Heterocycles

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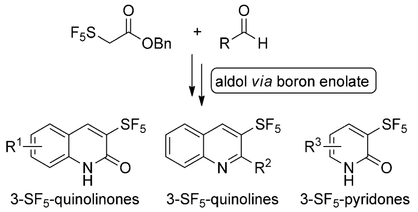
Formation of α-SF_5-Enolate Enables Preparation of 3-SF_5-Quinolin-2-ones, 3-SF_5-Quinolines, and 3-SF_5-Pyridin-2-ones: Evaluation of their Physicochemical Properties

*Adrien Joliton, Jean-Marc Plancher, and Erick M. Carreira**

Abstract: *This study describes, for the first time, the generation of a SF_5-substituted ester enolate from benzyl SF_5-acetate under soft enolization conditions, which in turn participates in aldol addition reactions in high yield. The reaction was applied in the synthesis of 3-SF_5-quinolin-2-ones, 3-SF_5-quinolines, and 3-SF_5-pyridin-2-ones, none of which have previously been reported. To provide guidelines for their use in drug discovery, the physicochemical properties of these building blocks were determined and compared with those of their CF_3- and t-Bu-analogues.*



Physicochemical properties
- log*D* (***t*Bu** > $\mathbf{SF_5}$ > $\mathbf{CF_3}$)
- pK_a ($\mathbf{SF_5}$ > $\mathbf{CF_3}$ > ***t*Bu**)
- aqueous solubility ($\mathbf{SF_5}$ and $\mathbf{CF_3}$ > ***t*Bu**)
- membrane permeability ($\mathbf{CF_3}$ > ***t*Bu** > $\mathbf{SF_5}$ for quinolinones; ***t*Bu** > $\mathbf{SF_5}$ > $\mathbf{CF_3}$ for pyridones)
- metabolic stability ($\mathbf{SF_5}$ ∪ $\mathbf{CF_3}$ > ***t*Bu**)

Figure 1. Synthesis of 3-SF_5-substituted quinolinones, quinolines and pyridones and physicochemical properties evaluated.

There have been impressive advances recently in methods for the synthesis of fluorinated building blocks.[1] Numerous studies attest to the benefits that may be accrued in property modulation in connection to their incorporation into structures of interest.[2] In this respect, new tactics for the introduction of groups such as CF_3,[1b–d] $(CF_2)_nCF_3$,[1e–g] OCF_3,[1h,i] or SCF_3[1j–m] provide fresh opportunities for the drug discovery process. In parallel with these exciting developments, the pentafluorosulfanyl group (SF_5) has recently gained increased attention because of its potential applications in medicinal chemistry, agricultural chemistry, and materials science.[3] However, the synthesis and chemistry of building blocks incorporating the SF_5 group lag behind. As part of a research program to access novel building blocks for drug discovery,[4,5] we have been interested in the development of new methods to obtain unprecedented SF_5-substituted heterocycles. Herein, we document approaches to 3-SF_5-substituted quinolinones, quinolines, and pyridones, as well as an evaluation of their physicochemical properties (log*D*, pK_a, aqueous solubility, membrane permeability, and metabolic stability) by comparison with those of their CF_3- and *t*-Bu-analogues (Figure 1).

The first SF_5-aryl compounds were prepared by Sheppard by oxidative fluorination of aryl disulfides with AgF_2.[6] Umemoto recently disclosed a two-step procedure with improved yields and substrate scope, relying on the synthesis of SF_4Cl-substituted arenes, which were converted into the corresponding SF_5-aryl products by treatment with ZnF_2, SbF_5, or HF-pyridine.[7]

The need for additional methods affording novel SF_5-containing building blocks, in particular SF_5-heterocycles, is an important endeavor as a means of increasing access to uncharted regions of chemical space, while at the same time providing compounds with bespoke physicochemical properties. In this regard, Dolbier recently described the efficient preparation of 2-SF_5-pyridines by treatment of 2-SF_4Cl-substituted pyridines neat with AgF.[8] Beier, Knochel, and Xu have independently reported the syntheses of benzannulated heterocycles from *para*- and *meta*-SF_5-substituted nitrobenzenes.[9] Dolbier has disclosed that 3-SF_5-furans could be obtained by retro-Diels–Alder reaction of bridged SF_5-substituted bicyclic compounds.[10] Pyrazoles,[11a] triazoles,[11a–c] pyrroles,[11d,e] thiophenes,[11e] pyrrolidines,[11f] isoxazoles,[11g] isoxazolines,[11g] and isoxazolidines[11h] bearing a SF_5 group have been accessed by 1,3-dipolar cycloaddition of SF_5-alkynes or SF_5-alkenes. However, to the best of our knowledge, there is no reported synthesis of quinolinones and quinolines bearing a SF_5 group on the heterocyclic moiety, or six-membered aromatic *N*-heterocycles with 3-SF_5-substitution.

A strategy was envisioned in which these entities could be accessed through addition of a SF_5-substituted acetate enolate to aldehydes as a key C–C bond forming step (Scheme 1). However, a critical issue in such an approach is the potential instability of the intermediate enolate, leading to decomposition of the starting material following fluoride elimination.[12] In this respect, the chemistry of SF_5-acetates is largely unexplored. Only one example of functionalization in the α-

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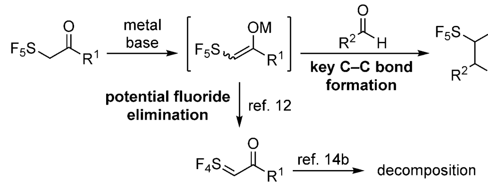
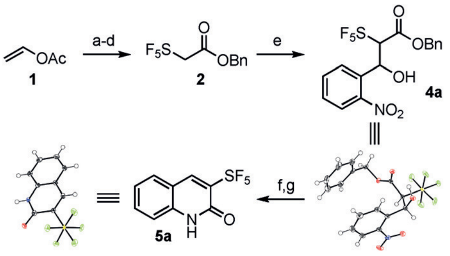


Scheme 1. Formation of α-SF_5-enolate.

position of the SF_5 group has been recently reported, in which Ireland–Claisen rearrangements and subsequent esterification of allyl SF_5-acetates were achieved, albeit in 3–33% yield with limited substrate scope.[13] Attempts to alkylate methyl SF_5-acetate using various bases have not been met with success, even if formation of the enolate was validated by deuterium quench experiments.[14b]

We decided to examine the chemistry of α-SF_5-substituted acetate **2** for the preparation of a wide range of building blocks (Scheme 2). The benzyl ester was selected on the basis of its assumed low volatility, making it convenient to handle. Benzyl SF_5-acetate **2** was prepared by addition of SF_5Cl to vinyl acetate **1** under the conditions developed by Dolbier,[14] followed by reduction of the intermediate 1-Cl-2-SF_5-ethyl acetate with $LiAlH_4$, subsequent oxidation of the ensuing alcohol to the carboxylic acid, and esterification with BnOH. Merely a single purification by column chromatography at the end of this four-step sequence was sufficient to obtain **2** in high yield on multigram-scale.



Scheme 2. Synthesis of 3-SF_5-quinolinone: a) SF_5Cl, Et_3B (10 mol%), pentane, −30 °C to −20 °C; b) $LiAlH_4$, Et_2O, 0 °C; c) H_5IO_6, CrO_3 (1 mol%), CH_3CN/H_2O (99:1), 0 °C; d) BnOH, DCC, DMAP (10 mol%), CH_2Cl_2, 0 °C to r.t., 80% over 4 steps; e) n-Bu_2BOTf, i-Pr_2NEt, CH_2Cl_2, −78 °C to −20 °C, then 2-NO_2-C_6H_4CHO (**3a**), −45 °C, 86%, d.r. = 4.2:1; f) H_2, $Pd(OH)_2$ (15 mol%), MeOH, r.t.; g) EDC, DMAP (20 mol%), THF, r.t., 83% over 2 steps. DCC = dicyclohexylcarbodiimide, DMAP = 4-dimethylaminopyridine, EDC = 1-ethyl-3-(dimethylaminopropyl)carbodiimide.

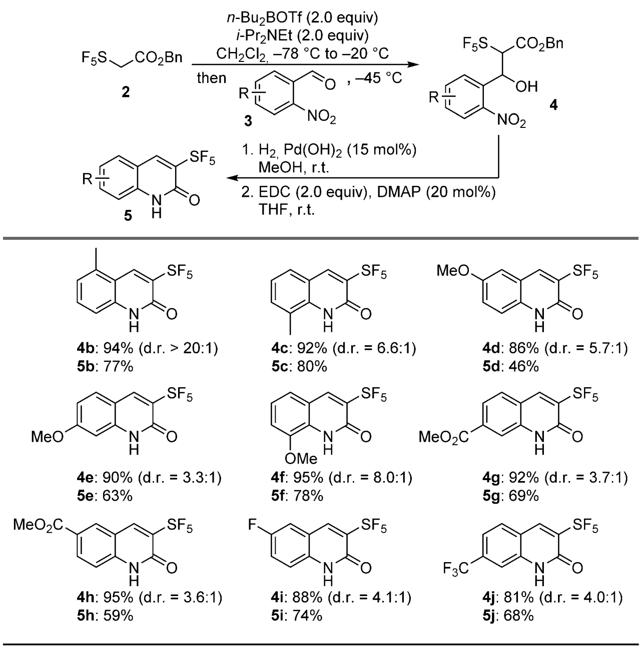
With an efficient route to **2** established, the key aldol reaction was investigated. Similar to previous observations,[14b] our initial attempts to effect aldol addition reaction following generation of lithium or sodium enolates of **2** using bases such as LDA or NaH were unsuccessful. The comparable instability of α-CF_3-enolates has been described in the literature, however, several reports have shown that titanium or boron enolates of α-CF_3-carbonyl derivatives can be used in aldol reactions.[15] Consequently, we suspected that benzyl SF_5-acetate **2** could be subjected to soft enolization conditions. Indeed, formation of the enolate was achieved by treatment of **2** with n-Bu_2BOTf (2.0 equiv) and i-Pr_2NEt (2.0 equiv) in CH_2Cl_2 for 30 min at −78 °C, then 30 min at −20 °C. Subsequent addition of 2-nitrobenzaldehyde **3a** at −45 °C afforded **4a** in 86% yield. Although it was inconsequential for our purposes, it is noteworthy that the product was formed with some diastereocontrol (d.r. = 4.2:1). Recrystallization of the major diastereoisomer from fluorobenzene afforded crystals, confirming that the *anti*-isomer was favored.[16] It is important to note that this represents the first example of the use of a SF_5-substituted enolate in an aldol addition reaction.

With **4a** in hand, 3-SF_5-quinolinone **5a** was obtained in excellent yield in two steps. Reduction of the nitro group and cleavage of the benzyl ester afforded a mixture of cyclic and acyclic products, as indicated by ^{19}F NMR spectroscopy. After extensive experimentation, it was found that treatment of this mixture with EDC and catalytic DMAP completed the desired cyclization along with elimination to produce **5a**. This three-step sequence could be achieved on gram-scale.

To showcase the generality of the method, we prepared a collection of 3-SF_5-quinolinones (Table 1). The conditions for the aldol reaction were suitable for a range of nitroaryl aldehydes **3**. Indeed, nitrobenzaldehydes bearing substituents such as methyl, ester, methoxy, fluorine, or trifluoromethyl were converted to alcohols **4** in excellent yields. Subsequent treatment with $Pd(OH)_2$ under H_2 atmosphere followed by cyclization afforded the corresponding quinolinones.

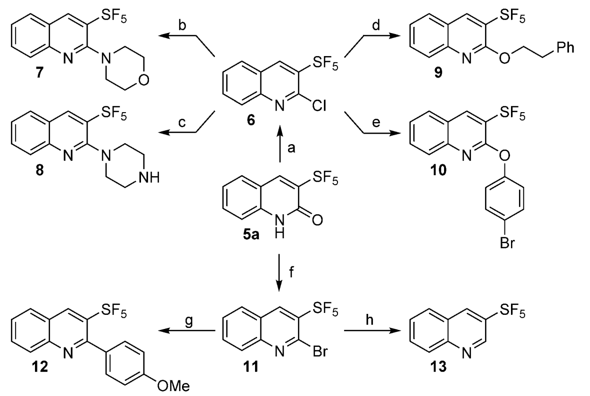
In order to demonstrate the synthetic utility of these SF_5-quinolinones, we prepared a variety of 3-SF_5-quinolines from **5a** (Scheme 3). Treatment with $POCl_3$ afforded 2-Cl-3-SF_5-quinoline **6**, which serves as an optimal platform for nucleophilic aromatic substitution. Accordingly, the chloride was displaced by amines such as morpholine or piperazine to

Table 1: Synthesis of 3-SF_5-quinolinones.[a]



4b: 94% (d.r. > 20:1)
5b: 77%
4c: 92% (d.r. = 6.6:1)
5c: 80%
4d: 86% (d.r. = 5.7:1)
5d: 46%
4e: 90% (d.r. = 3.3:1)
5e: 63%
4f: 95% (d.r. = 8.0:1)
5f: 78%
4g: 92% (d.r. = 3.7:1)
5g: 69%
4h: 95% (d.r. = 3.6:1)
5h: 59%
4i: 88% (d.r. = 4.1:1)
5i: 74%
4j: 81% (d.r. = 4.0:1)
5j: 68%

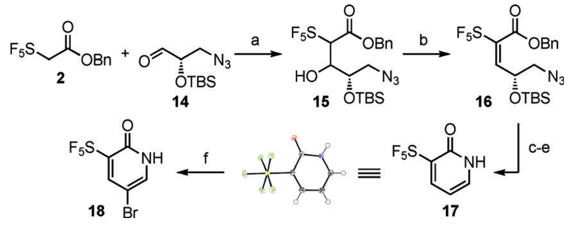
[a] Yields shown are those of isolated products; d.r. determined by ^{19}F NMR.



Scheme 3. Synthesis of 3-SF_5-quinolines: a) $POCl_3$, 110 °C, 96 %; b) K_2CO_3, morpholine, dioxane, 105 °C, 94 %; c) K_2CO_3, piperazine, dioxane, 105 °C, 97 %; d) *t*-BuOK, 2-phenylethanol, THF, r.t., 98 %; e) *t*-BuOK, 4-bromophenol, THF, 50 °C to 70 °C, 76 %; f) $POBr_3$, 120 °C, 97 %; g) 4-MeO-$C_6H_4B(OH)_2$, K_2CO_3, $Pd(PPh_3)_4$ (10 mol %), 115 °C, 60 %; h) *n*-Bu_3SnH, AIBN (2 mol %), benzene, 85 °C, 84 %. AIBN = azobisisobutyronitrile.

give compounds **7** and **8** in excellent yields. Moreover, treatment of **6** with phenylethanol in the presence of *t*-BuOK afforded **9** in 98 % yield. Nucleophilic substitution with 4-bromophenol furnished **10** in 76 % yield. Alternatively, when heated with neat $POBr_3$, **5a** could be converted to 2-Br-3-SF_5-quinoline **11**. The latter was arylated by a Suzuki–Miyaura coupling reaction, providing **12** in 60 % yield. Finally, the simple 3-SF_5-quinoline **13** was obtained by radical debromination.

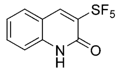
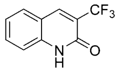
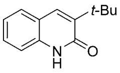
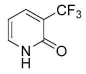
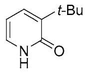
We next focused our attention on the preparation of 3-SF_5-pyridone (Scheme 4). Aldol adduct **15** was obtained by treatment of boron enolate of **2** with aldehyde **14**.[17] Thus, in addition to aromatic aldehydes, aliphatic aldehydes are also suitable for α-functionalization of the SF_5. Attempts to directly reduce and cyclize free alcohol **15** only led to low yields of the hydroxy-lactam. Consequently, the hydroxyl group was eliminated first, leading to *trans*-**16**. After azide reduction and benzyl removal, intramolecular amidation was achieved by treatment with EDC to give the corresponding unsaturated δ-lactam. 3-SF_5-pyridone **17** was obtained by heating of the TBS-protected alcohol in neat H_2SO_4. The compatibility of the SF_5 to such harsh conditions is notable, and emphasizes its high stability. We demonstrated that this building block is amenable to further elaboration by regioselective electrophilic bromination to obtain the potentially versatile pyridone **18**.



Scheme 4. Synthesis of 3-SF_5-pyridone: a) *n*-Bu_2BOTf, *i*-Pr_2NEt, CH_2Cl_2, −78 °C to −20 °C, then **14**, −45 °C, 91 %, d.r. = 5.1:2.7:1.8:1; b) Ac_2O, DMAP, CH_2Cl_2, 0 °C, 92 %, *E*:*Z* > 20:1; c) H_2, $Pd(OH)_2$ (20 mol %), MeOH, r.t.; d) EDC, THF, r.t., 57 % over 2 steps; e) H_2SO_4, 90 °C, 82 %; f) NBS, DMF, r.t., 74 %. NBS = *N*-bromosuccinimide.

The novelty associated with compounds incorporating SF_5 substituent leads to questions of their utility in drug discovery with respect to the modulation of physicochemical properties. To showcase the characteristic assets of the SF_5 group, we assessed the physicochemical properties of 3-SF_5-quinolinone **5a** and 3-SF_5-pyridone **17**. As previously shown by us[5b] and others,[18] the SF_5 group is considered as a bioisostere of CF_3 and *t*-Bu groups. Consequently, we compared the data collected for **5a** and **17** with their corresponding CF_3- and *t*-Bu-analogues (Table 2). As expected and illustrated by the

Table 2: Physicochemical data of **5a**, **17** and their corresponding CF_3 and *t*-Bu analogues.

Compound		log*D*[a]	PAMPA[b]	PAMPA details[c]	pK_a[d]	LYSA[e]	hCl[f]	mCl[f]	rCl[f]
5a		2.80 ± 0.02	4.22 ± 1.61	69; 18; 13	10.30 ± 0.01	23[g]	44 ± 10	15 ± 8	17 ± 10
19		2.18 ± 0.04	9.32 ± 0.81	68; 2; 28	10.75 ± 0.01	42 ± 3	42 ± 9	26 ± 6	< 10
20		3.59 ± 0.02	7.00 ± 0.28	26; 66; 8	> 12.00	1.9 ± 0.1	42 ± 13	116 ± 12	16 ± 10
17		–[h]	3.78 ± 0.16	85; 0; 15	9.24 ± 0.01	200 ± 8	< 10	< 10	< 10
21		0.43 ± 0.06	1.19 ± 0.05	88; 7; 5	9.92 ± 0.01	125 ± 2	< 10	< 10	< 10
22		1.87 ± 0.01	13.82 ± 0.04	64; 2; 35	> 12.00	55 ± 1	12 ± 10	38 ± 7	32 ± 11

[a] log*D* = intrinsic distribution coefficient between octanol and aqueous buffer (pH 7.4). [b] Membrane permeability ($nm\,s^{-1}$) as derived from the parallel artificial membrane permeability assay (PAMPA). [c] PAMPA retention values (%): in donor compartment; in membrane; in acceptor compartment. [d] Acidities determined spectrophotometrically at 23 ± 1 °C. [e] Solubility ($mg\,L^{-1}$) determined by lyophilisation solubility assay (LYSA) at pH 6.5. [f] Metabolic stability; values describe intrinsic clearance ($\mu M\,min^{-1}\,mg^{-1}$) in human (h), mouse (m), and rat (r) microsomes. [g] Measured only once. [h] Out of range (no MS peak detected).

log*D* values of the quinolinones, SF_5 exhibits a higher lipophilicity than CF_3, but lower than *t*-Bu. Unfortunately, log*D* for 3-SF_5-pyridone **5a** could not be determined and therefore could not be compared to its CF_3- and *t*-Bu analogues **21** and **22**. Interestingly, for those two types of compounds, no correlation between membrane permeability and the lipophilicity was observed. Indeed, for the pyridones, the membrane permeability increases in the order $CF_3 < SF_5 < t$-Bu, whereas for the quinolinones, the CF_3-analogue **19** displays the highest membrane permeability. The high electronegativity of the SF_5 group is well highlighted by the pK_a values observed, the SF_5-quinolinone and SF_5-pyridone being the most acidic in each series. Concerning the solubility, both CF_3- and SF_5-compounds possess considerably higher values than their *t*-Bu-counterparts. Metabolic stabilities of these compounds were also evaluated by determining the intrinsic clearance in human, mouse, and rat microsomes. For the quinolinones, the three compounds show similar stability in human and rat microsomes, but the *t*-Bu-analogue **20** possesses a much higher clearance rate than **5a** and **19** in mouse microsomes. The three substituted pyridones also display similar clearance values in human microsomes. However, *t*-Bu-pyridone **22** is less stable than **17** and **21** in mouse and rat microsomes.

In conclusion, we have documented an approach for the preparation of unprecedented SF_5-heterocyclic building blocks, namely quinolinones, quinolines, and pyridones. A significant development is the ability to generate an enolate derived from benzyl SF_5-acetate and its use in aldol reactions. This strategy, allowing functionalization in the α-position of the SF_5 group, offers new opportunities for the further development of pentafluorosulfanyl chemistry. Finally, by comparing the physicochemical data of these building blocks with their CF_3 and *t*-Bu analogues, we underscore that the SF_5 group can be regarded as a surrogate for these functional groups with property-modulating effects of interest to medicinal chemists.

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[16] CCDC 1415085 (**4a**), 1415086 (**5a**) and 1415087 (**17**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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