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First efficient synthesis of SF_5-substituted pyrrolidines using 1,3-dipolar cycloaddition of azomethine ylides with pentafluorosulfanyl-substituted acrylic esters and amides

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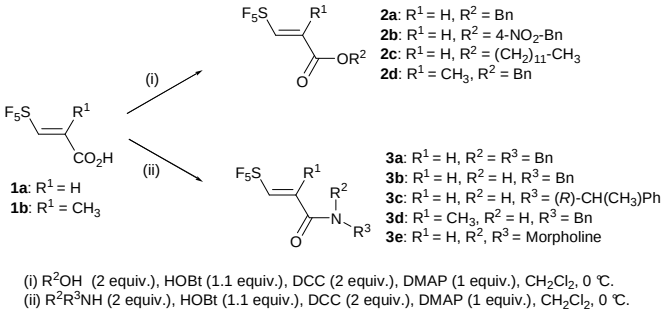
Ewelina Falkowska, [a] Vincent Tognetti, [a] Laurent Joubert, [a] Philippe Jubault, [a] * Jean-Philippe Bouillon, [a] * Xavier Pannecoucke [a]

For the first time, di-, tri- and tetrasubstituted pentafluorosulfanylated pyrrolidines have been efficiently synthetized via 1,3-dipolar cycloaddition. In the case of tetra-substituted 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.



(i) R^2OH (2 equiv.), HOBt (1.1 equiv.), DCC (2 equiv.), DMAP (1 equiv.), CH_2Cl_2, 0 °C.
(ii) R^2R^3NH (2 equiv.), HOBt (1.1 equiv.), DCC (2 equiv.), DMAP (1 equiv.), CH_2Cl_2, 0 °C.

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

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.[1] 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.[2] 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 ($(CF_2)_nCF_3$) onto a carbon skeleton.[3] 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.[4] This pentafluorosulfanyl group has been introduced quite efficiently in biologically active compounds leading in some cases to interesting properties.[5] 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.[6] Very recently, we have reported[7] a mild and efficient synthesis of new pentafluorosulfanyl-substituted acrylic esters **2** and amides **3** from 3-pentafluorosulfanyl-propenoic acids **1** (scheme 1).

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,[8a] 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*)-C,N-diphenylnitrone in the presence of strongly electrophilic dipolarophiles such as dimethyl 2,3-dicyanofumarate,[9a] gem-1,1-dinitroethene[9b] or α-phenylnitro-ethene,[9c] 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.[8b,c] In particular, trifluoromethylated pyrrolidines have been efficiently synthetized using the 1,3-dipolar cycloaddition of a non-stabilised azomethine ylide with electro-deficient alkenes (4,4,4-trifluorocrotonates) as initially reported by Bégué[10a,b] and then largely developed by Wang[10c,d] 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.

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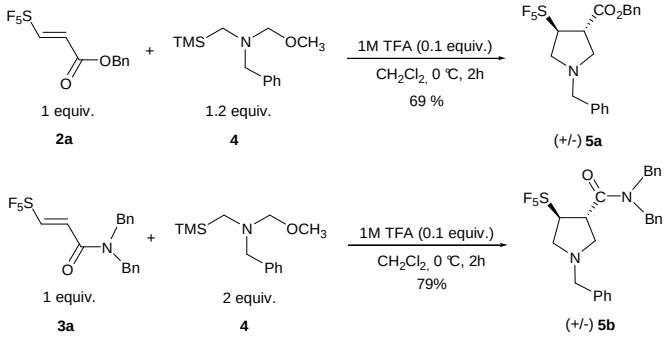
Our initial studies began with the reaction of *trans*-benzyl pentafluorosulfanylacrylate **2a** with *N*-(methoxymethyl)-*N*-[(trimethylsilyl)methyl]-*N*-benzylamine **4** in the presence of a catalytic amount of trifluoroacetic acid in dichloromethane (Scheme 2). To our delight, we obtained the expected SF_5-pyrrolidine **5a** in a good isolated yield (69%). When the same conditions were applied to SF_5-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 pentafluorosulfanyl-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_5-pyrrolidines in each series, several pentafluorosulfanylated esters and amides were engaged in order to study the scope of the reaction.

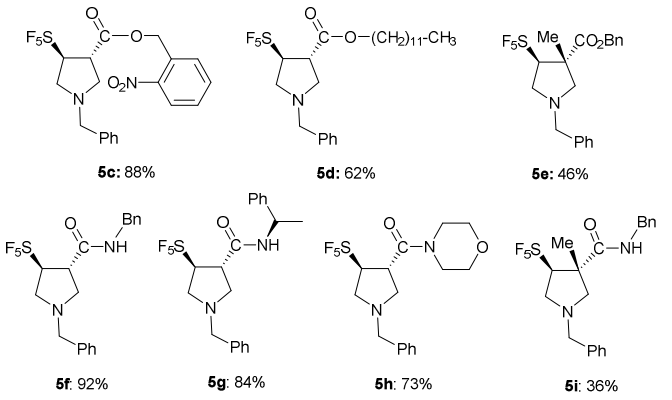
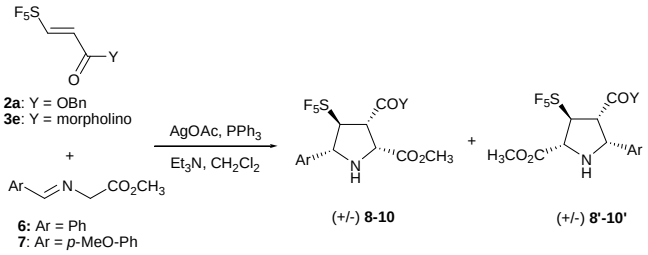


Figure 1 Scope of the 1,3-dipolar cycloaddition using precursor **4** of azomethine ylide.[11]

We demonstrated that 1,3-dipolar cycloaddition could be applied to various SF_5-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_5-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_5-pyrrolidines.

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



Entry	SF_5-derivative	**6** or **7** (equiv.)	AgOAc (mol%)	PPh_3 (mol%)	Time (h)	Yield[a] (%)
1[c]	**2a**	**6** (1.7)	10	10	17[e]	40 (1:1)[b]
2[d]	**2a**	**6** (3)	20	20	90[e]	75 (1:1)[b]
3[d]	**2a**	**6** (3)	20	20	21[f]	73 (1:1)
4[d]	**2a**	**7** (3)	20	20	21[f,g]	35 (2:1)[b]
5[d]	**3e**	**6** (3)	20	20	21[f,g]	48 (1:1.5)[b]

[a] Global isolated yield of regioisomers. [b] Ratio of regioisomers. [c] 0.15 equiv. of Et_3N. [d] 0.25 equiv. of Et_3N. [e] Room temperature. [f] Reflux. [g] Conv. ~ 55%.

Our study began with the reaction of SF_5-unsaturated ester **2a** with glycine derivative **6** (1.7 equiv.) in the presence of 10 mol% AgOAc/PPh_3 and 15 mol% Et_3N at room temperature. A promising 40% yield of pyrrolidines **8+8'** (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_3N 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_5-series compared to the previously reported CF_3-ones.[10a] 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 > 98:2) whereas a 1:1 mixture of regioisomers **8+8'** was obtained using **2a**. When **2a** was reacted with dipole precursor **7** (entry 4), only 55% conversion of SF_5-derivatives was observed after 21h. Longer reaction times led to degradation of the expected pyrrolidines **9+9'**. When SF_5-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_5-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_5-esters and the corresponding SF_5-amide, considering the imine forms a complex with $AgPMe_3^+$ ($\Delta G°_{form}$ = -22 kcal/mol).

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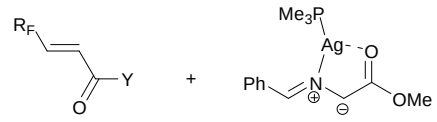

11: Y = OMe, $R_F = CF_3$
12: Y = OMe, $R_F = SF_5$
13: Y = NMe_2, $R_F = SF_5$

Scheme 3 Model systems **11-13** for the theoretical study.

The first step is the formation of a non-covalent adduct (without noticeable global electron charge transfer)[14] between the two reaction partners. For each model compound, six different orientations were studied, as depicted in Figure S1 (see Supplementary Information). They are classified according to the corresponding regiochemistry, the relative positions of the substituents, as well as the s-*cis* or s-*trans* possible isomerization (Table S1, Supplementary Information). This adducts formation (that is also encountered in other cycloaddition reactions)[15] can be qualitatively rationalized in the framework of conceptual DFT (using the recently developed first-state specific dual descriptor),[16] which shows the nucleophilic regions coming on top of the electrophilic areas. It also appeared that the most nucleophilic carbon atom on the imine moiety is that linked to the methoxycarbonyl substituent (Figure S2, Supplementary Information).

The formation of the C-C bonds can be then completed, a dichotomy being revealed by both static and dynamical approaches (see Graphs S1-S4, Figure S3, Supplementary Information): the pentacycle formation can occur in one step that is highly asynchronous (the process can thus be viewed as "one-step – two-stage")[17] as evinced by the reaction force profile,[18] or in two unconcerted steps. As deduced from Table S2 (Supplementary Information), the most thermodynamically stable products do not correspond to the experimentally obtained ones, suggesting that these reactions are ruled by kinetic control. Indeed, in terms of the lowest ΔG° activation barriers, the observed regiochemistry is retrieved, the following hierarchy emerging: CF_3-ester ($\approx$11 kcal/mol) < SF_5-ester (12 kcal/mol) < SF_5-amide (13 kcal/mol), the cycloaddition with SF_5-derivatives being slower, as experimentally observed.

Finally, in order to disentangle the main physicochemical properties involved in this regiochemistry, a detailed energetic decomposition (eq. S6, Supplementary Information) was performed for the most favoured approaches. The first striking point is that the reaction is spontaneous from an electronic energy viewpoint (Figure 2: all $\Delta E_{Solv}<0$) because of the important adduct stabilities. Besides (see Figure 2), ΔE_{Solv} predicts the regiochemistry described in path 1 to be univocally favoured. Such results differ from those obtained from Gibbs energies, notably because the overall activation energy is actually the sum of the adduct destabilization and the TS activation energy itself.

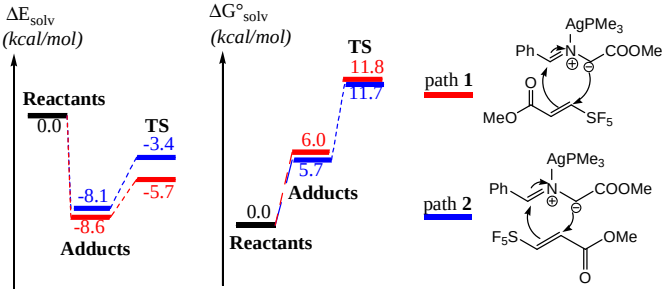

Figure 2 Regiochemistry according to ΔE_{Solv} and $\Delta G°_{Solv}$ viewpoints for the SF_5-ester compound **12**

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, at variance with the electronic stabilization energy of the adduct (E_{add}), the electronic activation barrier (E_{act}) from the adduct, and the vibrational entropies of both adduct and TS. E_{add} favours path 1 in the ester cases and path 2 for amide and is correctly predicted by the preference dual descriptor[19] (Graph S5, Supplementary Information). E_{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_5-ester **12**: the vibrational entropy 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_5-series.

Lastly, one can wonder whether $Ag(PMe_3)^+$ 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_3- (**11**) and SF_5-esters (**12**), respectively), so that the main role of the AgOAc and PPh_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_5-subtituted pyrrolidines using pentafluorosulfanyl-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_5-analogues of biorelevant molecules.

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Notes and references

[a] 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/

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11 Using PMB analogue of **4** and SF_5-ester **2a**, pyrrolidine **5j** was obtained in 66% yield. Using PMB analogue of **4** and SF_5-ester **2c**, pyrrolidine **5k** was obtained in 46 % yield. When the cycloaddition reaction was carried out between $SF_5CH{=}CH{-}CH_2OAc$ and dipole precursor **4** (same conditions as described in Scheme 2), pyrrolidine **5l** was obtained in 61% yield.

12 X-ray crystal structure determinations. For compound **5f**: $C_{19}H_{21}F_5N_2OS$, M=420.44, orthorhombic, Pna2$_1$ (33), a=9.2994(9)Å, b=12.5496Å, c=17.0351(2)Å, V=1988.1(3)Å^3, Z=4, d_{calc}=1.405. The data have been deposit to the Cambridge Crystallographic Data Centre (Nr CCDC1024824). For compound **8**: $C_{20}H_{20}F_5NO_4S$, M=465.4, monoclinic, $P2_1$, a=5.7359(6)Å, b=14.0228(15)Å, c=12.8595(14)Å, β=97.839 (2)°, V=1024.67(19)Å^3, Z=2, d_{calc}=1.509. The data have been deposit to the Cambridge Crystallographic Data Centre (Nr CCDC1024823).

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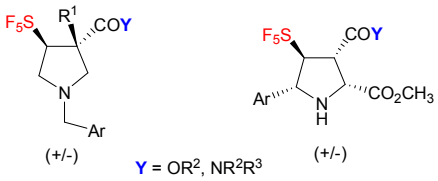
Di-, tri- and tetrasubstituted pentafluorosulfanylated pyrrolidines have been efficiently synthetized via 1,3-dipolar cycloaddition of azomethine ylides.



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