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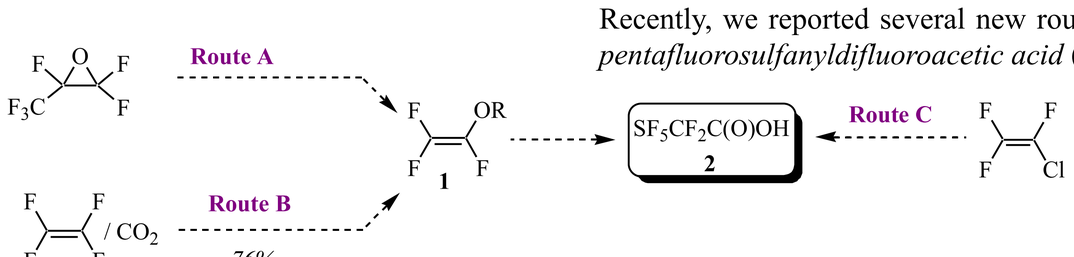
Introduction

It is well known that fluorinated molecules play an important role in daily life. For example, organic molecules bearing either a fluorine atom itself or a short polyfluorinated substituent such as mono-, difluoro-, and trifluoromethyl groups, or pentafluoroethyl and perfluoropropyl groups are already widely used in medicinal and agricultural chemistry. In contrast, molecules with long perfluorinated chains have found vast application in materials science. Among the fluorine-containing moieties, the pentafluorosulfanyl (SF_5) substituent occupies a special place.[1] The pentafluorosulfanyl group brings unique properties to organic compounds and often improves their biological activities due to the group's high chemical and metabolic stability, significant lipophilicity, substantial steric effect, unique geometry, and low surface energy. Here we present new routes towards SF_5-substituted aliphatic and heterocyclic compounds.

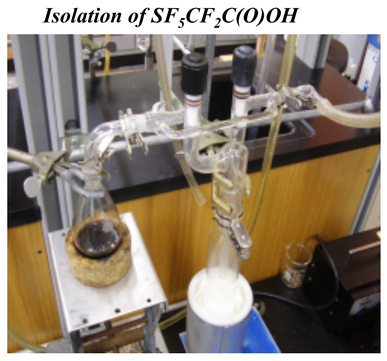
Synthesis of new SF_5-containing aliphatic compounds

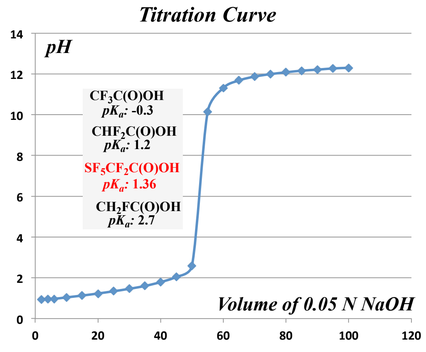
Synthesis of $SF_5CF_2C(O)OH$

Recently, we reported several new routes to *pentafluorosulfanyldifluoroacetic acid* (**2**).[2]



Among these three approaches, **Route B** seems to be the most promising in terms of the availability of the starting materials and cost efficiency.





Synthesis of SF_5CF_2C-containing aliphatic compounds

Mild heating of the acid **2** with a slight excess of PCl_5 produced the corresponding *acyl chloride* **3** in nearly quantitative yield. Ammonolysis of **3** with ammonia gas in dichloromethane gave *amide* **4,** which was converted into *pentafluorosulfanyldifluoroacetonitrile* (**5**) by dehydration in the presence of phosphorus(V) oxide.

$SF_5CF_2C(O)OH \xrightarrow[60 - 65\ ^oC,\ overnight]{PCl_5} \underset{\mathbf{3}}{SF_5CF_2C(O)Cl} \xrightarrow[-\ 78\ ^oC\ to\ RT,\ 12\ h]{NH_3} \underset{\mathbf{4}}{SF_5CF_2C(O)NH_2} \xrightarrow[140 - 170\ ^oC]{P_2O_5} \underset{\mathbf{5}}{SF_5CF_2CN}$

94% 93% 75%

Pentafluorosulfanyldifluoroacetyl chloride (**3**) can be reduced to the corresponding alcohol **6** with lithium aluminum hydride.

$SF_5CF_2C(O)Cl \xrightarrow[Et_2O,\ RT,\ overnight]{LiAlH_4} \underset{\mathbf{6}}{SF_5CF_2CH_2OH}$

quantitative (based on NMR)

Reaction of the acyl chloride **5** with Grignard reagents proceeded smoothly and led to the corresponding ketones **7a** and **7b** in moderate yield.

$SF_5CF_2C(O)Cl + RMgBr \xrightarrow[Et_2O,\ -78\ ^oC\ to\ RT,\ 6\ h]{} \underset{\mathbf{7a} = Ph\ (63\%)\quad \mathbf{7b} = n\text{-}Bu\ (54\%)}{R(C{=}O)CF_2SF_5}$

Borodin-Hunsdieker reaction of the silver salt of acid **2** led to *pentafluorosulfanyldifluoroiodomethane* (**8**), which later was reduced to *pentafluorosulfanyldifluoromethane* (**9**) by two different methods.

$SF_5CF_2C(O)OAg \xrightarrow[180\ ^oC]{I_2} \underset{\mathbf{8}}{SF_5CF_2I}$

63%

Method A $\underset{\mathbf{9}}{SF_5CF_2H} \xleftarrow[-\ 80\ ^oC\ to\ RT,\ overnight]{n\text{-}Bu_3SnH\ in\ toluene} SF_5CF_2I \xrightarrow[-\ 80\ ^oC\ to\ RT,\ overnight]{Et_3B\ in\ hexane} \underset{\mathbf{9}}{SF_5CF_2H}$ ***Method B***

38% 49%

Using the aforementioned methods we synthesized *pentafluorosulfanyltetrafluoroethane* (**11**)[3] from compound **10**, which was obtained via radical addition of SF_5Br to tetrafluoroethylene.

$SF_5Br + F_2C{=}CF_2 / CO_2 \xrightarrow[RT\ to\ 110\ ^oC,\ slowly]{BPO} \underset{\mathbf{10}}{SF_5CF_2CF_2Br} \xrightarrow[-\ 196\ ^oC\ to\ RT,\ 12\ h]{n\text{-}Bu_3SnH\ in\ tetraglyme} \underset{\mathbf{11}}{SF_5CF_2CF_2H}$

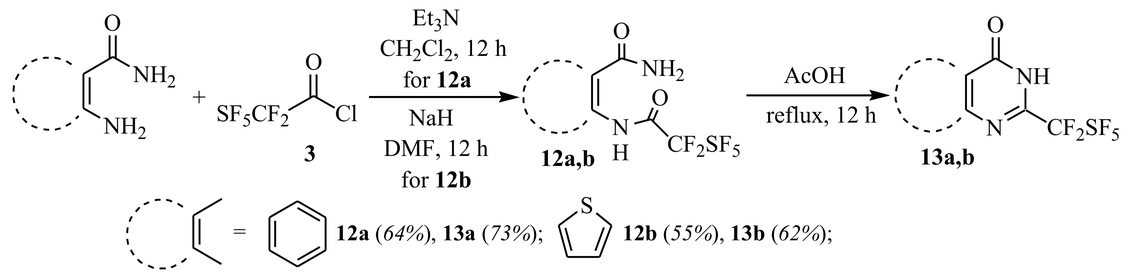
88% — *or* — Et3B in heptane, RT, 4-5 h

96% (NMR Yield) 63% (NMR Yield)

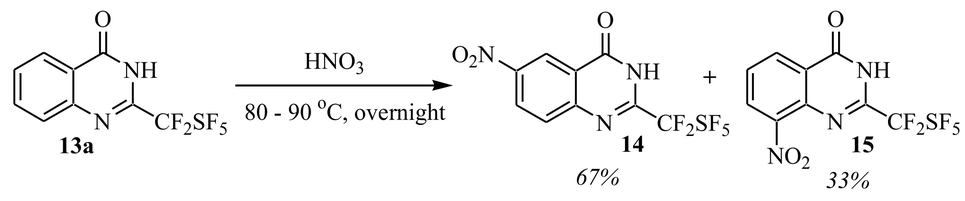
Synthesis of new SF_5-containing heterocycles

2-SF_5CF_2-substituted quinazolin-4(3H)-ones and quinazolines

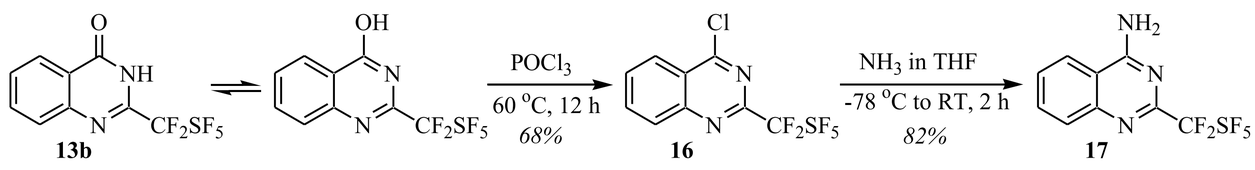
Quinazolinones often demonstrate biological activity and can be used as hypnotic, sedative, analgesic, antibacterial, and antitumor agents. Using *pentafluorosulfanyldifluoroacetyl chloride* (**3**), we synthesized the corresponding amides **12**, which upon refluxing in glacial acetic acid were transformed into *quinazolinones* **13**.



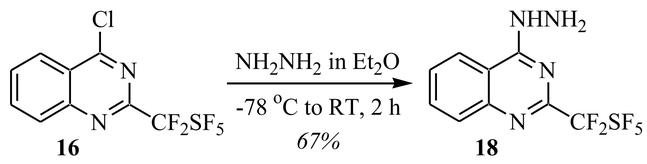
Nitration of **13a** with red HNO_3 led to the mixture of **14** and **15**.



2-Pentafluorosulfanyldifluoromethyl-4-chloroquinazoline (**16**) was synthesized by heating **13b** with $POCl_3$. The halogen atom in compound **16** is very reactive and easily undergoes nucleophilic substitution in anhydrous ammonia to produce the corresponding *2-pentafluorosulfanyldifluoromethyl-4-aminoquinazoline* (**17**).

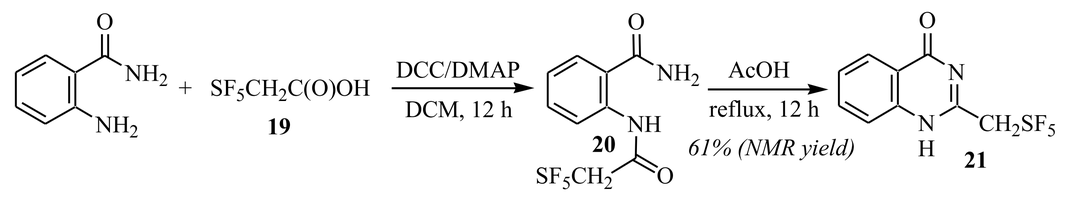


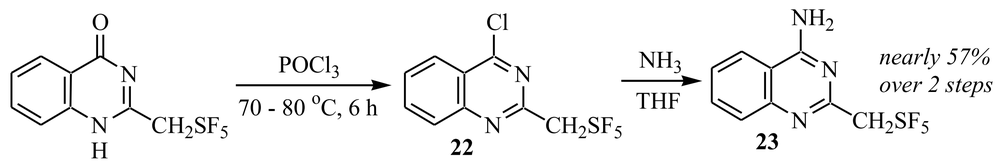
Treatment of quinazoline **16** with hydrazine led to **18**, which can be used for further cyclization.



2-SF_5CH_2-substituted quinazolin-4(3H)-ones and quinazolines

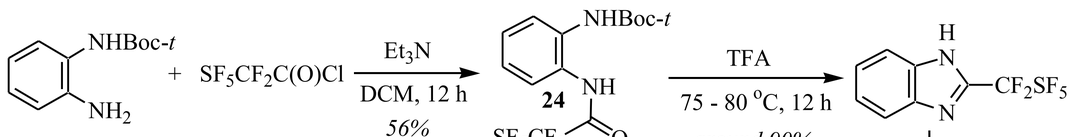
Using *pentafluorosulfanylacetic acid* (**19**),[4] we synthesized *quinazolinone* **21**, which upon heating with $POCl_3$ gave *quinazoline* **22** and with further reaction with ammonia gave *quinazoline* **23**.





2-SF_5CF_2-substituted benzimidazoles

We successfully synthesized the SF_5CF_2-containing benzimidazole **25** from *t*-Boc-protected *o*-phenylene-diamine **24** by acid catalyzed de-protection/cyclization reaction with trifluoroacetic acid.



-CF_2- region of SF_5CF_2- group of **25** — CF_3- region of **26**

However, **25** was found to be unstable and decomposed, possibly to the corresponding CF_3-substituted benzimidazole **26**.

References

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Acknowledgements

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