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# Recent Advances in the Synthesis and Application of SF<sub>5</sub>-Containing Organic Compounds

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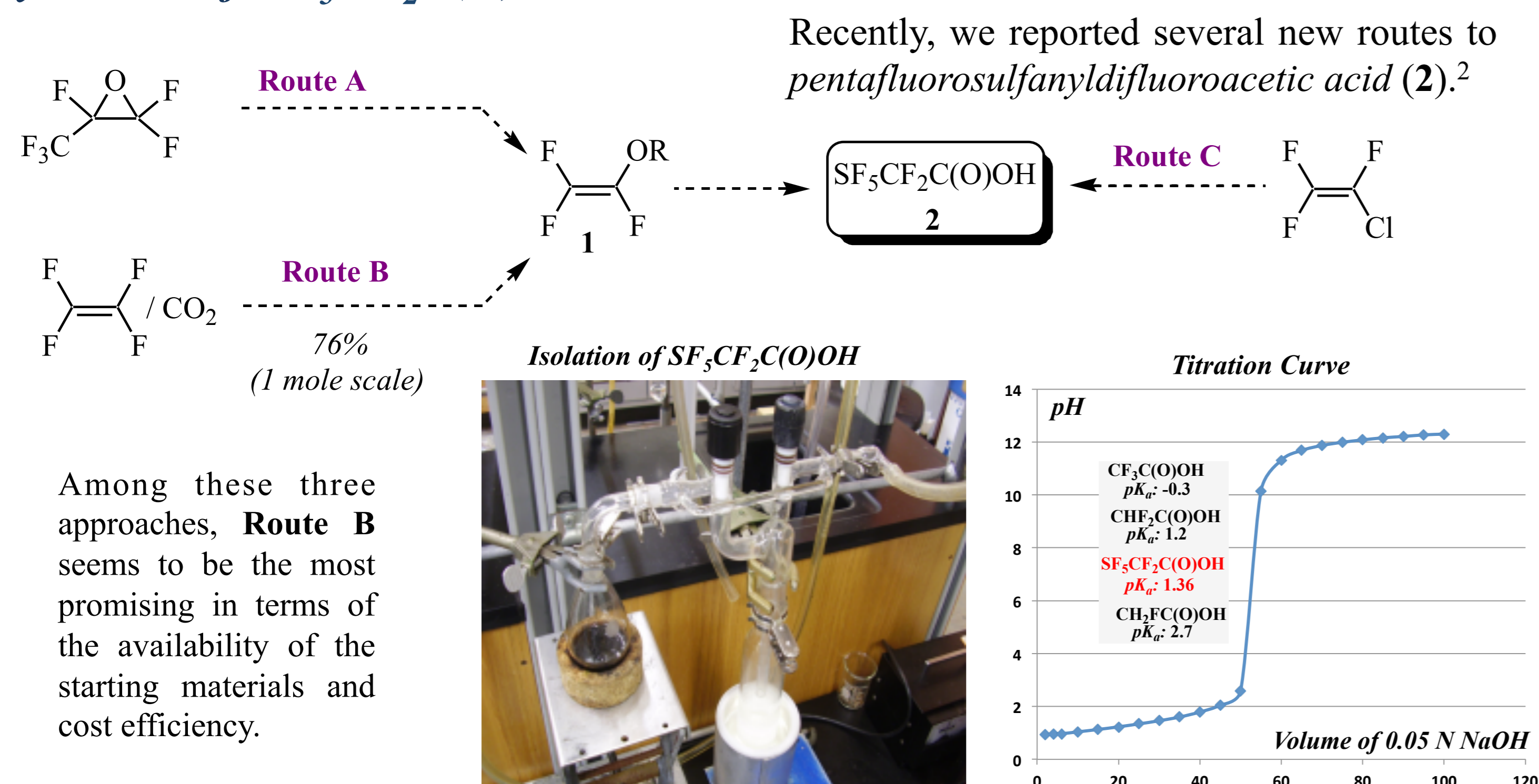
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## Introduction

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<sub>5</sub>) substituent occupies a special place.<sup>1</sup> 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<sub>5</sub>-substituted aliphatic and heterocyclic compounds.

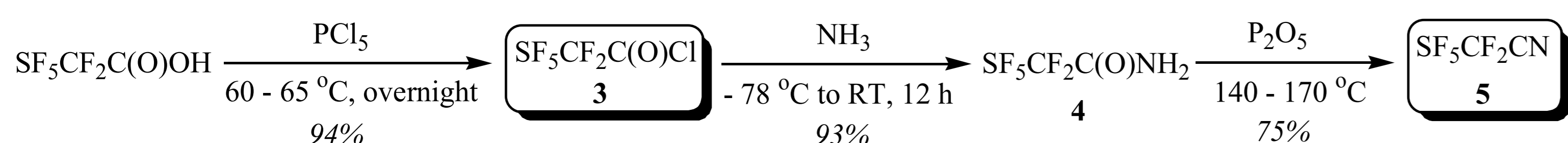
## Synthesis of new SF<sub>5</sub>-containing aliphatic compounds

### Synthesis of SF<sub>5</sub>CF<sub>2</sub>C(O)OH

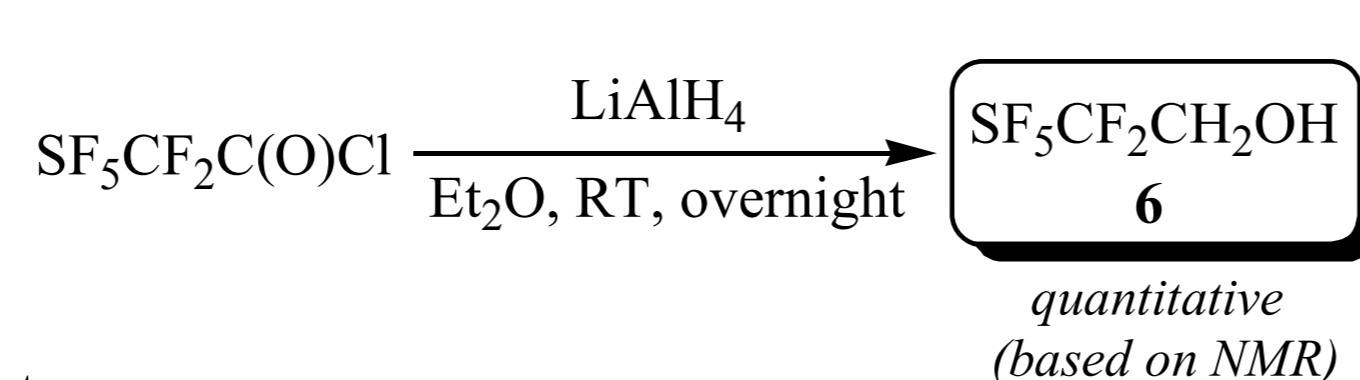


### Synthesis of SF<sub>5</sub>CF<sub>2</sub>-containing aliphatic compounds

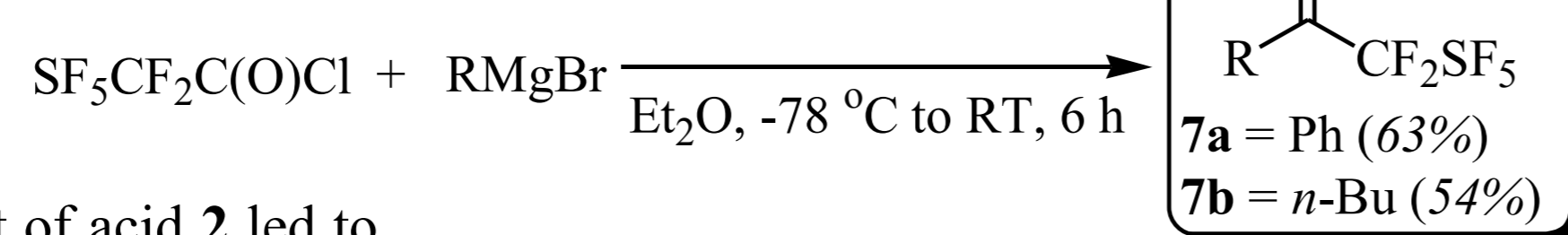
Mild heating of the acid **2** with a slight excess of PCl<sub>5</sub> produced the corresponding acyl chloride **3** in nearly quantitative yield. Ammonolysis of **3** with ammonia gas in dichloromethane gave amide **4**, which was converted into pentafluorosulfanyldifluoroacetonitrile (**5**) by dehydration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



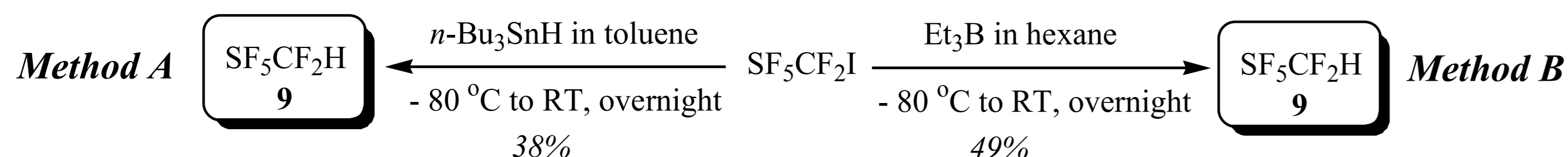
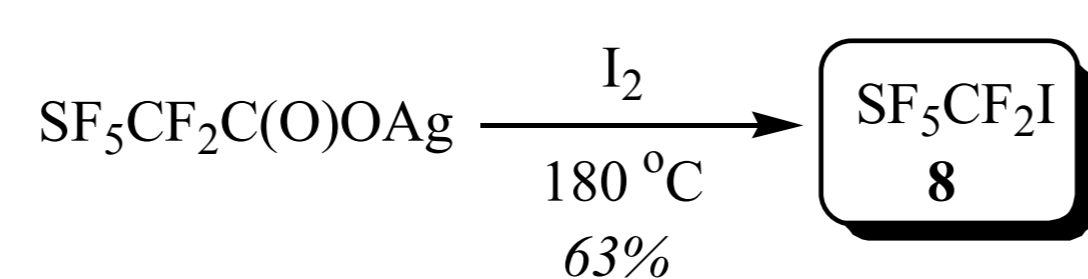
Pentafluorosulfanyldifluoroacetyl chloride (**3**) can be reduced to the corresponding alcohol **6** with lithium aluminum hydride.



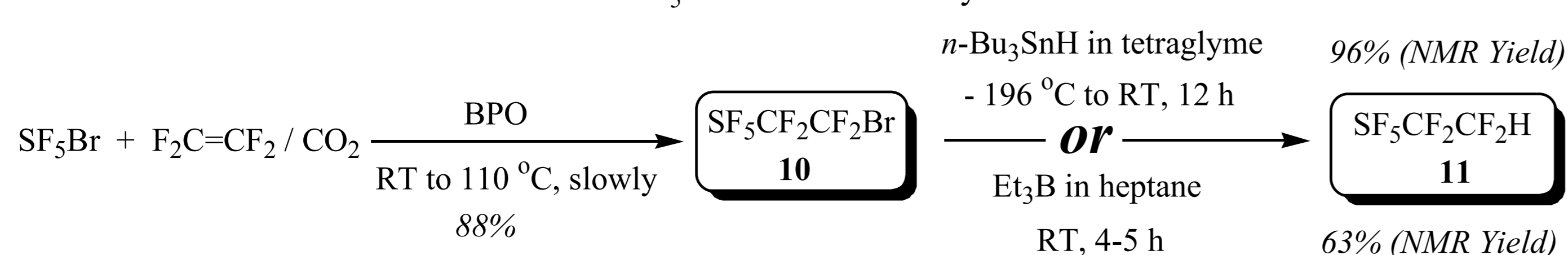
Reaction of the acyl chloride **5** with Grignard reagents proceeded smoothly and led to the corresponding ketones **7a** and **7b** in moderate yield.



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.



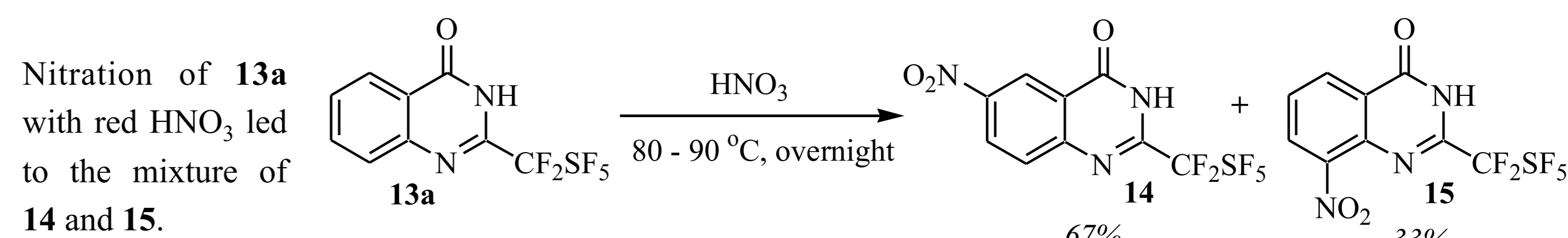
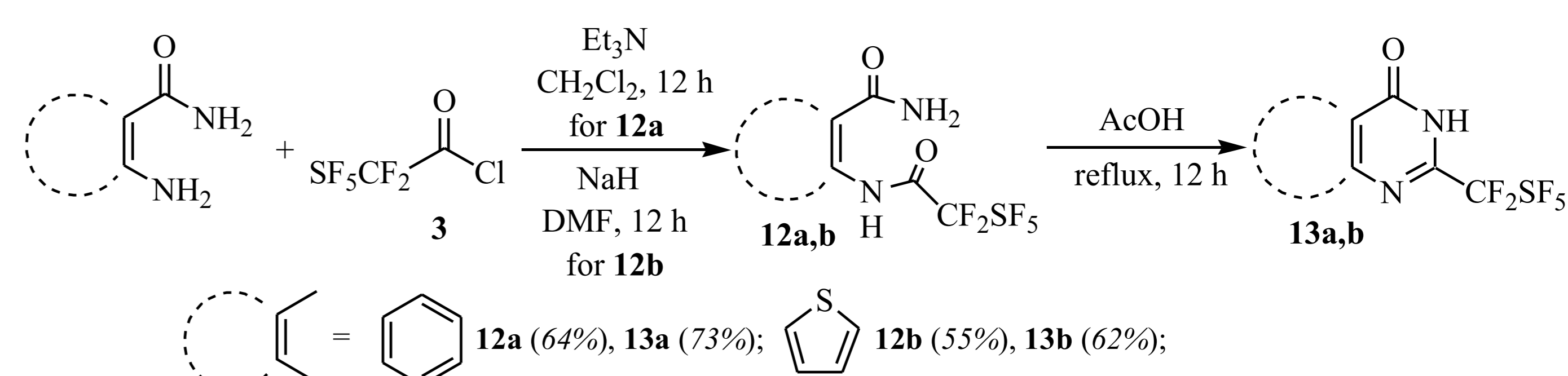
Using the aforementioned methods we synthesized pentafluorosulfanyltetrafluoroethane (**11**)<sup>3</sup> from compound **10**, which was obtained via radical addition of SF<sub>5</sub>Br to tetrafluoroethylene.



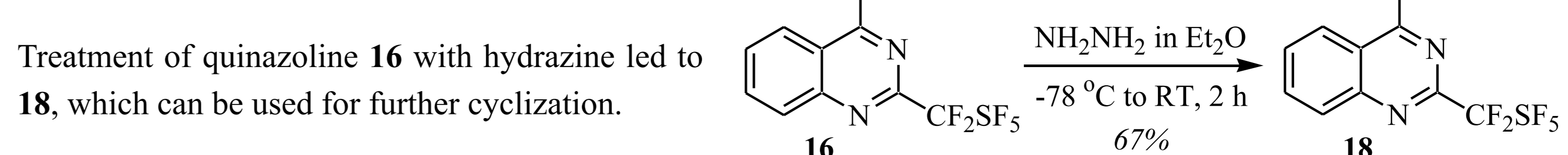
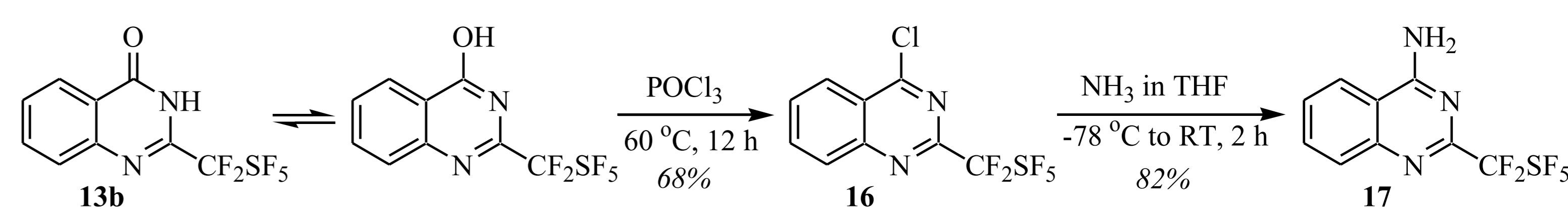
## Synthesis of new SF<sub>5</sub>-containing heterocycles

### 2-SF<sub>5</sub>CF<sub>2</sub>-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**.

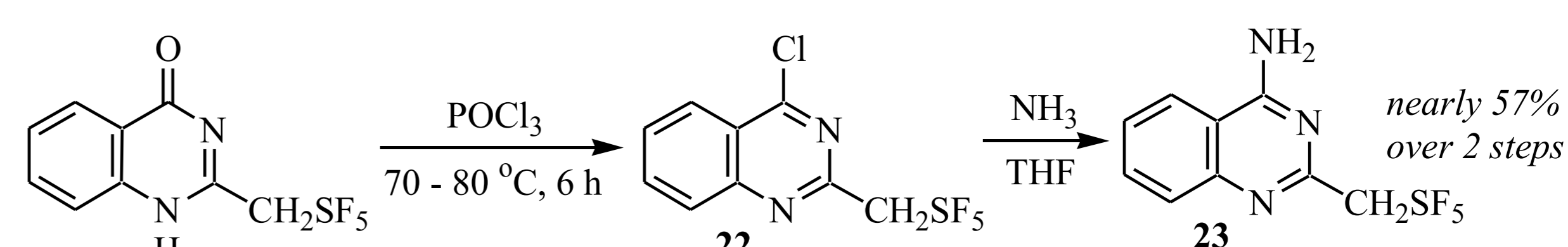
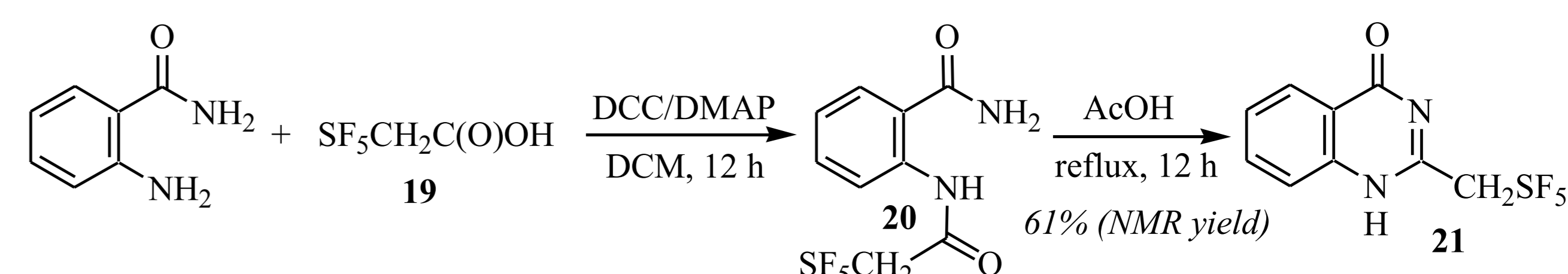


2-Pentafluorosulfanyldifluoromethyl-4-chloroquinazoline (**16**) was synthesized by heating **13b** with POCl<sub>3</sub>. The halogen atom in compound **16** is very reactive and easily undergoes nucleophilic substitution in anhydrous ammonia to produce the corresponding 2-pentafluorosulfanyldifluoromethyl-4-aminoquinazoline (**17**).



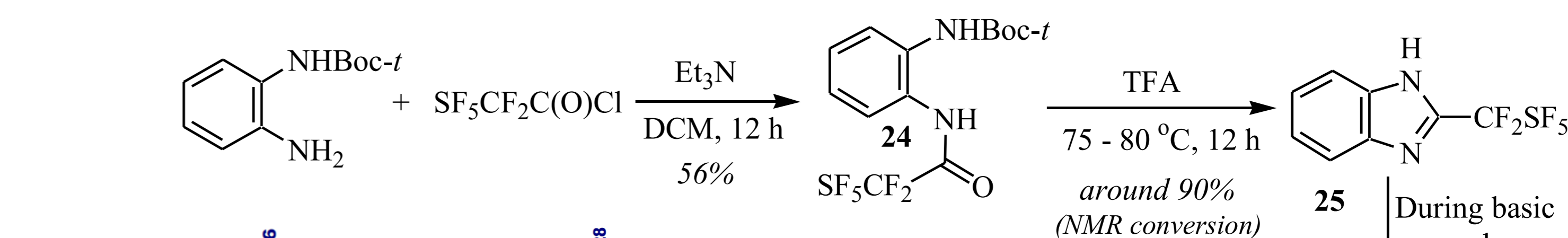
### 2-SF<sub>5</sub>CH<sub>2</sub>-substituted quinazolin-4(3H)-ones and quinazolines

Using pentafluorosulfanylacetic acid (**19**),<sup>4</sup> we synthesized quinazolinone **21**, which upon heating with POCl<sub>3</sub> gave quinazoline **22** and with further reaction with ammonia gave quinazoline **23**.



### 2-SF<sub>5</sub>CF<sub>2</sub>-substituted benzimidazoles

We successfully synthesized the SF<sub>5</sub>CF<sub>2</sub>-containing benzimidazole **25** from *t*-Boc-protected *o*-phenylenediamine **24** by acid catalyzed de-protection/cyclization reaction with trifluoroacetic acid.



However, **25** was found to be unstable and decomposed, possibly to the corresponding CF<sub>3</sub>-substituted benzimidazole **26**.

## References

[1] a) Altomonte, S.; Zanda, M. *J. Fluorine Chem.* **2012**, *143*, 57–93; b) Savoie P. R.; Welch, J. T. *Chem. Rev.* **2015**, *115* (2), 1130–1190. [2] Matsnev, A. V.; Qing, S.-Y.; Stanton, M. A.; Berger, K. A.; Haufe, G.; Thrasher, J. S. *Org. Lett.* **2014**, *16* (9), 2402–2405. [3] Dudziński, P.; Matsnev, A. V.; Thrasher, J. S.; Haufe, G. *Org. Lett.* **2015**, *17* (5), 1078–1081. [4] Martinez, H.; Zheng, Z.; Dolbier, Jr., W. R. *J. Fluorine Chem.* **2012**, *143*, 112–122.

## Acknowledgements

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