This is an Accepted Manuscript, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. This Accepted Manuscript will be replaced by the edited, formatted and paginated article as soon as this is available.

You can find more information about Accepted Manuscripts in the Information for Authors.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal’s standard Terms & Conditions and the Ethical guidelines still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this Accepted Manuscript or any consequences arising from the use of any information it contains.
First efficient synthesis of SF$_5$-substituted pyrrolidines using 1,3-dipolar cycloaddition of azomethine ylides with pentafluorosulfanyl-substituted acrylic esters and amides

Ewelina Falkowska, Vincent Tognetti, Laurent Joubert, Philippe Jubault, Jean-Philippe Bouillon, Xavier Pannecoque

For the first time, di-, tri- and tetrasubstituted pentafluorosulfanylated pyrrolidines have been efficiently synthesized via 1,3-dipolar cycloaddition. In the case of tetrasubstituted pyrrolidines, an unusual mixture of 1/1 regioisomers was obtained. Theoretical calculations have been carried out and the regioselectivity has been explained compared to the results previously obtained in the trifluoromethylated pyrrolidines series.

The chemistry of organofluorine compounds is a rapidly developing research area due to its wide range of applications in a number of important fields such as drug discovery, materials sciences and agrochemistry. This particular interest in fluorine chemistry is due to the physicochemical characteristics of fluorine atom, including its small size and high electronegativity. In particular the presence of this atom in organic molecules affects their properties such as conformation, acidity/basicity of the neighbouring functional groups, enhanced metabolic stability and increased lipophilicity. As a consequence, intensive efforts have been devoted to the development of original methods for the introduction of one or two fluorine atoms, trifluoromethyl (CF$_3$), trifluoromethylsulfanyl (SCF$_3$) and perfluoroalkyl groups ((CF$_2$)$_n$) onto a carbon skeleton. Among these fluorine containing functional groups, the pentafluorosulfanyl (SF$_5$) group, also called as “super-trifluoromethyl group”, is one of the emergent perfluorinated substituents. It displays unique and useful properties such as high electronegativity, high lipophilicity, an important steric hindrance, and high thermal and chemical stability. This pentafluorosulfanyl group has been introduced quite efficiently in biologically active compounds leading in some cases to interesting properties. Compared to other fluorinated moieties, the introduction of SF$_5$ group is less developed in the literature essentially because of the lack of efficient synthetic methods but also because few SF$_5$-building blocks are described up to date. Very recently, we have reported a mild and efficient synthesis of new pentafluorosulfanyl-substituted acrylic esters 2 and amides 3 from 3-pentafluorosulfanyl-propenoic acids 1 (scheme 1).

Scheme 1 Synthesis of pentafluorosulfanyl-substituted esters 2 and amides 3.

Having in hands these scaffolds, we were interested in their usefulness to access more valuable skeletons. 1,3-Dipolar cycloadditions which are described as involving a classical one-step mechanism, are a useful tool in organic synthesis. However, knowledge about these reactions has significantly evolved from the original concerted mechanism. Indeed, 1,3-dipolar cycloaddition reactions of thiocarbonyl ylides or (Z)-N,N-diphenyl nitrite in the presence of strongly electrophilic dipolarophiles such as dimethyl 2,3-dicyanofumarate, gem-1,1-dinitroethene or α-pentynitrilomethane, were reported as two-steps processes through zwitterionic intermediates, leading to various heterocycles. Among them, five-membered nitrogen derivatives, especially the highly substituted pyrrolidines, are widely encountered in pharmaceuticals, natural alkaloids, organocatalysts, and are also very useful building blocks in synthetic organic chemistry. In particular, trifluoromethylated pyrrolidines have been efficiently synthesized using the 1,3-dipolar cycloaddition of a non-stabilised azomethine ylide with electron-deficient alkenes (4,4,4-trifluoroacetonates) as initially reported by Bégue and then largely developed by Wang in an elegant catalytic enantioselective approach.

With our new type of electron-deficient alkenes, we were interested in studying the 1,3-dipolar cycloaddition of classical azomethine ylides with pentafluorosulfanyl-substituted acrylic esters 2 and amides 3 which could offer, for the first time, an efficient entry to SF$_5$-substituted pyrrolidines.
Our initial studies began with the reaction of trans-benzyl pentafluorosulfanylethylate 2a with N-(methoxymethyl)-N-[[trimethylsilyl]methyl]-N-benzylamine 4 in the presence of a catalytic amount of trifluoroacetic acid in dichloromethane (Scheme 2). To our delight, we obtained the expected SF$_3$-pyrrolidine 5a in a good isolated yield (69%). When the same conditions were applied to SF$_3$-unsaturated amide 3a, we did not observe a complete conversion (46%). Using 2 equivalents of dipolarophile precursor 4 enabled the conversion to reach 96% and the pentafluorosulfanylated-substituted pyrrolidine 5b was isolated in 79% yield.

Scheme 2 Synthesis of pentafluorosulfanyl pyrrolidines 5a and 5b.

Under the above-described reaction conditions for the synthesis of SF$_3$-pyrrolidines in each series, several pentafluorosulfanylated esters and amides were engaged in order to study the scope of the reaction.

Figure 1 Scope of the 1,3-dipolar cycloaddition using precursor 4 of azomethine ylide.$^{11}$

We demonstrated that 1,3-dipolar cycloaddition could be applied to various SF$_3$-unsaturated esters, secondary and tertiary amides as well as chiral amide, leading to the expected pyrrolidines 5 in moderate to excellent isolated yields. Interestingly trisubstituted ester 2d and amide 3d (Scheme 1) reacted also to give the corresponding pyrrolidines 5e and 5i in moderate yields (46% and 36% respectively), probably due to the steric hindrance of the starting materials. It is worth noting that the reaction proved to be totally diastereoselective. Indeed, in all cases, starting from (E) acrylates 2 or acrylamides 3, only the trans pyrrolidines were obtained, as racemic mixtures, except in the case of the product 5g which was obtained as a 1:1 mixture of trans diastereoisomers, which could be separated by silica gel column chromatography. Trans relationship between the two substituents was confirmed by X-ray diffraction analysis of pyrrolidine derivative 5f.$^{12}$

After demonstrating that 1,3-dipolar cycloaddition occurred efficiently between SF$_3$-dipolarophiles and precursor of azomethine ylide 4, we turned our attention to the use of N-benzylidene glycine methyl ester 6 which could give us an access to tetrasubstituted SF$_3$-pyrrolidines.

Table 1 Study of optimal conditions for 1,3-dipolar cycloaddition with imino ester 6 or 7

<table>
<thead>
<tr>
<th>Entry</th>
<th>SF$_3$-derivative 6 or 7 (equiv.)</th>
<th>AgOAc (mol%)</th>
<th>PPh$_3$ (mol%)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1$^{*}$</td>
<td>2a 6 (1.7)</td>
<td>10</td>
<td>10</td>
<td>17$^{*}$</td>
<td>40 (1:1)$^{*}$</td>
</tr>
<tr>
<td>2$^{*}$</td>
<td>2a 6 (3)</td>
<td>20</td>
<td>20</td>
<td>21$^{*}$</td>
<td>73 (1:1)$^{*}$</td>
</tr>
<tr>
<td>3$^{*}$</td>
<td>2a 6 (3)</td>
<td>20</td>
<td>20</td>
<td>21$^{*}$</td>
<td>73 (1:1)$^{*}$</td>
</tr>
<tr>
<td>4$^{*}$</td>
<td>2a 6 (3)</td>
<td>20</td>
<td>20</td>
<td>21$^{*}$</td>
<td>73 (1:1)$^{*}$</td>
</tr>
<tr>
<td>5$^{*}$</td>
<td>3e 6 (3)</td>
<td>20</td>
<td>20</td>
<td>21$^{*}$</td>
<td>73 (1:1)$^{*}$</td>
</tr>
</tbody>
</table>

$^{*}$ Global isolated yield of regioisomers. $^{b}$ Ratio of regioisomers. $^{c}$ 0.15 equiv. of Et$_3$N. $^{d}$ 0.25 equiv. of Et$_3$N. $^{e}$ Room temperature. $^{f}$ Reflux. $^{g}$ Conv. = 55%.

Our study began with the reaction of SF$_3$-unsaturated ester 2a with glycine derivative 6 (1.7 equiv.) in the presence of 10 mol% AgOAc/PPh$_3$, and 15 mol% Et$_3$N at room temperature. A promising 40% yield of pyrrolidines 8a$^{*}$ (Table 1, entry 1), as a 1:1 mixture of two regioisomers, was obtained. By increasing the quantity of AgOAc/PPh$_3$ to 20 mol% and Et$_3$N to 25 mol%, the expected pyrrolidines were obtained in 75% yield but in a quite long reaction time (90h, Table 1, entry 2). When allowed to warm to reflux, pyrrolidines 8 and 8$^{*}$ were obtained in 73% yield after 21h (Table 1, entry 3). Stereochemistry of the products 8 and 8$^{*}$ was elucidated based on NOESY experiments and was independently confirmed by the X-ray analysis in the case of 8.$^{12}$

Two major differences appeared concerning the cycloaddition of this dipole precursor 6 in the SF$_3$-series compared to the previously reported CF$_3$-ones.$^{20}$ The first one concerns the kinetic of the reaction which is much slower (21h in refluxed dichloromethane) with 2a compared to the one observed using the CF$_3$ analog (5h at room temperature). The second one is the regiochemistry. Indeed, in the CF$_3$ series, the reaction was almost totally regioselective (dr $\geq$ 98:2) whereas a 1:1 mixture of regioisomers 8a$^{*}$-8$^{*}$ was obtained using 2a. When 2a was reacted with dipole precursor 7 (entry 4), only 55% conversion of SF$_3$-derivatives was observed after 21h. Longer reaction times led to degradation of the expected pyrrolidines 9a$^{*}$-9$^{*}$. When SF$_3$-amide 3e was engaged in the cycloaddition reaction with 6, a lower yield of 10+10$^{*}$ (48%, entry 5) was observed compared to the one during the reaction with SF$_3$-ester 2a (entry 3).

Theoretical calculations were then carried out in order to cast light on the factors governing the observed regiochemistry. To this aim, three theories were combined, all based on the primary quantum observable (the electron density), namely DFT (to determine the mechanism), conceptual DFT (to characterize reactive behaviours), and Bader’s theory (QTAIM) to quantify interactions.$^{13}$ Three model systems 11-13 (Scheme 3) were investigated: unsaturated CF$_3$- and SF$_3$-esters and the corresponding SF$_3$-amide, considering the imine forms a complex with AgPMe$_3$ (r$_{\text{A}}$ = 22 kcal/mol).
From Table S3 (Supplementary Information), it could be inferred that the highest contribution in absolute value stems from the adducts’ non-vibrational entropy. However it cannot account for regiochemistry, as variance with the electronic stabilization energy of the adduct (ΔE\textsubscript{add}), the electronic activation barrier (ΔE\textsubscript{act}) from the adduct, and the vibrational entropies of both adduct and TS. ΔE\textsubscript{add} favours path 1 in the ester cases and path 2 for amide and is correctly predicted by the preference dual descriptor\textsuperscript{19} (Graph S5, Supplementary Information). ΔE\textsubscript{act} is lower for path 1 in any case, a result that can be explained using QTAIM (by focusing on local critical point properties, Graph S6, Supplementary Information). As for entropy effects (see Graph S7, Supplementary Information), we epitomize their role for the SF\textsubscript{5}-ester 12: the vibrational energy change from the adduct to the TS is 2.1 kcal/mol more destabilizing in path 1 than in path 2, effectively counterbalancing the pure electronic features. As a consequence, a mixture of regioisomers is expected in the SF\textsubscript{5}-series.

Lastly, one can wonder whether Ag(PMe\textsubscript{3})\textsubscript{3} may have a catalytic effect. The corresponding activation barriers without it are actually slightly lower (8.4 and 7.4 kcal/mol for the CF\textsubscript{3}-SF\textsubscript{5} and SF\textsubscript{5}-esters (12), respectively), so that the main role of the AgOAc and PPh\textsubscript{3} combination may be assumed (at the retained theoretical model) to concern precursor deprotonation.

**Conclusions**

In conclusion, a straightforward single step procedure for the preparation of SF\textsubscript{5}-substituted pyrrolidines using pentafluorosulfonyl-substituted acrylic esters and amides was developed. Moreover, a convergent DFT-Conceptual DFT-QTAIM theoretical strategy was defined and applied to unravel the main factors accounting for the observed regiochemistry. Further developments especially devoted to an asymmetric version of this 1,3-dipolar cycloaddition process are currently under investigation in our laboratory. This approach can also be further used for the synthesis of SF\textsubscript{5}-analogues of biorelevant molecules.

This work was financially supported by MESR (Ministère de l’Enseignement Supérieur et de la Recherche), the Région Haute-Normandie (CRUNCH program), CNRS, Rouen University, INSA of Rouen and Labex SynOrg (ANR-11-LABX-0029). The CRUHAN is acknowledged for computational resources. The authors also thank Pr. H. Oulyadi and L. Truong for NOESY experiments.

**Notes and references**

\textsuperscript{4} Normandie Univ., COBRA, UMR 6014 & FR 3038, Univ. Rouen, INSA Rouen, CNRS, 1 rue Tesnière, F-76821 Mont-Saint-Aignan Cedex, France. E-mails: philippe.jubault@insa-rouen.fr; jean-philippe.bouillon@univ-rouen.fr

Electronic Supplementary Information (ESI) available: experimental section and computational details. CCDC N°1024823 and N°1024824. See DOI: 10.1039/c000000x/


Di-, tri- and tetrasubstituted pentafluorosulfanylated pyrrolidines have been efficiently synthesized via 1,3-dipolar cycloaddition of azomethine ylides.

\[
\begin{align*}
&\text{Ar} \quad \text{Ar} \\
&{^{(+/-)}}\quad {^{(+/-)}} \\
&Y = OR, NR^2R^3 \\
&Ar = \text{Ph, } p\text{-MeO-Ph}
\end{align*}
\]