Synthetic Methods

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Reaction of 2-(2,2,2-Trifluoroethylidene)-1,3-dithiane 1-Oxide with Ketones under Pummerer Conditions and Its Application to the Synthesis of 3-Trifluoromethyl-Substituted Five-Membered Heteroarenes**

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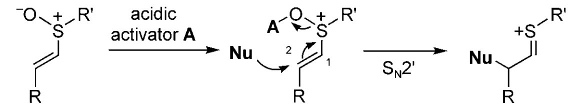
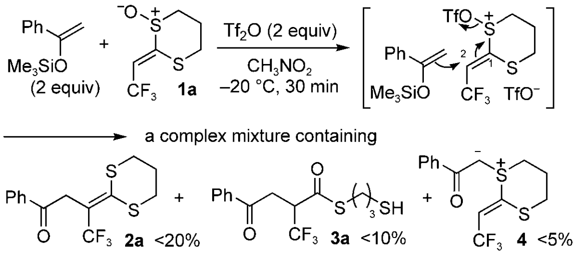
The Pummerer rearrangement is an important method for the synthesis of α-substituted alkyl sulfides from alkyl sulfoxides, and is widely used in organic synthesis. Recently, the extended use of aryl sulfoxides in Pummerer chemistry has attracted increasing attention, especially in the field of synthesis of complex heterocycles.[1,2] On the other hand, the extended Pummerer reactions of 1-alkenyl sulfoxides have been much less investigated.[3]

In general, 1-alkenyl sulfoxide reacts with a nucleophile at the 2-position under Pummerer conditions (Scheme 1). Our research group has recently developed 2-(2,2,2-trifluoroethylidene)-1,3-dithiane 1-oxide (**1a**; see Scheme 2) as a trifluoromethyl-containing substrate for Pummerer chemistry.[4] We envisioned that **1a** would react with silyl enolate[5] at the 2-position in the usual fashion to provide **2a**. In turn, **2a** would be a promising precursor of generally unavailable 2-trifluoromethyl-1,4-diketones[6] en route to potentially useful yet difficult-to-synthesize 3-trifluoromethyl five-membered heteroaromatic compounds.[7] However, the case proved to be rather complicated. Treatment of **1a** with the trimethylsilyl enolate of acetophenone with the aid of trifluoromethanesulfonic anhydride (Tf_2O) afforded a complex mixture, even after extensive optimization (Scheme 2). The mixture indeed contained the expected product **2a** and its hydrolyzed form **3a** (albeit in less than 30 % combined yield), as well as ylide **4**, which was formed by direct nucleophilic substitution at the cationic sulfur atom. In addition, an attempt to use 1-phenylvinyl triflate instead of the enolate resulted in no trace of the products and 48 % of unchanged **1a** was recovered.

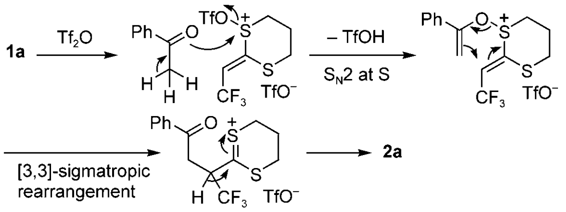


Scheme 1. Typical behavior of 1-alkenyl sulfoxide under Pummerer conditions.



Scheme 2. Unsuccessful Tf_2O-mediated reaction of **1a** with silyl enolate.

We then turned our attention to acetophenone itself—instead of the corresponding enolate—even though use of a carbonyl group as a nucleophile in the Pummerer reaction has not been reported. Our working hypothesis is outlined in Scheme 3. The reagent Tf_2O would preferentially activate the sulfoxide moiety of **1a** over the carbonyl group of acetophenone. Regioselective nucleophilic attack of acetophenone would then take place at the cationic sulfur atom.[4] The resulting vinyl vinyloxy sulfonium species would undergo rapid [3,3]-sigmatropic rearrangement at a low temperature to eventually form a carbon–carbon bond between the trifluoromethylated carbon atom and the α-carbon atom of acetophenone.



Scheme 3. Our working hypothesis.

To our delight, treatment of **1a**[8] with acetophenone (2 equiv) in the presence of Tf_2O (2 equiv)[9] in nitroethane at −40 °C for 30 minutes cleanly afforded a mixture of adducts **2a** and **3a** after aqueous workup. The crude mixture was

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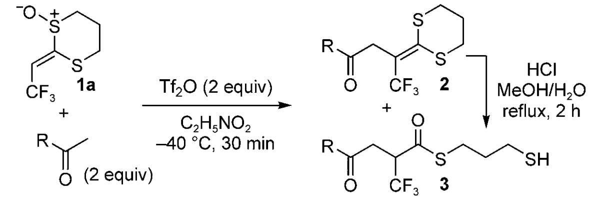
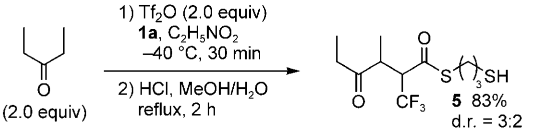
subsequently subjected to acidic hydrolysis and yielded **3a** as the sole product in 73 % overall yield (Table 1, entry 1).

The wide scope of ketones used is exemplified in Table 1 and [Eqs. (1) and (2)]. Acetophenone derivatives having a functional group at the para position reacted smoothly (entries 2, and 4–8). The electronic nature of the substituents had little effect on the reaction efficiency (entries 5–8), however, an ortho substituent retarded the reaction (entry 3). The reactions of aliphatic ketones such as pinacolone (entry 9) and 3-pentanone [Eq. (1)] gave good yields.

Table 1: Reactions of **1a** with various methyl ketones.

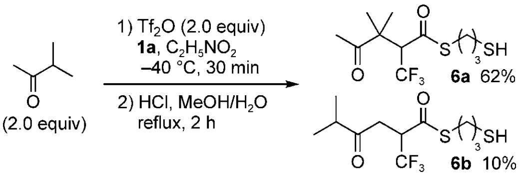


Entry	R	3	Yield of 3 [%]
1	Ph	**3a**	73
2	p-MeC$_6$H$_4$	**3b**	69
3	o-MeC$_6$H$_4$	**3c**	40
4	p-PhC$_6$H$_4$	**3d**	77
5	p-ClC$_6$H$_4$	**3e**	70
6	p-BrC$_6$H$_4$	**3f**	81
7	p-MeOC$_6$H$_4$	**3g**	66
8	p-MeO$_2$CC$_6$H$_4$	**3h**	71
9	tBu	**3i**	64

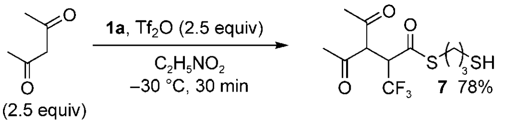


(1)

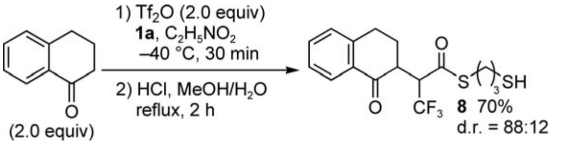
Interestingly, unsymmetrical aliphatic ketone, 3-methyl-2-butanone, underwent regioselective transformation to predominantly yield **6a** bearing a quaternary carbon atom [Eq. (2)]. The carbon–carbon bond formation in the reaction of 2,4-pentanedione proceeded at the 3-position selectively [Eq. (3)]. Secondary product **7** was obtained without the treatment of hydrochloric acid because the corresponding primary product was unstable enough to undergo hydrolysis upon aqueous workup. Another enolizable ketone, α-tetralone, reacted as smoothly as other methyl ketones shown in Table 1 and Equation (4).



(2)

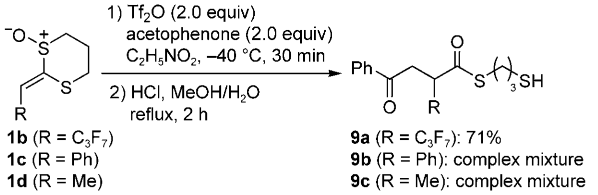


(3)

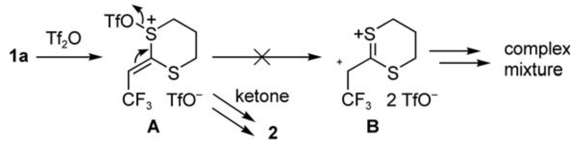


(4)

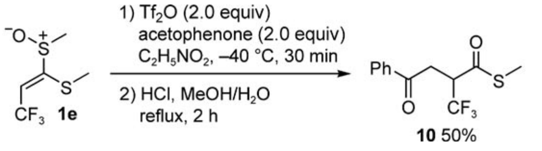
The trifluoromethyl group of **1a** plays an important role in this reaction. The heptafluoropropyl group of **1b** proved to be as efficient as a trifluoromethyl group [Eq. (5)]. However, treatment of **1c** or **1d** bearing a phenyl or methyl group under the same reaction conditions yielded a complex mixture. The trifluoromethyl group would give moderately reactive monocationic intermediate **A** ample chance to react with the ketone by preventing the formation of much more reactive dicationic intermediate **B** (Scheme 4).[10] Acyclic sulfoxide **1e** also reacted with a ketone in a similar manner, albeit in lower yield [Eq. (6)].



(5)



Scheme 4. Inhibitive effect of the CF$_3$ group on the formation of dicationic intermediate.



(6)

To clarify the effect of the CF$_3$ group of **1a** and the reaction mechanism, we performed DFT calculations on the CF$_3$-containing putative intermediates **A** and **B** and their CH$_3$-analogues **C** and **D** (Figure 1). The calculations were performed by using the Spartan‘04 program.[11] All the structures were optimized and the energies were obtained at the B3LYP/6-31G* level.[12] The energies determined with aqueous solvation—used as a model for solvation with polar nitroethane—were obtained by the SM5.4 procedure.[13] Intermediate **A** can take two stable conformations **A$_{eq}$** and **A$_{ax}$**, in which the TfO group is located at either the equatorial

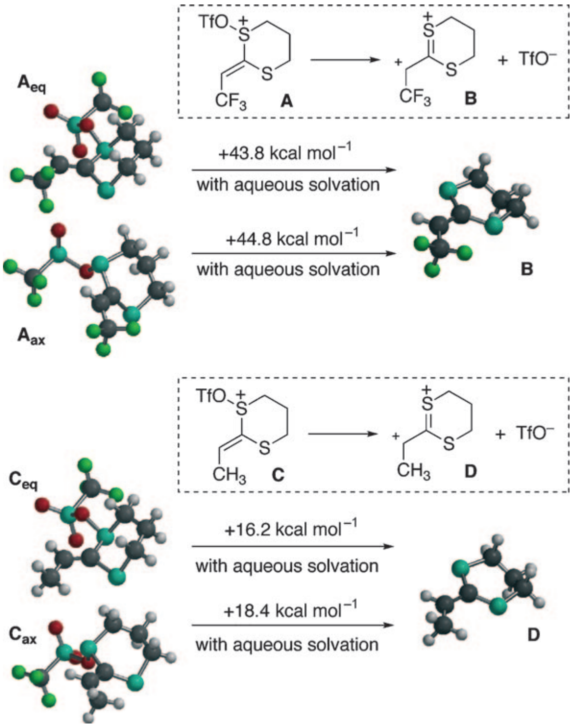
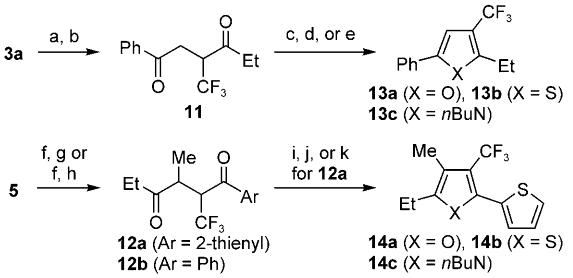


Figure 1. DFT calculations for the putative intermediates.



Scheme 5. Transformation of **3a** and **5** into CF_3-substituted 1,4-diketones and five-membered heteroaromatic compounds. Reagents and conditions: a) MeI (2 equiv), $i\text{Pr}_2\text{EtN}$ (2 equiv), acetone, 25 °C, 8 h, 80 %; b) $[\text{PdCl}_2(\text{PPh}_3)_2]$ (10 mol %), EtZnI (2 equiv), toluene, reflux, 12 h, 65 %; c) p-TsOH·H_2O (1.1 equiv), toluene, reflux, 10 h, 75 %; d) Lawesson's reagent (2.4 equiv), 1,2-dichloroethane, 25 °C, 8 h, 62 %; e) $n\text{BuNH}_2$ (2 equiv), $\text{Ti}(O i\text{Pr})_4$ (1.5 equiv), toluene, reflux, 10 h, 81 %; f) MeI (2 equiv), $i\text{Pr}_2\text{EtN}$ (2 equiv), acetone, 25 °C, 8 h, 78 %; g) $[\text{PdCl}_2(\text{dppf})]$ (10 mol %), (2-thienyl)ZnI·LiCl (5.6 equiv), toluene, 0 °C, 1 h, 87 %, d.r. = 3:2; h) $[\text{PdCl}_2(\text{dppf})]$ (10 mol %), PhZnI·LiCl (3 equiv), toluene, 0 °C, 1 h, 93 %, d.r. = 3:2; i) p-TsOH·H_2O (1.1 equiv), toluene, reflux, 8 h, 82 %; j) Lawesson's reagent (2.4 equiv), 1,2-dichloroethane, 60 °C, 8 h, 47 %; k) $n\text{BuNH}_2$ (4 equiv), $\text{Ti}(O i\text{Pr})_4$ (3 equiv), toluene, 25 °C, 4 h, 83 %. dppf = 1,1′-bis(diphenylphosphanyl)ferrocene, Ts = 4-toluenesulfonyl.

and axial position, respectively. Dicationic intermediate **B** is calculated to be much more unstable than $\mathbf{A}_{\mathbf{eq}}$ and $\mathbf{A}_{\mathbf{ax}}$ by 43.8 and 44.8 kcal mol^{-1}, respectively, with aqueous solvation. Thus, the departure of TfO$^-$ would never take place via an S_N1-type process at −40 °C but may proceed via an S_N2-type mechanism. The CF_3 group would destabilize the dicationic intermediate **B**. On the other hand, dication **D** is calculated to be less stable than the CH_3-analogues $\mathbf{C}_{\mathbf{eq}}$ and $\mathbf{C}_{\mathbf{ax}}$ by 16.2 and 18.4 kcal mol^{-1}, respectively, with aqueous solvation. The formation of **D** is much more likely than that of **B** and can occur at low temperatures. These calculations support the reaction mechanism in Scheme 3 and Scheme 4.

Trifluoromethylated arenes play important roles in medicinal, agricultural, and material sciences.[14] The unusual chemical properties of a trifluoromethyl unit often render the synthesis of trifluoromethylated arenes difficult, and the development of reliable routes to trifluoromethylated arenes has been eagerly anticipated.[15]

Thiol esters **3a** and **5** have proved to be versatile precursors of 3-trifluoromethylfurans, -thiophenes, and -pyrroles (Scheme 5). Methylation of the mercapto groups of **3a** and **5** and subsequent cross-coupling reactions of the resulting thiol esters with organozinc reagents[16–18] yielded 2-trifluoromethyl-1,4-diketones **11** and **12**, respectively. Classic Paal–Knorr condensation[19] of **11** and **12** afforded a diverse range of highly substituted 3-trifluoromethyl five-membered heteroaromatics **13** and **14**, which would be difficult to synthesize by the conventional methods.[7]

In summary, we have devised a novel Pummerer transformation using ketones as substrates. The transformation includes a new combination of nucleophilic attack of the carbonyl oxygen atom onto the activated cationic sulfur atom and a subsequent [3,3]-sigmatropic rearrangement. The present reaction greatly expands the scope of nucleophile in the Pummerer reaction.

The products are precursors of generally unavailable 2-trifluoromethyl-1,4-diketones en route to 3-trifluoromethylfurans, -thiophenes, and pyrroles of latent use. The new protocol provides the only access to fully substituted 3-trifluoromethyl five-membered heteroaromatics. The trifluoromethyl group of **1a** not only play an important role in the success of the new Pummerer process but will undoubtedly lead to heteroaromatic products with interesting chemical, biological, and physical properties.

Experimental Section

Typical procedure for the reaction of **1a** with ketone in the presence of Tf_2O (Table 1, entry 1): Trifluoromethanesulfonic anhydride (0.067 mL, 0.40 mmol) was added to a solution of acetophenone (0.047 mL, 0.40 mmol) in $C_2H_5NO_2$ (2 mL) and **1a** (43.2 mg, 0.20 mmol) under argon at −78 °C, and the reaction mixture was stirred for 30 min at −40 °C. The mixture was poured into saturated aqueous $NaHCO_3$ (10 mL), and the product was extracted with $CHCl_3$ (20 mL × 3). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude residue was dissolved in MeOH (2 mL) and water (1 mL). Aqueous HCl (11 M, 0.18 mL, 2.0 mmol) was added, and the whole mixture was heated at reflux for 2 h. The mixture was diluted with H_2O (10 mL) and extracted with EtOAc (10 mL × 3). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude residue was purified by chromatography on silica gel (eluent: toluene/n-hexane = 3:2) and provided S-(3-mercaptopropyl) 4-oxo-4-phenyl-2-trifluoromethylbutanethioate (**3a**, 49.1 mg, 0.147 mmol, 73 %).

Typical procedure for the synthesis of 2-trifluoromethyl-1,4-diketone (Scheme 5, steps f and g): Iodomethane (0.47 mL, 7.6 mmol) and $i\text{Pr}_2\text{EtN}$ (1.3 mL, 7.6 mmol) were added to a solution of **5** (1.14 g, 3.78 mmol) in acetone (5 mL). The resulting reaction mixture was stirred for 8 h at 25 °C. The mixture was poured into H_2O (10 mL) and extracted with EtOAc (10 mL × 3). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude residue was purified by chromatography on silica gel (eluent: *n*-hexane/EtOAc = 10:1) and provided (*S*)-(3-methylthiopropyl) 3-methyl-4-oxo-2-trifluoromethylhexanethioate (0.933 g, 2.95 mmol, 78 %).

A solution of (*S*)-(3-methylthiopropyl) 3-methyl-4-oxo-2-trifluoromethylhexanethioate (63.3 mg, 0.20 mmol) in toluene (2.0 mL) was added to [$PdCl_2$(dppf)] (16.3 mg, 0.02 mmol) under argon. After the mixture was cooled to 0 °C, (2-thienyl)ZnI·LiCl complex (1.06 mL, 1.12 mmol, 1.06 M in THF) was added, and the resulting reaction mixture was stirred for 30 min. The mixture was poured into aqueous HCl (1 M, 10 mL) and extracted with EtOAc (10 mL × 3). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude residue was purified by chromatography on silica gel (eluent: *n*-hexane/EtOAc = 10:1) and provided 3-methyl-1-(2-thienyl)-2-trifluoromethyl-1,4-hexanedione (**12a**, 48.1 mg, 0.173 mmol, 87 %).

Typical procedure for the Paal–Knorr condensation (Scheme 5, step k): A solution of **12a** (55.7 mg, 0.20 mmol), *n*BuNH_2 (0.080 mL, 0.80 mmol), and Ti(O*i*Pr)$_4$ (0.18 mL, 0.60 mmol) in toluene (2 mL) was stirred for 4 h at 25 °C. Water (10 mL) was added to the reaction mixture, and the product was extracted with EtOAc (10 mL × 3). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude residue was purified by chromatography on silica gel (eluent: *n*-hexane/EtOAc = 20:1) and provided 1-butyl-5-ethyl-4-methyl-2-(2-thienyl)-3-trifluoromethylpyrrole (**14c**, 52.5 mg, 0.166 mmol, 83 %).

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