Diastereoselectivity in the Staudinger reaction of pentafluorosulfanylaldimines and ketimines

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Abstract

β-Lactams were diastereoselectively formed by the reaction of SF₅-containing aldimines, or an SF₅-containing ketimine, with benzylketene in a conrotatory ring closure process. Imine formation and cyclization were possible in spite of the acidification of protons on the carbon bound to SF₅. The reactions of the aldimines demonstrated very good 1,2-diastereoselectivity, however lack of stereochemical control of the C–N ketimine geometry was reflected in the stereochemistry of the product β-lactam. Cyclization of imines with a stereogenic center bearing SF₅ was reflected in the 1,2,1,lk,lk selectivity of the β-lactam.

Introduction

The pentafluorosulfanyl (SF₅) group is one of the few truly new functional groups to be introduced to synthetic organic chemistry in the last 100 years [1-6]. With pseudoctahedral geometry around sulfur, the SF₅ group is a unique substituent for the medicinal or pharmaceutical chemist. While the electron withdrawing properties of the SF₅ and CF₃ groups are similar [7,8], the electronegativity of the SF₅ group has been suggested to be as high as 3.65 in contrast to 3.36 for CF₃ [9]. The inductive σᵢ and σᵣ values for SF₅, 0.55 and 0.11 [10], contrast with σᵢ and σᵣ values for CF₃ of 0.39 and 0.12 [11,12] illustrating the increased inductive effect of the SF₅ group relative to the CF₃ group. This effect can also be seen in the calculated dipole moments of 1,1,1-trifluoroethane and pentafluorosulfanyl-methane of 2.589 and 3.556 Debye respectively [7,8]. When these electronic effects are combined with an occupied volume only slightly less than that of a tert-butyl group [3,13], the SF₅ group can have unanticipated influences on the structure such as anchoring side chain and neighboring hydroxy group conformations [14,15].

Given the unique potential of the SF₅ group, the rarity of its application in medicinal or agrochemical materials may be
surprising. However, synthesis of aliphatic SF$_5$-containing building blocks (SF$_5$-substituted aromatic compounds are more accessible) [1,6], is challenging and often beset by confusing reactivity, largely because of the very properties that make SF$_5$ an attractive substituent. Studies of aliphatic compounds have lagged as a consequence, a fact that is compounded by the lack of commercially available aliphatic SF$_5$-containing building blocks. Although the number of known aliphatic pentafluorosulfanylated compounds is constantly increasing [2], this expansion has not generally been accompanied by applications of these materials. Among aliphatic SF$_5$-substituted compounds α-pentafluorosulfanylated aliphatic carbonyl compounds [16], readily prepared from the corresponding enol acetates or enol ethers, are especially valuable as starting materials [17-22]. In these compounds the profound steric influence of the SF$_5$ group [14,15] is accompanied by a dramatic increase in the acidity of the adjacent α-proton, a phenomenon underlying the abstraction of protons by methyllithium and a number of different ylides [16]. The reactions of α-pentafluorosulfanyl carbonyl compounds are governed by a combination of the substantial dipole moment and unique steric effects of the octahedral SF$_5$ group. Aliphatic SF$_5$-containing derivatives of biologically active compounds are not well-known. One exception is the inclusion of an α-SF$_5$-substituted amino acid incorporated at the crucial first and fourth positions of a heptapeptide [23]. When introduced at these positions, the SF$_5$-substituted amino acid had a strong propensity to drive α-helix formation of even this short heptapeptide presumably by minimization of unfavourable hydrophobic interactions.

Results and Discussion

The use of fluoroalkylimines to form β-lactams has proven especially useful in synthesis [24-26] especially in the Ojima β-lactam synthons [27-29] used to prepare docetaxel analogs [26]. The general utility of the familiar Staudinger reaction of imines to transform readily accessible aldehydes to β-lactams has been well reviewed [30-33], yet in spite of this familiarity, the mechanism of this process remains a topic of interest [34-36].

Previously, it has been shown that fluorinated imines can undergo a manifold of reactions that are difficult to access with fluorinated aldehydes or ketones [37-40]. While there are many reports of the utility of trifluoroacetaldimines [41-44], there is only a single report of the preparation of N-ethyl 3,3,3-trifluoropropenaldimine [45], the trifuoroethyl analog of pentafluorosulfanylacetaldehyde (1a). The imine (3,3,3-trifluoropropenaldimine), in combination with the isomeric trifluoropropenamine, was not formed by the condensation of an amine with the aldehyde but rather by addition of an amine to 3,3,3-trifluoropropene. The imine was described as “extremely unstable” [45] with no selective reactions reported. In light of this precedence the reaction of α-SF$_5$-substituted aldehydes and ketones with amines was particularly intriguing.

α-SF$_5$-Substituted aldehydes and ketones

In this work the SF$_5$-bearing aldehyde 1 was prepared by the addition of SF$_5$Cl to the enol ether 2 instead of the previously described additions to enol acetates [16] (Scheme 1). In earlier studies, it was found that the yield of SF$_5$Cl addition to enol acetates was highly dependent upon the purity of the enol acetate substrate, compounds surprisingly difficult to purify. Since vinyl acetate is the only enol acetate readily accessible for this reaction, the commercial availability of high purity propenyl and butenyl ethers 2b and 2c rendered these starting materials highly attractive for the formation of SF$_5$-bearing aldehydes.

![Scheme 1](image)

After addition of SF$_5$Cl to 2, intermediate 3 was typically formed as a 9:1 mixture of diastereomers. Hydrolysis of 3 was easily followed by $^{19}$F NMR, e.g., the resonance for 3b appeared approximately 7 ppm upfield from that of the aldehyde 1b. The $J_{HF}$ coupling constant of 5.0 Hz contrasts with the $J_{Feq,Fax}$ value of 144 Hz.

The ready availability of the α-pentafluorosulfanyl carbonyl compounds facilitated an effort to dramatically expand the utility of these intriguing materials by synthesis and characterization of the corresponding pentafluorosulfanylated β-lactams.

α-SF$_5$-Substituted aldimines and ketimines

The aldehydes 1 were readily converted to the corresponding imine 5 in dichloromethane using anhydrous magnesium sulfate as a dehydrating agent (Scheme 2). Other desiccants, especially inherently basic materials, such as potassium carbonate lead to extensive decomposition. While the crude imine solution likely contained unreacted amine, attempted separation by silica gel chromatography led to extensive decomposition. The product imine consisted of a single stereoisomer as determined by $^{19}$F NMR, tentatively assigned as the E-isomer. Similar to the formation of 1, it was easy to follow formation of the imine by

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19F NMR with the resonance attributed to the equatorial fluorines of the imine 5a (δ 68.8 ppm) appearing upfield of those assigned to the aldehyde 1a (δ 72.4 ppm). In the case of imines 5b–d, the solution also contained between 15–20% of the putative enamine 6b–d, where, for example, the equatorial fluorine resonances of 6b appeared at δ 65.5 ppm in contrast to those of 5b that appeared at δ 59.5 ppm. The tendency for the enamine resonances to appear downfield of imine resonances was confirmed by the preparation of the morpholine enamine of 1a for which the equatorial fluorine resonance is also shifted downfield [46]. As mentioned above, the preparation of N-ethyl 3,3,3-trifluoropropanaldimine, the Schiff base of 3,3,3-trifluoropropanal, was accompanied by enamine formation, likely as a consequence of the acidity of the proton α to the trifluoromethyl group [45,47]. Not surprisingly, 5 was relatively reactive. After careful filtration of the desiccant, the dichloromethane solution of the imine was used in further reactions without purification or separation of unreacted amine or the enamine side product.

Ketene imine cycloaddition reactions of α-SF5-substituted aldimines and ketimines

Dropwise addition of the crude dichloromethane solution of 5 to benzyloxyacetyl chloride and triethylamine in dichloromethane was completed at 0 °C. The solution was then allowed to warm to room temperature with stirring overnight. Not surprisingly, the use of the crude solution of the imine led to the formation of a complex mixture where the desired product β-lactam 7a was a minor constituent. However, the yields of 7 are of product purified by silica gel chromatography and crystallization. The only other fluorinated products observed prior to purification were unreacted imine 5 and the tentatively designated N-acyl-enamine 8. In the case of 7b–d the de of the 1,2-ik to 1,2-ul products was 76%, 84% and 50% respectively. The relative proportion of the product mixture that was comprised of enamine 8b–d was 10%, 4% and 21% respectively.

In an effort to improve the reaction, the addition of triethylamine to a solution of the acid chloride and imine 5 resulted only in decomposition. Excess amine 4 that was present was acylated by benzyloxyacetyl chloride to form the corresponding amide.

The utility of the ketene–imine cyclization was not limited to aldimines. The addition of SF5Br to the enol acetate of ethyl pyruvate 9 formed ethyl pentafluorosulfanylprouvate 11 (Scheme 3). The ketimine 12, prepared via amine condensation with 11, was reacted as described for the aldimines 5 to form the desired β-lactam 7e.

Formation of 7e was accompanied by significantly greater decomposition of 12 and hence 7e was formed in lower overall yields. In contrast to the stereoselective formation of 7b–d, the diastereoselectivity of the Staudinger reactions as determined by 19F NMR was dramatically reduced for 7e to a de of 14%, a value consistent with the Z/E ratio for 12 of 0.7. While the isolated yields of purified 7b–e are especially modest, the reaction conditions have not been optimized. But the significance of these findings lies not only in the difference in reactivity in comparison with trifluoropropanaldimine but also in the relative diastereoselectivity of the ketene–imine cycloaddition reaction in comparison with the other reactions of SF5-bearing aldehydes [16].
Structural characterization of SF$_5$-containing β-lactams

Isolated as a single diastereomer, the relative stereochemistry of 7a, the product of the Staudinger reaction of 5a, is shown in Figure 1. The cis relative stereochemistry of β-lactam is consistent with 1,2-ⅼk conrotatory ring closure of the E-imine 5a as would be predicted for a reaction with the Bose–Evans ketene formed from benzyloxyacetyl chloride [30]. The low yield of β-lactam product is better understood when the reactivity of the intermediate pentafluorosulfanylated imine and the subsequently formed iminium ion are considered. The SF$_5$ group increases the acidity of the α-proton of the imine 5 and of the iminium ion intermediate B formed on the initial nucleophilic attack of the imine on the ketene as illustrated in Scheme 4. The ring closure step requires bond formation between the iminium ion carbon and the enolate carbon B to be particularly facile for the stereoselectivity of the process to be preserved. The ring closure process must compete successfully with loss of the acidic proton from B to form 8 [16]. Another indication of the rapidity of ring closure is the failure to detect the 1,2-ⅼul product. The absence of 1,2-ⅼul product is consistent with retardation of the E/Z imine isomerization by the electron withdrawing pentafluorosulfanyl group [35]. In the reaction of 12, the E/Z ratio of the imine was reflected very well in the 1,2-diastereomeric excess of the product β-lactam 7e.

The ketene–imine condensation of 7c is influenced by the presence of the pentafluorosulfanyl group at a stereogenic center. The 1,2-ⅼk,ⅼk (Si,Si-S) (or (Re,Re-R)) stereochemistry of 7c (Figure 2) suggests the profound dipole associated with the introduction of the SF$_5$ group may influence the diastereoselectivity of ring closure. The initial approach of the ketene (A in Scheme 4) appears to be influenced by avoidance of unfavorable interaction of the ketene with the sterically demanding SF$_5$ group. Previously it was found in single crystal X-ray diffraction studies that the pentafluorosulfanylated group [48] is predictably orthogonal to a carbonyl group as shown in A. Cornforth control of the ring closure step of the zwitterion (B in Scheme 4) where the SF$_5$ would be antiperiplanar to the iminium ion would lead to the observed diastereoselectivity (Scheme 1). This finding is consistent with dipole effects being most important in reactions with highly charged transition states such as B.

In both structures, consistent with the opposing dipole geometry of the Cornforth transition state, the N–C–C–S torsional angles remain near 170° (169° and 167° for 7a and 7c respectively).

The 1,2-ⅼk,ⅼu ring closure product may be formed in the reaction of 5c with benzyloxyketene and simply remain undetected, but it is clear that the control of diastereofacial selectivity in the formation of the principal β-lactam is strongly under the control of the SF$_5$ group.
Conclusion

Low molecular weight pentafluorosulfanylated aldehydes 1 were prepared by addition of SF₅Cl to enol ethers and the subsequent acidic hydrolysis of 3. Formation of Schiff base 5 is problematic but, in contrast to the reactions of the analogous trifluoromethyl compounds, does successfully proceed. Even with a manifold of possible side reactions, β-lactam formation by the ketene-imine cycloaddition reaction of 5 occurs, albeit in very modest yields. The 1,2-β stereochemistry of the β-lactam 7 was consistent with rapid cyclization and a failure of the imines 5 to isomerize. The presence of a pentafluorosulfanylated stereogenic carbon as in 5c, apparently also influences the 2,3-β stereochemistry. Optimization of β-lactam synthesis will require a better understanding of the nature of the competing, undesirable reactions and enable utilization of this unique construct in further synthetic transformations. The product β-lactams are a useful entrée to the diastereoselective synthesis of pentafluorosulfanyl β-amino acids and suggest a path to the preparation of more extensively functionalized SF₅-containing β-lactams.

Supporting Information

Supporting Information File 1
Detailed experimental procedures and spectroscopic data for 1a–e, 10, 5a–d, 7a–e and 11.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-9-303-S1.pdf]

Supporting Information File 2
X-ray crystallographic data for 7a and 7c, CCDC 937908 and 937909.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-9-303-S2.cif]

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References

1. Welch, J. T. Applications of pentafluorosulfanyl substitution in life sciences research. In Fluorine in Pharmaceutical and Medicinal Chemistry; Gouveneur, V.; Müller, K., Eds.; Imperial College Press: London, 2012; pp 175–207.
2. Altomonte, S.; Zanda, M. J. Fluorine Chem. 2012, 143, 57–93. doi:10.1016/j.jfluchem.2012.06.030
3. Lentz, D.; Seppelt, K. The –SF₅, –SeF₅, and –TeF₅ groups in organic chemistry. In Chemistry of Hypervalent Compounds; Akba, K.-y., Ed.; Wiley-VCH: New York, 1999; pp 295–323.
4. Winter, R. W.; Dodean, R. A.; Gard, G. L. SF₅ synths: Pathways to organic derivatives of SF₅. In Fluorine-Containing Synthons; Soloshonok, V. A., Ed.; American Chemical Society: Washington, D. C., 2005; pp 87–118. doi:10.1021/bk-2005-0911.ch004
5. Gard, G. L. Chim. Oggi 2009, 27, 10–13.
6. Kirsch, P. Modern Fluororganic Chemistry. Synthesis, Reactivity and Applications; Wiley-VCH: Weinheim, Germany, 2004. doi:10.1002/352760393X
7. Brant, P.; Berry, A. D.; DeMarco, R. A.; Carter, F. L.; Fox, W. B.; Hashmian, J. A. J. Electron Spectrosc. Relat. Phenom. 1981, 22, 119–129. doi:10.1016/0368-2048(81)90021-7
8. True, J. E.; Thomas, T. D.; Winter, R. W.; Gard, G. L. Inorg. Chem. 2003, 42, 4437–4441. doi:10.1021/ic0345298
9. Sæthre, L. J.; Bernah, N.; Bozek, J. D.; Barve, K. J.; Carroll, T. X.; Kukk, E.; Gard, G. L.; Winter, R.; Thomas, T. D. J. Am. Chem. Soc. 2001, 123, 10729–10737. doi:10.1021/ja016395j
10. Sheppard, W. A. J. Am. Chem. Soc. 1962, 84, 3072–3076. doi:10.1021/ja00875a007
11. Taft, R. W., Jr.; Lewis, I. C. J. Am. Chem. Soc. 1959, 81, 5343–5352. doi:10.1021/ja01529a025
12. Taft, R. W., Jr. J. Phys. Chem. 1960, 64, 1805–1815. doi:10.1021/jp00841ai003
13. Anthony, M. Aust. N. Z. J. Med. 1994, 14, 888–895. doi:10.1111/j.1445-5994.1994.tb03802.x
14. Savoie, P. R.; Higashiyama, S.; Lin, J.-H.; Wagle, D. V.; Welch, J. T. J. Fluorine Chem. 2012, 143, 281–286. doi:10.1016/j.jfluchem.2012.06.027
15. Savoie, P. R.; Welch, J. M.; Higashiyama, S.; Welch, J. T. J. Fluorine Chem. 2013, 148, 1–5. doi:10.1016/j.jfluchem.2013.01.013
16. Ngo, S. C.; Lin, J.-H.; Savoie, P. R.; Hines, E. M.; Pugliese, K. M.; Welch, J. T. Eur. J. Org. Chem. 2012, 4902–4905. doi:10.1002/ejoc.201200763
17. Winter, R.; Gard, G. L. J. Fluorine Chem. 1994, 66, 109–116. doi:10.1016/0022-1139(93)03005-7
18. Ray, N. H. J. Chem. Soc. 1963, 1440–1441. doi:10.1039/UR63000001440
19. Kleemann, G.; Seppelt, K. Chem. Ber. 1979, 112, 1140–1148. doi:10.1002/cber.19791120409
20. Dobnier, W. R., Jr.; Ali-Mohand, S.; Schertz, T. D.; Sergeeva, T. A.; Cradlebaugh, J. A.; Mitani, A.; Gard, G. L.; Winter, R. W.; Thrasher, J. S. J. Fluorine Chem. 2006, 127, 1302–1310. doi:10.1016/j.jfluchem.2006.05.003
21. Coffman, D. D.; Tullock, C. W. Carbonylic compounds containing the SF₅ function. U.S. Patent US3,102,303, Sept 3, 1963.
22. Winter, R.; Willett, R. D.; Gard, G. L. Inorg. Chem. 1989, 28, 2499–2501. doi:10.1021/ic00311e054
23. Lim, D. S.; Lin, J.-H.; Welch, J. T. Eur. J. Org. Chem. 2012, 3946–3954. doi:10.1002/ejoc.201200327
24. Abouaibdallah, A.; Bégué, J.-P.; Bonnet-Delpon, D.; Thanh Nga, T. T. J. Org. Chem. 1997, 62, 8826–8833. doi:10.1021/jo971381a
25. Petrik, V.; Röschenhalter, G.-V.; Cahard, D. Tetrahedron 2011, 67, 3254–3259. doi:10.1016/j.tet.2011.03.001
26. Pepe, A.; Kuznetsova, L.; Sun, L.; Ojima, I. Fluoro-taxoid anticancer agents. In Fluorine in Medicinal Chemistry and Chemical Biology; Ojima, I., Ed.; John Wiley & Sons Ltd.: Chichester, 2009; pp 117–139. doi:10.1002/9781444312096.ch7
27. Ojima, I. β-Lactam synthon method: enantiomERICly pure β-lactams as synthetic intermediates. In Organic Chemistry of β-lactams; Georg, G., Ed.; VCH: New York, NY, 1993; pp 197–255.
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28. Kamath, A.; Ojima, I. Tetrahedron 2012, 68, 10640–10664. doi:10.1016/j.tet.2012.07.090
29. Ojima, I.; Zuniga, E. S.; Seitz, J. D. Top. Heterocycl. Chem. 2013, 30, 1–63. doi:10.1007/7081_2012_86
30. Georg, G. I.; Ravikumar, V. T. Stereocontrolled ketene-imine cycloaddition reactions. In Organic Chemistry of β-lactams; Georg, G. I., Ed.; VCH: New York, NY, 1993; pp 295–368.
31. Palomo, C.; Aizpurua, J. M.; Garboa, I.; Oiarbide, M. Eur. J. Org. Chem. 1999, 3223–3235. doi:10.1002/(SICI)1099-0690(199912)1999:12<3223::AID-EJOC3223>3.0.CO;2-1
32. Palomo, C.; Aizpurua, J. M.; Garboa, I.; Oiarbide, M. Curr. Med. Chem. 2004, 11, 1837–1872. doi:10.2174/0929867043364900
33. Thompson, S.; Coyne, A. G.; Keipe, P. C.; Smith, M. D. Chem. Soc. Rev. 2011, 40, 4217–4231. doi:10.1039/c1cs15022g
34. Cossio, F. P.; Arrieta, A.; Sierra, M. A. Acc. Chem. Res. 2008, 41, 925–936. doi:10.1021/ar800933
35. Jiao, L.; Liang, Y.; Xu, J. J. Am. Chem. Soc. 2006, 128, 6060–6069. doi:10.1021/ja056711k
36. Xu, J. Tetrahedron 2012, 68, 10696–10747. doi:10.1016/j.tet.2012.04.007
37. Fuster, S.; Jiménez, D.; Sanz-Cervera, J. F.; Sánchez-Roselló, M.; Esteban, E.; Simón-Fuentes, A. Org. Lett. 2005, 7, 3433–3436. doi:10.1021/o505791f
38. Zanda, M.; Bravo, P.; Volonterio, A. Stereoselective synthesis of β-fluoroalkyl β-amino alcohol units. In Asymmetric Fluororganic Chemistry; Ramachandran, P. V., Ed.; American Chemical Society: Washington, D.C., 2000; Vol. 746, pp 127–141.
39. Welch, J. T.; De Corte, B.; De Kimpe, N. J. Org. Chem. 1990, 55, 4981–4983. doi:10.1021/jo00304a002
40. Welch, J. T.; Seper, K. W. J. Org. Chem. 1988, 53, 2991–2999. doi:10.1021/jo00248a017
41. Carroccia, L.; Floravanti, S.; Pellacani, L.; Tardella, P. A. Synthesis 2010, 4096–4100. doi:10.1055/s-0030-1258280
42. Nie, J.; Guo, H.-C.; Cahard, D.; Ma, J.-A. Chem. Rev. 2011, 111, 455–529. doi:10.1021/cr100168a
43. Magueur, G.; Legros, J.; Meyer, F.; Ourélevitch, M.; Crousse, B.; Bonnet-Delpin, D. Eur. J. Org. Chem. 2005, 1258–1265. doi:10.1002/ ejoc.200400719
44. Crousse, B.; Narizuka, S.; Bonnet-Delpin, D.; Bégué, J.-P. Synlett 2001, 679–681. doi:10.1055/s-2001-13364
45. Stepanova, N. P.; Lebedev, V. B.; Orlova, N. A.; Turbanova, E. S.; Petrov, A. A. Zh. Org. Khim. 1988, 24, 692–699.
46. Welch, J. T.; Penger, A. unpublished results.
47. Yamazaki, T.; Kobayashi, R.; Kitazume, T.; Kubota, T. J. Org. Chem. 2006, 71, 2498–2502. doi:10.1021/jo0524340
48. Welch, J. T.; Zhong, L.; Filatov, A. S. unpublished results.