Simultaneous introduction of trifluoromethyl and \( \lambda^6 \)-pentafluorosulfanyl substituents using \( F_5S-C\equiv C-CF_3 \) as a dienophile†

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F\( _5S-C\equiv C-CF_3 \) can be easily prepared in high yields in two steps from 3,3,3-trifluoropropyne. It is a powerful, versatile dienophile in Diels–Alder reactions. Reactions at room temperature provide the corresponding products in up to quantitative yields allowing the introduction of the pentafluorosulfanyl group and trifluoromethyl group at the 1,2 position.

Since the discovery of the Diels–Alder reaction (DA) in 1928,\(^1\) its value in organic chemistry as a perfect synthetic protocol towards the formation of six-membered rings has been continuously growing.\(^2\) The use of this methodology has also been applied in modern medicinal, agrochemical and materials science.\(^2\) It is well known that introducing fluorinated groups into organic molecules remarkably alters their physical, chemical and biological properties.\(^3\) As the CF\(_3\) group is one of the most important substituents there are several reviews concerning its introduction including radical, nucleophilic and electrophilic reactions.\(^4\) The incorporation of the trifluoromethyl group via DA reactions produces new six-membered heterocyclic and carbocyclic compounds.\(^5\) In this matter, CF\(_3\)-substituted alkynes are used instead of the corresponding dienes.

So far there exist no comparable protocols for the introduction of the pentafluorosulfanyl group, which possesses unique features, including high stability (chemical and thermal) and lipophilicity of SF\(_5\)-substituted molecules.\(^6\) Because it is regarded as a larger version of the CF\(_3\) group, the SF\(_5\) group is very often referred to as a “super CF\(_3\)” group. In comparison with trifluoromethyl, the chemistry of SF\(_5\) is still largely unexplored probably because of the limited availability of SF\(_5\)-containing reagents.\(^7\) Therefore, new methods to introduce this group into organic molecules are challenging and highly required.

Despite the significance of organofluorine chemistry, there are no reports of using a reagent that can introduce these two particularly interesting groups simultaneously. Thus, a suitable protocol that will give rise to substituted organic molecules with unique physical, biological and chemical properties is undoubtedly very important. We envisioned that 3,3,3-trifluoromethyl-1-pentafluorosulfanyl-1-propyne,\(^7\) \( F_5S-C\equiv C-CF_3 \) (2) would be the ideal reagent for this purpose (Scheme 1).

The synthesis of the dienophile (2) follows the literature protocol and involved the addition of SF\(_5\)Br to terminal CF\(_3\)-alkyne (1) to form the alkenes \( \text{1a-b} \) as a mixture of \( E/Z \) isomers (1 : 2) (Scheme 1) in 80% yield.\(^8\) Carrying out the reaction in dry DCM or \( n \)-hexane at \(-40\) °C and \(-10\) °C in the presence of catalytic BEt\(_3\) as described by Dolbier et al.\(^9\) for other systems gave lower yields (47–50%, 1 : 1 ratio of \( E/Z \) isomers). A mixture of \( \text{1a-b} \) was subsequently treated with KOH resulting in the target alkyne (2) in 65% yield.\(^7\)

Diphenylbenzoisofuran (3a) was chosen as a model substrate for the DA reaction. The progress of the reaction in dry DCM at room temperature was controlled by \( ^{19}\)F NMR spectroscopy. Within 1 h we observed 100% conversion of 2 towards the target product 4a (Scheme 2). Lowering the reaction temperature to \(-60\) °C results in a 50% conversion after

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†Electronic supplementary information (ESI) available: The experimental details and copies of \( ^1\)H, \( ^{13}\)C and \( ^{19}\)F NMR spectra. CCDC 1020179 and 1020180. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c5ob00610d
1 h. Screening of the reaction conditions, by using different solvents, revealed that this cycloaddition was not affected by the polarity of solvents. For instance, performing such a process in DCM and n-pentane gave comparable isolated yields within the same reaction time. Based on the $^{19}$F NMR spectroscopic analysis no side-reactions occurred even when performing this process at elevated temperatures. For instance, performing such a process in DCM and n-pentane gave comparable isolated yields within the same reaction time. Based on the $^{19}$F NMR spectroscopic analysis no side-reactions occurred even when performing this process at elevated temperatures. The crude mixture was purified by flash column chromatography using DCM/n-pentane (1:2 v/v) as the eluent giving 4a in almost quantitative yield. Compound 4a was easily identified by $^{19}$F NMR spectroscopy. The resonance of the trifluoromethyl group splits into a quintet ($J_{FF(eq)} = 12$ Hz) due to coupling with the four cis fluorine nuclei of the SF$_3$ group. As expected we observed a characteristic inversion of the axial and equatorial chemical shifts of the SF$_3$ group.$^{10}$ With the reaction conditions established, 2 was then treated with selected dienes (Scheme 2), such as furan (3b), 2,5-dimethylfuran (3c), cyclopentadiene (3d), pentamethylcyclopentadiene (3e), 6,6-dimethylfulvene (3f), cyclohexa-1,3-diene (3g), and cyclohepta-1,3,5-triene, which is in equilibrium with 3h. Apart from 4f and 4h conversions and yields are excellent although due to steric hindrance longer reaction times can be required.

The $^1$H NMR spectrum of 4d exhibits a doublet at $\delta$ 2.09 ($J_{HH} = 7$ Hz) and a doublet of quintets at 2.37 ($J_{HH} = 7$ Hz, $J_{HF(eq)} = 1$ Hz) (see the ESI$^+$) for the chemically inequivalent protons of the –CH$_2$ group. The regiochemistry of the endo and exo-4e was determined by $^1$H NMR spectroscopy. The bridged C–H proton shows characteristic splittings: for exo-4e the resonance is split into a quartet with a coupling constant of $J_{HH} = 6$ Hz; whereas for endo-4e we observed a quartet of quintets ($J_{HH} = 6$ Hz, $J_{HF(eq)} = 1$ Hz) due to additional coupling to the four equatorial fluorine nuclei of the SF$_3$ group.

The ratio of endo/exo-4e depends on the reaction temperature; at ambient temperature the isomers are formed in a 1:3 ratio whereas at $-40$ °C a 1:1 ratio is obtained. Thus we can conclude that endo-4e is kinetically favored due to less steric hindrance in the transition state.

Cyclopentadienones and 2H-pyran-2-ones (3i) are ideal precursors for the synthesis of substituted aromatic compounds by Diels–Alder reaction with an alkyne in one step. The latter reacted with 2 in toluene at 110 °C affording a benzene ring.

Scheme 2 Diels–Alder reaction of 2 with selected dienes. Reaction conditions: (a) 2 (1 mmol), 3a–g (1.2 mmol), DCM (or n-pentane) 5 mL, RT, 3 h; (b) 2 (1 mmol), 3h–i (1.2 mmol), PhMe 5 mL, 110 °C, 24 h.
with only CF₃ and SF₅ substituents 4i in 54% isolated yield (Scheme 2). The former has been used by us and others in reactions to construct fluoranthene derivatives with adjacent substituents as precursors of substituted corannulenes. Theacenaphthquinone derivative (5) reacts with pentan-3-one in the presence of KOH yielding the cyclopentadienone derivative (6) (see Scheme 3). Compound 6 is usually not isolated and treated directly as a dimer, for example 2 in Ac₂O at 80 °C for 24 h furnishing the target fluoranthene 7 in 75% yield containing both SF₅ and CF₃ groups in the ortho position (Scheme 3). The structures of compounds 6 and 7 were elucidated by single-crystal X-ray diffraction (Fig. 1). Compound 6 forms perfect planar molecules with columnar stacks along the crystallographic c axis with the shortest intermolecular C–C distance of 3.28 Å. The cyclopentadienone 6 is not stable in the solution and undergoes rapid dimerization (see the ¹H NMR spectrum in the ESIF). Compound 7 showed a characteristic Cᵥ-fold configuration of the methyl groups.

In conclusion, we have reported a protocol for the synthesis of compounds with SF₅ and CF₃ in the 1,2-position via Diels–Alder reaction by employing a corresponding alkyne. The reaction occurs at room temperature or below within a few hours and in the absence of any side-reactions. Further studies using SF₅ substituted alkynes as synthones for a variety of novel organic compounds with interesting new physical, biological and chemical properties are currently underway in our group.

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Notes and references

† Crystal data for 6: C₁₀H₈O₂, M = 260.32, orthorhombic, a = 11.088(2) Å, b = 18.5665(4) Å, c = 13.258(3) Å, V = 3591(2) Å³, T = 138(2) K, space group C222₁, Z = 8, μ(Mo Ka) = 0.077 mm⁻¹, 15171 reflections measured, 4184 independent reflections (Rint = 0.0231), The final R₁ value was 0.0476 (I > 2σ(I)). The final ωR² value was 0.1150 (I > 2σ(I)). The final R₁ value was 0.0565 (all data). The final ωR² value was 0.1215 (all data). The goodness of fit on F² was 1.119.

Crystal data for 7: C₁₁H₄SF₅, M = 452.40, monoclinic, a = 16.519(6) Å, b = 12.951(5) Å, c = 17.532(6) Å, β = 106.652(7)°, V = 2729.2(10) Å³, T = 133(2) K, space group C2/c, Z = 8, μ(Mo Ka) = 0.266 mm⁻¹, 28650 reflections measured, 5477 independent reflections (Rint = 0.0241), The final R₁ value was 0.0468 (I > 2σ(I)). The final ωR² value was 0.1210 (I > 2σ(I)). The final R₁ value was 0.0636 (all data). The final ωR² value was 0.1411 (all data). The goodness of fit on F² was 1.099.

5 (a) G. Pawlowski and M. Hanack, Synth. Commun., 1981, 11, 351; (b) M. Kuwabara, K. Fukunishi, M. Nomura and...


