mol% of **3c** (with three acidic carbon centers) for the complete consumption of starting lactone.[13] In contrast, the same reaction gave the *Z*-vinyl ether **8** in 79% yield by using only 1 mol% of the zwitterion **5d** instead of **3c** [Eq. (3)]. This result suggests that **5d** shows higher catalyst activity than **3c**, which bears three Tf$_2$CH groups in the molecular structure. In addition, it should be noted that, in contrast to deliquescent nature of pyridinium *p*-toluenesulfonate,[11a] the zwitterions including **5d** did not deliquesce when open to air.



(1)



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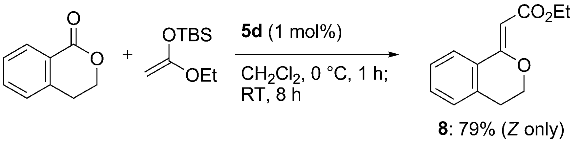
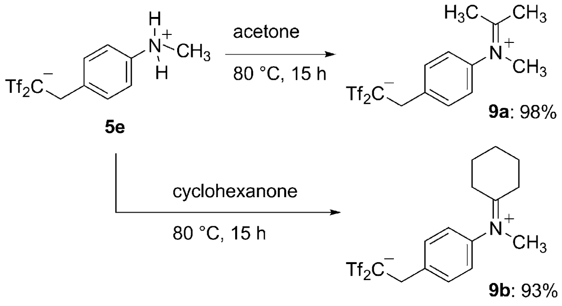


(3)

As another application for the zwitterions, we also explored an utility of the bis(triflyl)ethanide (Tf$_2$C$^-$CH$_2$R) functionality as a stabilizing substituent for unstable ammonium species. It is well known that iminium species derived from ketones containing α-hydrogen atoms and secondary amines are usually unstable and they are rapidly converted into the corresponding enamines by tautomerizm.[14] In contrast, we found that by stirring a solution of the zwitterion **5e** in acetone at 80 °C, the intramolecular iminium salt **9a** was formed in 98% yield (Scheme 4). Likewise, the reaction with cyclohexanone afforded the corresponding iminium **9b** in 93% yield.

The structure of **9a** was also confirmed by an X-ray crystallographic analysis of a sample recrystallized from acetone (Figure 2). The notably short length of the N1-C10 bond (125.4 pm) and acceptable lengths of the C10-C11 and C10-C12 single bonds (151.8 pm and 146.2 pm, respectively) support the present iminium structure. Since torsion angles for C7-C6-N1-C10 (−95.7°) and of C5-C6-N1-C10 (85.1°) suggest an orthogonal relationship for the C=N π plane and the benzene plane, the resonance between the iminium moiety and benzene moiety would not be a major factor for the stabilization. That is, ionic bond between the iminium and carbanion, in an intermolecular manner, as well as the significantly low basicity of the carbanion should play crucial roles for stabilizing this iminium species.



Scheme 4. Synthesis of the stabilized iminium **9**.

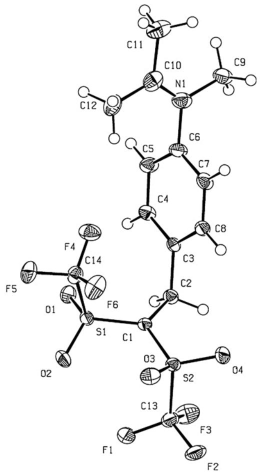


Figure 2. ORTEP drawing of **9a**. The thermal ellipsoids are shown at 50% probability.[16]

In summary, we found that the reaction of *N*-alkylated anilines with Tf$_2$CHCH$_2$CHTf$_2$ (**1**) gives the corresponding bis(triflyl)ethylated products in a *para*-selective manner. The obtained products form a unique zwitterion structure in both the solution and solid phase. There are few studies of compounds containing the bis(triflyl)alkanide functionality,[15] but detailed structural studies have not been reported. The X-ray crystallographic studies of **5a** and **9a** discussed herein provide useful knowledge on the structure and behavior of the compounds. The Brønsted acidity of these zwitterions was also sufficient to permit their use as organic acid catalysts. For instance, the zwitterion **5d** nicely catalyzed some acid-catalyzed reactions, including an acetal-forming reaction and a Mukaiyama-aldol-type reaction. In addition, since the zwitterions are not deliquescent, they are a novel and easy-to-use acid catalyst. Furthermore, the reaction of the zwitterion **5e**, derived from *N*-methylaniline, with ketones containing α-hydrogen atoms gave stable zwitterionic iminium products. This result suggests that the bis(triflyl)alkanide functionality can be used as a stabilizing group for usually unstable cationic species. Further studies on this chemistry are progressing in our laboratory.

Experimental Section

Preparation of 2-(4-(dimethylammonio)phenyl)-1,1-bis((trifluoromethyl)-sulfonyl)ethan-1-ide (**5a**): *N*,*N*-dimethylaniline (**4a**; 45.0 μL, 0.36 mmol) was added to a solution of $Tf_2CHCH_2CHTf_2$ (**1**; 203 mg, 0.36 mmol) in acetonitrile (0.4 mL) at room temperature. After being stirred at 80 °C for 3 h, the resultant precipitates were collected, washed with CH_2Cl_2 (ca. 5 mL), and dried under reduced pressure to give the zwitterion **5a** in 95 % yield (140 mg, 0.34 mmol). The structure of this compound was also confirmed by an X-ray crystallographic analysis. Colorless crystals (acetone); Mp. 195–197 °C (dec.); IR (ATR): $\tilde{\nu}$ =3146, 3091, 1516, 1335, 1325, 1178, 1107, 587 cm^{-1}; ^1H NMR (400 MHz) in [D$_6$]acetone: $\delta = 3.57$ (6 H, s), 3.75 (2 H, s), 7.61 (2 H, d, $J = 8.7$ Hz), 7.66 (2 H, d, $J = 8.7$ Hz), 10.4 ppm (1 H, br, N*H*); in CD_3CN: $\delta = 3.20$ (6 H, s), 3.73 (2 H, s), 7.44 (2 H, d, $J = 8.7$ Hz), 7.58 (2 H, d, $J = 8.7$ Hz), 8.82 ppm (1 H, br, N*H*); ^{13}C NMR (100 MHz) in [D$_6$]acetone: $\delta = 34.0$, 48.1, 65,9 120.6, 122.5 (q, $J_{C\text{-}F} = 329.2$ Hz), 131,3, 141.2, 146.7 ppm; in CD_3CN: $\delta = 33.8$, 48.0, 65.6, 120.8, 122.4 (q, $J_{C\text{-}F} = 327.9$ Hz), 131.3, 140.9, 146.5 ppm; ^{19}F NMR (376 MHz, [D$_6$]acetone): $\delta = -16.7$ ppm (6 F, s); MS (ESI-TOF) *m*/*z* 414 $[M+H]^+$; HRMS calcd for $C_{12}H_{14}F_6NO_4S_2$ $[M+H]^+$, 414.0268; found, 414.0255.

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Keywords: aldol reaction · carbanions · homogeneous catalysis · synthetic methodology · zwitterions

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[12] The dipropyl derivative **5d** was adopted as a suitable acid catalyst because of its better solubility in chlorinated hydrocarbon solvents.

[13] In this reaction, it was also found that the carbon acid **3c** shows the higher catalyst activity compared to $Tf_2CHCH_2CHTf_2$ (**1**), $Tf_2CHC_6F_5$, Tf_2NH, and TfOH. See Ref. [6a].

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[16] CCDC 908758 (**5a**) and CCDC 908763 (**9a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.