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A novel effective electrophile: β-trifluoroacetylketene diphenyldithioacetal *S*,*S*-tetroxide

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Abstract—A synthesis of a novel electrophilic reagent—β-trifluoroacetylketene diphenyldithioacetal *S*,*S*-tetroxide **3** is described. The reaction of **3** with various electron-rich aromatics such as 1,3-dimethoxybenzene, 2-methylthiophene, *N*-methylpyrrole, and 2-methylindole was investigated. In the course of these reactions an unusual migration of a phenylsulfonyl group takes place. An easy and ready for scale-up procedure for the synthesis of previously unknown β-aryl, α-phenylsulphonyl substituted α,β-unsaturated trifluoromethyl ketones is reported.

Introduction of fluorine into organic compounds often leads to enhanced physiological activity.[1,2] During our studies on nucleophilic substitution at olefinic carbon atoms, it was found that β-trifluoroacetylvinylsulfones react readily with various N-,[3] S-,[4] and C-nucleophiles[5] to give β-substituted trifluoromethylketones in high yields. Moreover it was shown that β-trifluoroacetylvinylsulfones are excellent bielectrophiles[6] and dienophiles.[7] Introduction of an additional phenylsulfonyl group at the α-position of β-trifluoroacetylvinylsulfones leads to an increase in their electrophilicity and the presence of a phenylsulfonyl group in products. Moreover, the presence of an RSO_2-group enlarges the range of further possible modifications of products. These facts prompted us to develop a convenient synthetic method for β-trifluoroacetylketene diphenyldithioacetal tetroxide starting from β-trifluoroacetylketene *S*,*S*-acetal,[8] which was expected to be an excellent electrophile. Trifluoroacetylketene diphenyldithioacetal tetroxide could serve as a versatile building block for the construction of functionalized heterocycles bearing trifluoromethyl groups.

We prepared the β-trifluoroacetylketene *S*,*S*-acetal **1** using the Hojo procedure[8] by the trifluoroacetylation of readily available triphenyl trithioorthoacetate. The next task was the oxidation of **1** to the corresponding tetroxide **3**. Earlier we found trifluoroperacetic acid in non-aqueous media to be an excellent oxidant for electron-deficient sulfur atoms in alkenes containing several strongly electron-withdrawing groups.[4,9] The use of trifluoroacetic acid or its anhydride and aqueous hydrogen peroxide for this purpose had been previously reported[10] and its higher oxidative ability over that of commonly used *m*-CPBA was demonstrated. However, oxidation of **1** in aqueous trifluoroacetic acid yielded bis(phenylsulfonyl)methane **2**. We believe that water easily adds to the electron-deficient double bond even in strongly acidic media, followed by retro-Knövenagel reaction (Scheme 1). We found that the preparation of trifluoroacetylketene diphenyldithioacetal tetroxide **3** demands water-free conditions[11] using CF_3CO_3H prepared by cautious addition of trifluoroacetic anhydride to ice-cold 98–99% hydrogen peroxide.[12] It should also be noted that the ketenedithioacetal tetroxide **3** is an extremely reactive electrophile and easily reacted with water to form bis(phenylsulfonyl)methane **2**.

We found that trifluoroacetylketene diphenyldithioacetal tetroxide **3** being a highly reactive electrophile easily reacts at room temperature with 1,3-dimethoxybenzene and 2-methylthiophene to form ketones **4**, **5** in high yields (Scheme 2).[13] It was found that the reaction of **3** with electron-rich aromatics proceeds in an unusual way to form 1,1,1-trifluoro-4-aryl-3-(phenylsulfonyl)-but-3-en-2-ones that could be important structural units

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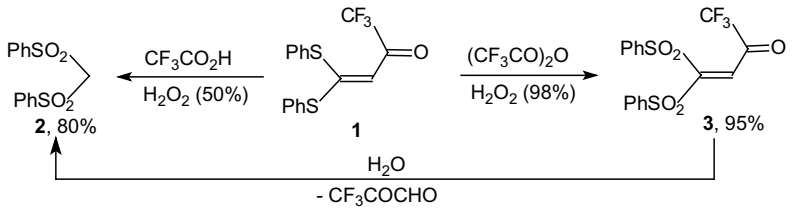
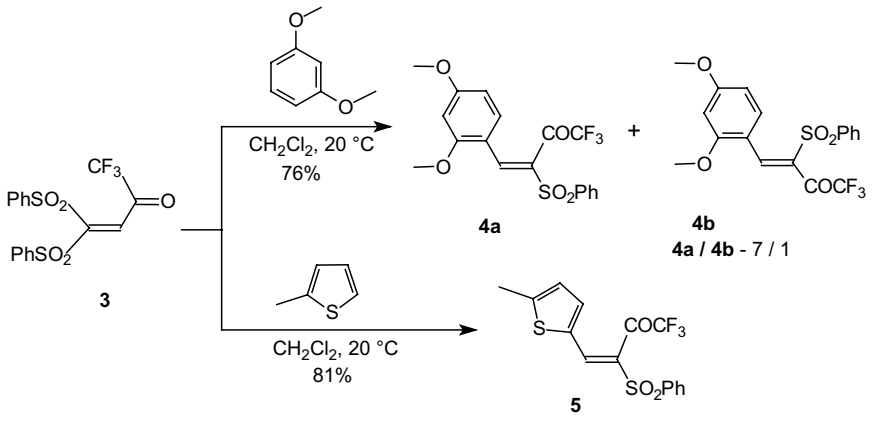


Scheme 1.



Scheme 2.

for the synthesis of fluorine containing biologically active compounds. It should be noted that this type of compound was previously unknown. This is obviously due to the absence of appropriate methods for the synthesis of unsaturated CF_3 ketones.

The structure of **4a** was unambiguously established by X-ray crystallography[14] (Fig. 1). It was found that a migration of a phenylsulfonyl group had taken place and the adduct **4a** has the *E*-configuration. We believe that the predominance of *E*-isomer **4a** and the absence of *Z*-isomer in the case of reaction with 2-methylthiophene is connected to the size of the trifluoroacetyl group in comparison with a phenylsulfonyl group.

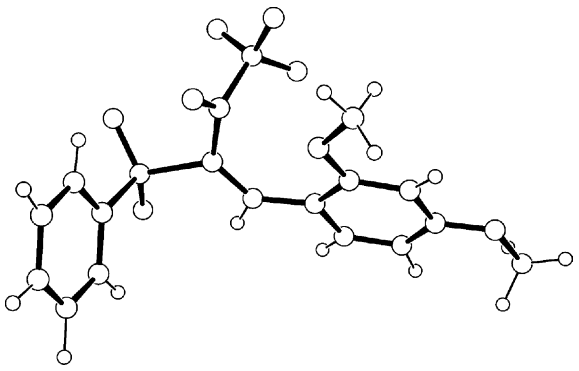
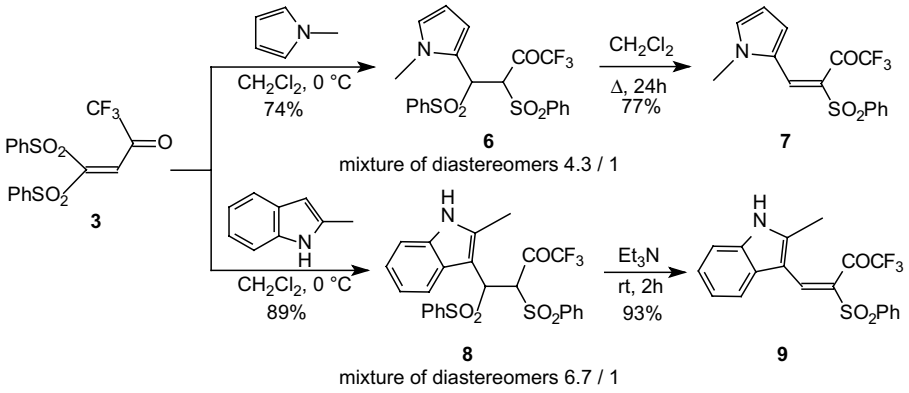


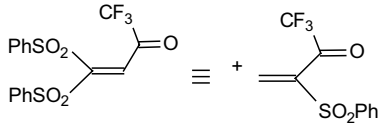
Figure 1. ORTEP molecular structure of **4a**.

It is interesting that in the case of reaction of tetroxide **3** with more electron-rich compounds such as 2-methylindole and *N*-methylpyrrole, elimination of a sulphonyl group at room temperature does not take place. Saturated adducts **6**, **8** with a migrated phenylsulfonyl group were obtained as a mixture of diastereomers. The reactions proceed stereoselectively under very mild conditions. The phenylsulfonyl group could be easily eliminated from the adduct with *N*-methylpyrrole **6** by reflux in dichloromethane with the formation of corresponding unsaturated ketone **7**, whereas 2-methylindole substituted ketone **9** could be obtained only using triethylamine-promoted elimination, prolonged refluxing in dichloromethane did not lead to the elimination of the phenylsulfonyl group. In both cases, only elimination of β-phenylsulfonyl group occurred due to deprotonation of the more acidic α-hydrogen between the two electron-withdrawing groups (Scheme 3).

In conclusion, we have prepared a new highly active electrophile-β-trifluoroacetylketene diphenyldithioacetal tetroxide **3**. We have investigated tetroxide **3** in Michael reactions with electron rich aromatics, which permits access to various previously unknown 1,1,1-trifluoro-4-aryl-3-(phenylsulfonyl)but-3-en-2-ones in good yields. Tetroxide **3** was proved to be a good synthetic equivalent of a 1,1,1-trifluoro-3-(phenylsulfonyl) but-3-en-2-one cation in reactions with electron-rich aromatics (Scheme 4). The procedure is extremely simple and can be easily scaled up. These results allow us to expect that it can be extended to the synthesis of a variety of β-substituted α-sulfonyl vinyl trifluoromethyl ketones.



Scheme 3.



Scheme 4.

This work is in progress in our laboratory and the results will be reported in due course.

Acknowledgements

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11. *Preparation of* β-*trifluoroacetylketene diphenyldithioacetal tetroxide* **3**: To a solution of the β-trifluoroacetylketene *S*,*S*-acetal **1**[8] (10 mmol) in TFA (15 mL), a mixture of trifluoroacetic anhydride (10 mL) and 98–99% hydrogen peroxide (60 mmol) was added at 0 °C. The solution was stirred at 0 °C for 3 h. Removal of the solvent under reduced pressure at 0 °C afforded the product as the light-brown oil that was used for the further reactions without additional purification. ^{1}H NMR (400 MHz, $CDCl_3$) 7.52 (m, 4H, *m*-Ph), 7.62 (m, 2H, *p*-Ph), 7.81 (m, 4H, *o*-Ph), 8.01 (s, 1H, =C—H). ^{13}C NMR (400 MHz, $CDCl_3$) 114.6 (q, CF_3, *J* 290.3 Hz), 129.7, 130.1, 135.9, 136.2, 137.5, 138.1, 142.2, 153.4, 182.7 (q, C=O, *J* 40.9 Hz). Found: C, 47.07; H, 2.41; Anal. Calcd for $C_{16}H_{11}F_3O_5S_2$: C, 47.52%; H, 2.74%.
12. Highly concentrated H_2O_2 was obtained according to: Giguere, P. A. *Bull. Chem. Soc. Fr.* **1954**, 720.
13. *General procedure for the reaction of* β-*trifluoroacetylketene diphenyldithioacetal tetroxide* ***3*** with aromatics: To a solution of **3** (5 mmol) in dichloromethane (20 mL) the aromatic compound (6 mmol) in dichloromethane (20 mL) was added at rt (in the case of 2-methylindole and *N*-methylpyrrole at 0 °C). Then the reaction mixture was stirred at rt for the appropriate time (TLC control). The organic solvents were removed in vacuo. The products were purified by column chromatography (silica gel, hexane).
Selected spectra ***E*-4a**: yellow crystals, mp 147–150 °C (dec.) ^{1}H NMR (400 MHz, $CDCl_3$) 3.63 (s, 3H, CH_3); 3.85 (s, 3H, CH_3); 6.38 (br s, 1H); 6.55 (br d, 1H, *J* 8.8 Hz); 7.33 (br d, 1H, *J* 8.8 Hz); 7.53 (br t, 2H, *J* 7.5 Hz); 7.62 (br t, 1H, *J* 7.3 Hz); 7.90 (br d, 2H, *J* 7.3 Hz); 8.12 (br s, 1H, =CH). Found: C, 53.73; H, 3.61; Anal. Calcd for $C_{18}H_{15}F_3O_5S$: C, 54.00%; H, 3.78%.
8 white crystals, mixture of diastereomers **a**/**b** 6.7/1, mp 123–124 °C ^{1}H NMR ($CDCl_3$) 2.51 (s, 3H, **a**+**b**); 5.36 (d, 1H, *J* 11.9 Hz, **a**); 5.42 (d, 1H, *J* 11.7 Hz, **b**); 5.73 (d, 1H, *J* 11.7 Hz, **b**); 5.86 (d, 1H, *J* 11.9 Hz, **a**); 6.57 (br t, 1H, *J* 7.6 Hz, **a**); 6.65–7.30 (m, 9H, Ph+indole, **a**+**b**), 7.62 (br t, 2H, *J* 7.7 Hz, Ph, **a**+**b**); 7.71 (br t, 1H, *J* 7.4 Hz, Ph, **a**+**b**); 7.93 (br s, 1H, NH, **b**); 8.04 (d, 1H, *J* 7.5 Hz, Ph, **b**); 8.09 (d, 1H, *J* 7.5 Hz, Ph, **a**); 8.38 (br s, 1H, NH, **a**). Found: C,

55.82; H, 3.64; Anal. Calcd for $C_{25}H_{20}F_3NO_5S_2$: C, 56.07%; H, 3.76%.

14. Crystallographic data (excluding structure factors) for the structures in this paper, have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 161708. The structure is refined from the 1589 independent reflections to the values $RF = 0.0370$, $wRF = 0.0990$. Monoclinic, space group $P2_1/n$, $Z = 4$, $a = 19.879(4)$, $b = 11.510(2)$, $c = 8.181(2)$, $\beta = 101.33(3)$.