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2-Trimethylsilylethanesulfonyl (SES) versus Tosyl (Ts) Protecting Group in the Preparation of Nitrogen-Containing Five-Membered Rings. A Novel Route for the Synthesis of Substituted Pyrrolines and Pyrrolidines

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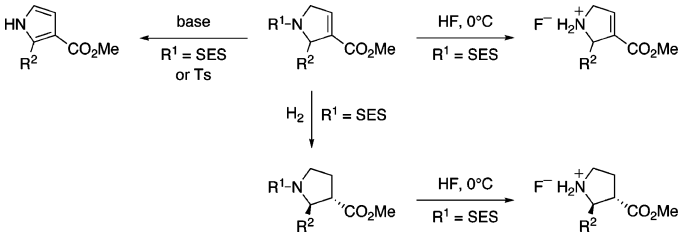
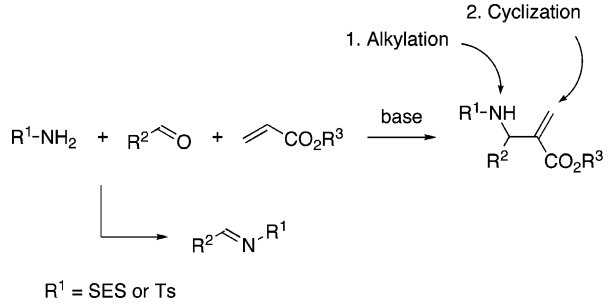


The 2-trimethylsilylethanesulfonyl (or SES) protecting group was compared to the tosyl (Ts) group in the preparation of a nitrogen-containing five-membered ring obtained by the aza-Baylis−Hillman/alkylation/RCM route. While deprotection of Ts-protected pyrrolines gave only pyrroles, deprotection of the same SES-protected compounds gave either pyrroles or free amine pyrrolines depending on the deprotection conditions. The SES-protected pyrrolines were hydrogenated to yield pyrrolidines with an excellent diastereoselectivity. Free amine pyrrolidines were obtained by HF-mediated deprotection of the SES group.

The three component aza-Baylis−Hillman reaction[1−9] is a powerful method for the preparation of useful synthons in organic synthesis. The reaction between protected ammonia, an aldehyde, and an acrylate derivative yields highly functionalized α-methylene *β*-aminoesters which can be used in further transformations (Scheme 1).

SCHEME 1



One intermediate involved in the reaction is an imine derivative arising from the reaction of protected ammonia with the aldehyde. The best results are obtained when the protecting group is a sulfonyl group which activates ammonia as a sulfonamide. The newly formed sulfonamide can be easily alkylated using a mild base or a Mitsunobu reaction. Further transformations can provide an efficient access to heterocyclic compounds.

The tosyl (Ts) group is a protecting sulfonyl group, widely used for the preparation of heterocycles. One major drawback of this protecting group is the difficulty of cleavage at the end of the synthesis to release a free amine. Many examples in the area of heterocyclic chemistry do not provide methods for the deprotection step[10] unless an oxidative elimination is possible usually leading to an aromatic compound.[11] Recently, we have investigated the use of the 2-trimethylsilylethanesulfonyl (or SES) group[12,13] as an alternate to the Ts group in the aza-Baylis−Hillman reaction and for the further preparation of heterocycles.[8] We report herein that, in contrast to the Ts group, the cleavage of the SES group in five-membered cyclic compounds can be tuned to provide either an aromatic heterocycle by oxidative elimination or a free-amino deprotected compound. The first examples of free amine pyrrolines and pyrrolidines obtained by the aza-Baylis−Hillman/ring closing metathesis (RCM) route are presented.

Ts- and SES-protected *β*-aminoesters, **1a** and **1b**, respectively, were prepared according to previously described methods[4,8] (Scheme 2). Both of the aminoesters were allylated using allyl bromide in the presence of potassium carbonate to yield dienes **2a** and **2b**, respectively, in quantitative yield.[8,14] Both dienes

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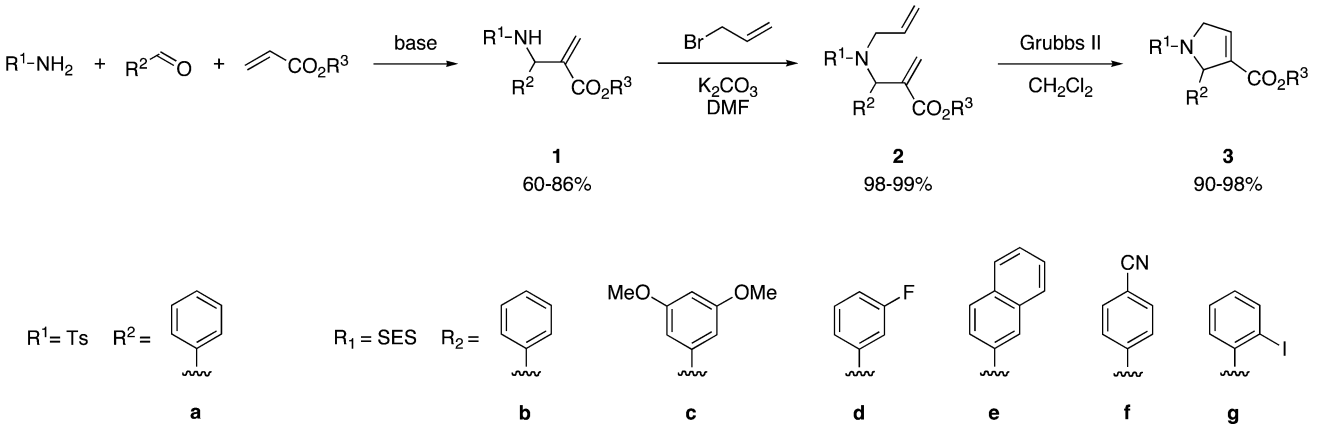
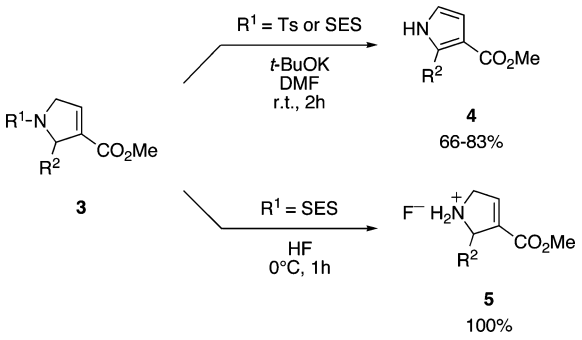
SCHEME 2



SCHEME 3



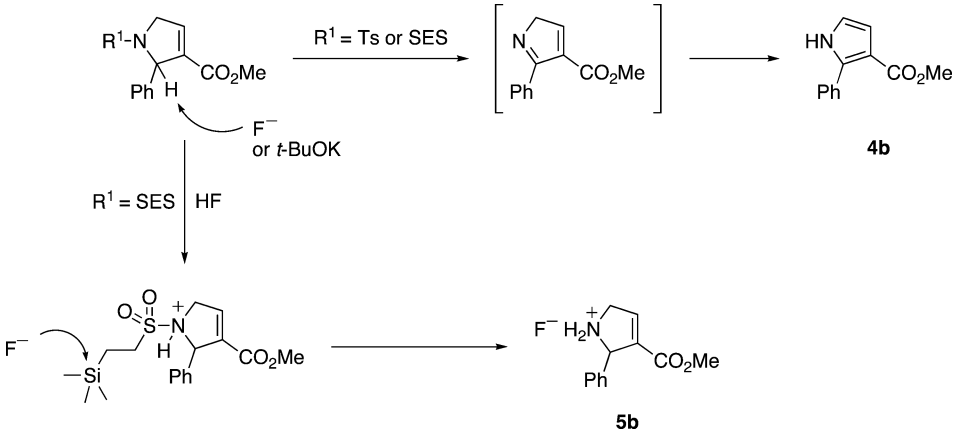
were subjected to ring closing metathesis using the second generation Grubbs' catalyst to provide pyrrolines **3a** and **3b** in a very good yield.

We have explored the deprotection step for both compounds **3a** and **3b** (Scheme 3). SES-protected pyrroline **3b** was easily deprotected by dehydrodesulfinylation/aromatization to yield the corresponding pyrrole **4**. This deprotection was performed with *t*-BuOK in DMF. Under the same conditions, Ts-protected pyrroline **3a** gave the same product in a similar yield. It has to be noted that preparation of pyrrole **4** starting from **3a** and **3b** has been previously reported, but in these cases, the fluoride-mediated oxidative elimination gave lower yields.[11]

Then we investigated other fluoride sources which should give the free amino compound rather than the pyrrole **4**, starting from **3b**. The SES protecting group is usually removed in the presence of fluoride ions to provide the deprotected molecule by elimination of SO_2 and ethylene.[13] In some cases, harsh conditions are needed to achieve deprotection, and the oxidative elimination can be a competitive process.[8,11,15,16] When **3b** was reacted with a variety of fluoride sources in THF or DMF (CsF, *n*-Bu_4NF (TBAF), *n*-$Bu_4NSiF_2Ph_3$ (TBAT), $((CH_3)_2N)_3S((CH_3)_3SiF_2)$ (TASF)), only pyrrole **4** was obtained, albeit in lower yield than in the case of the base-promoted deprotection. The presence of the unprotected pyrroline could not be detected. Finally, **3b** was reacted with neat hydrofluoric acid.[17] (Caution: HF is an extremely dangerous and toxic chemical). In this case, pyrroline **3b** was completely deprotected to give the pyrroline **5b** as an hydrofluoride salt, with no traces of pyrrole **4**. As a comparison, Ts-protected **3a** was reacted with HF. Neither trace of the pyrrole nor trace of the pyrroline could be detected; the starting material was completely recovered. Other HF-based reagents such as HF·pyridine and HF in H_2O were tried to deprotect **3b**, but no reaction occurred.

As described in Scheme 4, the two deprotection pathways are conceivable. In the first one, performed with a base or a fluoride salt with either the Ts or SES protecting group, the acidic proton, in the α position to the phenyl ring, was abstracted. Elimination followed by aromatization yielded the pyrrole. Alternatively, in the case of the SES group, reaction with HF resulted first in the protonation of the nitrogen atom,[18] which prevented proton abstraction in the α position to nitrogen. The attack of the fluoride anion on the trimethylsilyl group triggered the elimination of the SES group to release the

SCHEME 4



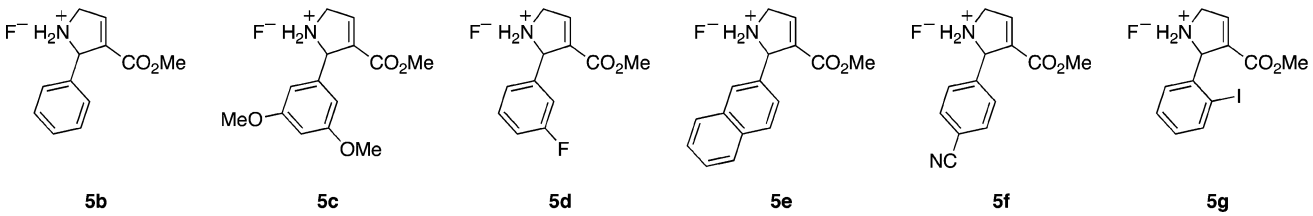


FIGURE 1. Examples of free amine pyrrolines.

TABLE 1. Yields of 3, 5, 6, and 7

SES pyrrolines **3**	pyrrolines **5** yield (%)	SES pyrrolidines **6** yield (%)	SES pyrrolidines **6** *trans*/*cis*	pyrrolidines **7** yield (%)
b	100	99	99:1	100
c	100	99	95:5	100
d	100	99	99:1	100
e	100	99	91:9	100
f	100	100	91:9	100
g	100	*a*		*b*

[a] Hydrogenation resulted in the formation of a mixture of **6g** and **6b** in a 9/1 ratio. [b] Not performed.

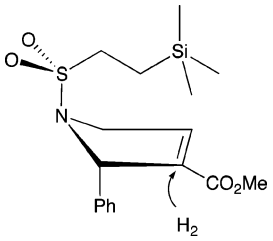
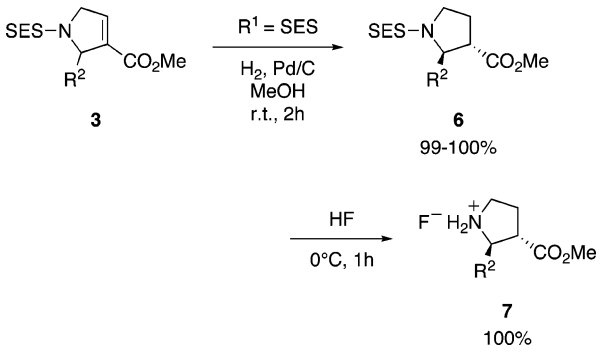


FIGURE 2. Hydrogen attack from the bottom face of **3b**.

SCHEME 5



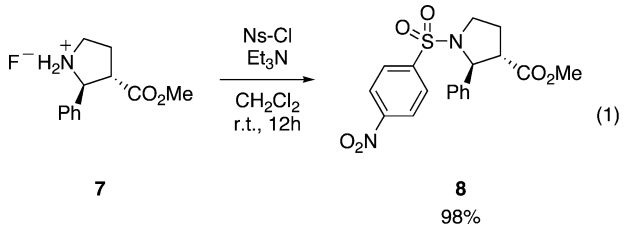
pyrroline. This elimination was all the more facilitated since the protonated nitrogen was electron deficient. In this reaction, the methyl ester was not hydrolyzed.

The deprotection procedure was applied to various SES-protected pyrrolines **3b**−**g** to give **5b**−**g** (Figure 1) in quantitative yields (Table 1).

To further enlarge the scope of this strategy, we decided to reduce the SES-protected pyrrolines **3b**−**g** to pyrrolidines and investigate the deprotection step of the SES group (Scheme 5).

Pyrroline **3b** (R^2 = Ph) was hydrogenated using H_2 in the presence of Pd/C to give the SES-protected pyrrolidine **6b** in a quantitative yield. Deprotection of **6b** with neat HF yielded quantitatively the pyrrolidine **7b**. Deprotection with other fluoride salts did not provide any tractable substance.

6b and **7b** were obtained as only one diastereoisomer, and their relative stereochemistry was deduced from X-ray analysis of a crystalline derivative obtained by reaction of **7b** with 4-nitrobenzenesulfonylchloride in the presence of triethylamine to give the Ns-pyrrolidine **8** (eq 1). X-ray analysis of compound **8** shows that the substituents are in a *trans* position relative to each other. The deprotection conditions were not tested on the Ns-protected pyrrolidine **8**.



In contrast to reported results obtained with a similar five-membered ring carbocycle,[19] hydrogenation did not occur opposite to the phenyl ring, which would lead to the formation of the *cis* isomer. In the case of the pyrroline, most probably for steric reasons, the SES group is hindering the face of the cyclic structure opposite to the phenyl moiety. Consequently, hydrogen will react on the olefin from the same side as the phenyl ring. This will result in a *trans* relationship between the phenyl and the methoxycarbonyl substituents, as shown in Figure 2.

An alternative pathway would be the possibility for **6** to epimerize during the course of the hydrogenation. In all cases, a good diastereoselectivity was obtained as long as pyrrolines **3** were exempt from ruthenium traces which could remain from the RCM step. When some ruthenium was present, pyrrolidines **3** were obtained as a mixture of *cis*/*trans* isomers. Conditions for epimerization (Pd/C in MeOH or DBU in refluxing toluene) were tested on these pyrrolidines **3**. The *cis*/*trans* ratio remained unchanged, showing that the diastereoselectivity did not result from epimerization.

Hydrogenation of pyrrolines **3c**−**f** was performed and gave a quantitative yield of the pyrrolidines **6c**−**f**. In the case of **3g**, the iodine carbon bond present on the phenyl ring was partially reduced, and a 9/1 ratio of **6g/6b** was obtained.

In conclusion, we have extended the utility of the SES as a versatile protecting group for the preparation of heterocyclic structures. The presence of the sulfonamide contributed to the efficiency of the aza-Baylis−Hillman, alkylation, and RCM

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reactions. In the case of the five-membered ring synthesized herein, deprotection of the SES can be tuned to obtain from one intermediate either aromatic pyrroles[20,21] or pyrrolines. In this regard, the SES group proved to be superior to the tosyl group. Hydrogenation of the SES-protected pyrrolines followed by HF-mediated deprotection yielded pyrrolidines with an excellent yield and diastereomeric ratio.

Experimental Section

General Protocol for Deprotection of the SES Pyrrolines 3 with HF. SES pyrroline **3** (0.1 mmol) was treated with 1 mL of anhydrous HF at 0 °C for 1 h in a Teflon vessel. The HF was removed by distillation. The residue was dissolved in methanol and evaporated to give HF·pyrroline **5**.

Methyl 2-Phenyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate Hydrofluoride (5b). Deprotection of the compound **3b** according to the general procedure yielded 22.3 mg (100%) of the title compound as a white solid: ^{1}H NMR (CD_3OD, Me_4Si) δ 3.65 (s, 3H), 4.30−4.50 (m, 2H), 5.80−5.90 (m, 1H), 7.11 (dd, 1H, $J_4 = 4.0$ Hz, $J_4 = 2.1$ Hz), 7.40−7.50 (m, 5H); ^{13}C NMR (CD_3OD, Me_4Si) δ 52.6, 52.7, 68.9, 129.4, 130.5, 131.1, 134.7, 135.4, 138.7, 163.1; ESIMS *m*/*z* 204.1 $(M - F)^+$; FAB+ *m*/*z* 204 $(M - F)^+$; HRMS calcd for $C_{12}H_{14}NO_2$ 204.1025, found 204.1021.

General Protocol for Hydrogenation of SES Pyrrolines 3. To a solution of the SES pyrroline **3** (0.20 mmol) in 4 mL of methanol was added palladium on charcoal (10%, 10% w/w). The mixture was placed under hydrogen atmosphere. After 2 h, the mixture was filtered through Celite and evaporated to yield the SES pyrrolidine **6**.

Methyl 2-Phenyl-1-(2-(trimethylsilyl)ethanesulfonyl)pyrrolidine-3-carboxylate (6b). Hydrogenation of the SES pyrroline **3b** yielded 73.2 mg (99%) of the SES pyrrolidine **6b** (*trans*/*cis* ratio = 99:1). ***trans* Isomer:** IR 2955 (m), 1736 (s), 1332 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, Me_4Si) δ −0.06 (s, 9H), 0.75−1.00 (m, 2H), 2.20−2.30 (m, 2H), 2.50−2.80 (m, 2H), 3.00−3.10 (m, 1H), 3.55−3.70 (m, 1H), 3.70 (s, 3H), 3.75−3.95 (m, 1H), 5.17 (d, 1H, $J_3 = 4.8$ Hz), 7.20−7.40 (m, 5H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ −2.1, 9.8, 28.3, 47.9, 48.6, 52.3, 53.3, 65.3, 126.4, 127.8, 128.7, 141.6, 172.7; ESIMS *m*/*z* 370.1 $(M + H)^+$, 392.1 $(M + Na)^+$, 739.2 $(2M + H)^+$, 761.2 $(2M + Na)^+$; FAB+ *m*/*z* 370 $(M + H)^+$, 392 $(M + Na)^+$; HRMS calcd for $C_{17}H_{28}NO_4SSi$ 370.1508, found 370.1478.

General Protocol for Deprotection of the SES Pyrrolidines 6 with HF. SES pyrrolidine **6** (0.1 mmol) was treated with 1 mL of anhydrous HF at 0 °C for 1 h in a Teflon vessel. The HF was removed by distillation. The residue was dissolved in methanol and evaporated to give HF·pyrrolidine **7**.

Methyl 2-Phenylpyrrolidine-3-carboxylate Hydrofluoride (7b). Deprotection of the compound **6b** according to the general procedure yielded 22.5 mg (100%) of the title compound (*trans*/*cis* ratio = 99:1) as a white solid. ***trans* Isomer:** ^{1}H NMR (CD_3OD, Me_4Si) δ 2.25−2.65 (m, 2H), 3.40−3.60 (m, 3H), 3.68 (s, 3H), 4.17 (d, 1H, $J_3 = 9.8$ Hz), 7.40−7.50 (m, 5H); ^{13}C NMR (CD_3OD, Me_4Si) δ 29.8, 46.3, 49.8, 53.0, 66.4, 129.0, 130.4, 130.7, 135.6, 173.3; ESIMS *m*/*z* 206.1 $(M - F)^+$; FAB+ *m*/*z* 204 $(M - F)^+$; HRMS calcd for $C_{12}H_{16}NO_2$ 206.1181, found 206.1187.

Supporting Information Available: Experimental details, spectral data, and copies of ^{1}H and ^{13}C NMR spectra for all new compounds, X-ray structure and crystal data for compound **8** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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