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First synthesis of 2-aminosubstituted-2-perfluoroalkyl-3,6-dihydro-2*H*-thiopyrans by hetero-Diels–Alder reactions of fluorinated thioamides under microwave heating

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ABSTRACT

This Letter presents the first examples of hetero-Diels–Alder reactions of polyfluoroalkanethiocarboxylic acid amides and 2,3-dimethylbutadiene under microwave heating. Cycloaddition reactions proved to be dependent on the nature of perfluoroalkyl chain and on the substituents attached to the nitrogen atom. Formation of ammonium salts was also performed by simple treatment of the corresponding cycloadducts with trifluoromethanesulfonic acid. In the case of octafluorobutyl-substituted derivative, one spontaneous desamination reaction took place leading to new 2*H*-thiopyran.

1. Introduction

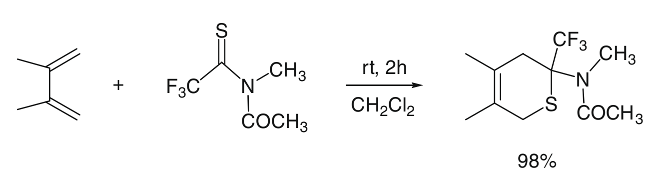
Addition of perfluoroalkyl substituents to a thiocarbonyl group substantially rises its dienophilic character in hetero-Diels–Alder reactions with electron-rich 1,3-dienes giving the possibility to synthesize fluorine-containing thiopyrane derivatives. Fluorine-containing thioaldehydes,[1–4] thioketones,[3,5–7] halogenides of polyfluoroalkanethioncarboxylic acids[5,8,9] and dithiocarboxylic acid esters[10–14] are used as such dienophiles. At the same time, polyfluoroalkanethioncarboxylic acid amides are inert in the reactions with 1,3-dienes. The only successful example of such cycloaddition reaction was described by Viehe and co-workers for *N*-methyl-*N*-acetyl-trifluorothioacetamide and was explained by the electron-withdrawing influence of amide substituents on the thiocarbonyl group (Scheme 1).[12]

In this Letter, we present the pioneering examples of hetero-Diels–Alder reactions between fluorinated aliphatic thioamides and electron-rich 1,3-dienes. Implementation of such reactions would allow obtaining fluorinated thiopyran derivatives bearing a basic amino group.

2. Results and discussion

The first attempt was performed using thioamide **1a** and 2,3-dimethylbutadiene (10 equiv) under standard conditions (Scheme 2, Table 1, entry 1). Unfortunately, at room temperature, no conversion of **1a** into 3,6-dihydro-2*H*-thiopyran **2a** was observed (by ^{19}F NMR) in the reaction mixture after 24 h.

Then, we turned our attention to more drastic conditions. First of all, a mixture of thioamide **1a** and 2,3-dimethylbutadiene (10 equiv) was heated in a sealed tube, at 200 °C and for 20 h,



Scheme 1.

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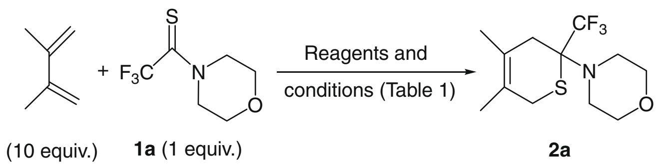
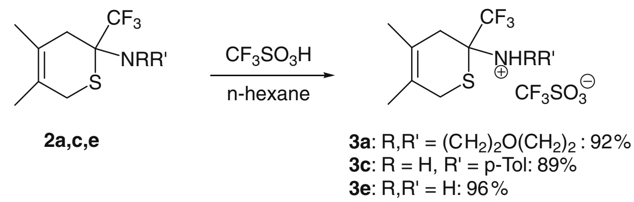


Scheme 2.

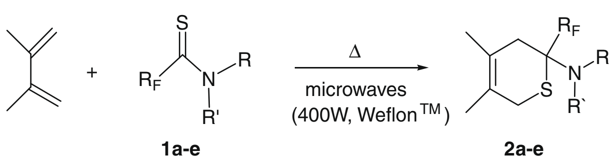


Scheme 4. Ref. [22].

Table 1
Reaction of thioamide **1a** with 2,3-dimethylbutadiene under various conditions

Entry	Reagents and conditions	Conversion[a] (%)
1	Neat, 25 °C, 24 h	0
2	Neat, sealed tube, 200 °C, 20 h	<5
3	High pressure (16 kbar), 25 °C, 24 h	<5
4	NMP, sealed tube, 180 °C, 16 h	<5
5	NMP, microwave (400 W), Weflon™, 180 °C, 3 h	50

[a] Conversion of **1a** into **2a** was measured by ^{19}F NMR in the reaction mixture.



Scheme 3. Ref. [20].

leading to very low conversion (Table 1, entry 2). Activation using high pressure apparatus (16 kbar, 25 °C, 24 h) or heating in *N*-methylpyrrolidone (NMP) at 180 °C for 16 h, was also used without success (Table 1, entries 3 and 4).

The last method consists in the use of microwave irradiation and its capacity to heat rapidly reaction mixtures as described in various examples.[15,16] Despite rate enhancement, higher product yields and easier handling of reaction mixtures are the main benefits usually described for this methodology.[17]

After experimental design, we found that thioamide **1a** reacted for 3 h with an excess (10 equiv) of 2,3-dimethylbutadiene in NMP in a sealed tube under microwave irradiation[18] at 180°C (400 W), in the presence of Weflon™ (Teflon™ filled with graphite). This material is heated by the microwave field and subsequently transfers this heat to the reaction mixture (the same heating effect may be obtained with graphite but in the case of Weflon™ dispersion of the powder and dangerous hot-spots are suppressed). Analysis of the reaction mixture showed 50% conversion of the starting thioamide into 2-morpholino-2-trifluoromethyl-3,6-dihydro-2*H*-thiopyrane **2a** (Table 1, entry 5). The choice of NMP as the solvent was justified by its efficiency to transform electromagnetic energy into thermal energy.[19] This polar aprotic solvent allows to work until 200 °C without troublesome with vapor and high pressure in the tubes. It is now a common replacement for more sensitive solvents (e.g., DMSO and DMF) in lots of pharmaceutical applications under microwaves and it may be eliminated by simple extraction with water during the work up.

In a second step, careful optimization of microwave conditions was undertaken. Investigating various parameters (time, temperature, and power input) we observed that longer heating (>3 h) of the reaction mixture decreased the yield of cycloadduct **2a**. In addition, several other minor fluorinated by-products appeared. This result could be explained by possible retro-Diels–Alder reaction or polymerization of 2,3-dimethylbutadiene under these conditions. We also observed that the pressure in the vials was very close to the security values (near 15–16 bars) and that lower quantities of starting reactants allowed working under more acceptable conditions. Because we also estimated that an excess of 2,3-dimethylbutadiene was necessary for the success of the synthesis, we decided to conduct the reaction stepwise, adding new portions of 2,3-dimethylbutadiene to the reaction mixture every 30 min of heating. The butadiene derivative was rapidly introduced via a syringe without opening the vial, avoiding release of chemicals into atmosphere. The overall reaction time was 2.5 h and the global quantity of 2,3-dimethylbutadiene reached 12.5 equiv. Under these optimized conditions (Scheme 3),[20] a 77% conversion of **1a** into heterocycle **2a** was estimated in accordance to ^{19}F NMR spectroscopy data of the crude reaction mixture. Cycloadduct **2a**[21] was purified by silica gel column chromatography affording a 43% yield of a thermally stable liquid (Table 2).

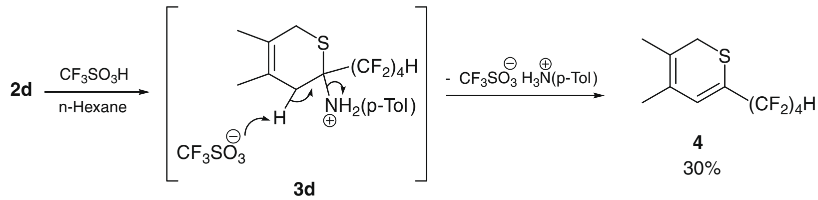
The scope of this new hetero-Diels–Alder reaction was then extended to other perfluorinated thioamides **1b–e** bearing different types of substituents on the amino group (primary and secondary thioamides) and various perfluoroalkyl chains (n-C_3F_7, $(CF_2)_4H$). Applying the conditions described above, novel 3,6-dihydro-2*H*-thiopyrans **2b–e** were synthesized for the first time in low to moderate yields (Table 2, 15–35%).

The basicity of amino group in compounds **2** may be sufficient for expecting formation of the corresponding ammonium salts in the presence of a strong acid. Thus, reaction of **2a,c,e** with trifluoromethanesulfonic acid gave salts **3a,c,e** in almost quantitative yields (Scheme 4).[22] Compounds **3a**[23] and **3e** are viscous water soluble liquids, while **3c** is a crystalline product. The basic property of heterocycles **2a,c,e** is very important for further biological applications, especially in order to increase water solubility and biodisponibility of possible active compounds. Indeed, we have earlier shown that some fluorine-containing dihydrothiopyran derivatives possess a high inotropic activity.[24]

Table 2
Reactions of thioamides **1a**–**e** with 2,3-dimethylbutadiene under microwaves[20]

Entry	Thioamide	R	R′	R_f	T (°C)	Conv. (%)	Cycloadduct[a] (%)
1	**1a**	$(CH_2)_2O(CH_2)_2$		CF_3	185	77	**2a**: 43
2	**1b**	$(CH_2)_2O(CH_2)_2$		$(CF_2)_2CF_3$	180	50	**2b**: 28
3	**1c**	H	*p*-Tol	CF_3	125	54	**2c**: 26
4	**1d**	H	*p*-Tol	$(CF_2)_4H$	145	50	**2d**: 15[b]
5	**1e**	H	H	CF_3	85	57	**2e**: 35

[a] Isolated yields. All pure cycloadducts were obtained after purification by silica gel column chromatography.
[b] Desamination of cycloadduct **2d** took place during heating the reaction mixture under microwave irradiation.



Scheme 5. Ref. 25.

Compared to its congeners, the behavior of compound **2d** bearing a longer perfluoroalkyl substituent was slightly different. Under analogous conditions, **2d** afforded first the corresponding salt **3d** which underwent spontaneous desamination into 2*H*-thiopyran **4** (Scheme 5).[25] Influence of ammonium and octafluorobutyl substituents (which is more electron-withdrawing than trifluoromethyl one) would probably facilitate deprotonation of intermediate **3d**. To the best of our knowledge, compound **4** is one of the first examples of the 6-perfluoroalkyl-2*H*-thiopyrans. Only one highly fluorinated compound of this type was already described in the literature using a complex thermal rearrangement of 2,3-diazabicyclo[3.2.0]heptadiene.[26]

3. Conclusion

In conclusion, we have described the first microwave-assisted hetero-Diels–Alder reactions of perfluoroalkanethioamides **1a–e** with 2,3-dimethylbutadiene affording new 3,6-dihydro-2*H*-thiopyrans **2a–e**. The use of rapid and controlled microwave heating in sealed vials allowed good conditions of work and reproducibility. We also observed that the nature of perfluoroalkyl chains and substituents on the nitrogen atom of thioamides have a significant influence on the yields of **2**. Treatment of cycloadducts **2a,c,e** with trifluoromethanesulfonic acid gave the corresponding ammonium salts **3a,c,e** in almost quantitative yields, except for 2-octafluorobutyl-substituted derivative **3d** which underwent a spontaneous desamination reaction. Investigation of the scope and limitations of these novel hetero-Diels–Alder reactions in the presence of various thioamides and other electron-rich 1,3-dienes (symmetrical and unsymmetrical) is actually in course in our laboratories.

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References and notes

1. Shermolovich, Y. G.; Slyusarenko, E. I.; Markovski, L. N. *Zh. Org. Khim. (Russ.)* **1988**, *24*, 1931–1934.
2. Schuler, B.; Sundermeyer, W. *Tetrahedron Lett.* **1989**, *30*, 4111–4112.
3. Schuler, B.; Sundermeyer, W. *Chem. Ber.* **1990**, *123*, 177–184.
4. Markovski, L. N.; Slyusarenko, E. I.; Shermolovich, Y. G. *Zh. Org. Khim. (Russ.)* **1990**, *26*, 912–914.
5. Middleton, W. J. *J. Org. Chem.* **1965**, *30*, 1390–1394.
6. Schwab, M.; Sundermeyer, W. *Chem. Ber.* **1986**, *119*, 2458–2465.
7. Timoshenko, V. M.; Bouillon, J. P.; Shermolovich, Y. G.; Portella, C. *Tetrahedron Lett.* **2002**, *43*, 5809–5812.
8. Middleton, W. J.; Howard, E. G.; Sharkey, W. H. *J. Am. Chem. Soc.* **1961**, *83*, 2589–2590.
9. Gradel, J.; Sundermeyer, W. *Chem. Ber.* **1992**, *125*, 1889–1894.
10. Shermolovich, Yu. G.; Slyusarenko, Y. I.; Timoshenko, V. M.; Roshenko, A. B.; Markovski, L. N. *J. Fluorine Chem.* **1991**, *55*, 329–333.
11. Portella, C.; Shermolovich, Y. G.; Tschenn, O. *Bull. Soc. Chim. Fr.* **1997**, *134*, 697–702.
12. Laduron, F.; Nyns, C.; Janousek, Z.; Viehe, H. G. *J. Prakt. Chem/Chem-Ztg.* **1997**, *339*, 697–707.
13. Bouillon, J. P.; Shermolovich, Y. G.; Portella, C. *Tetrahedron Lett.* **2001**, *42*, 2133–2135.
14. Pfund, E.; Lequeux, T.; Vazeux, M.; Masson, S. *Tetrahedron Lett.* **2002**, *43*, 2033–2036.
15. For a recent book see: *Microwaves in Organic Synthesis*; Loupy, A., Ed.; Whiley-VCH Gmbh: KGaA, Weinhein, 2006.
16. For recent reviews see: (a) Caddick, S.; Fitzmaurice, R. *Tetrahedron* **2009**, *65*, 3325–3355; (b) Kappe, C. O.; Dallinger, D. *Mol. Div.* **2009**, *13*, 71–193; (c) De la Hoz, A.; Diaz-Ortiz, A.; Moreno, A. *Chem. Soc. Rev.* **2005**, *34*, 164–178.
17. Complete description of instrument and methodology was published in: Ferguson, J. D. *Mol. Div.* **2003**, *7*, 281–286.
18. Focused microwave irradiations were carried in pressurized (0–20 bar) sealed vials (0–20 bar, tubes of 10 mL, sealed with a septum) with a CEM Discover™ focused microwave reactor (monomode system).[17] Power input (0–400 W) was monitored by computer as infrared measurement and continuous feedback temperature control. The experiments were performed using stirring option whereby the contents of a vessel are stirred by means of a rotating plate located below the floor of the microwave cavity and a Teflon-coated magnetic stir bar in the vessel. In all experiments a target temperature was selected together with a power. The target temperature was reached with a ramp of 2 min and the chosen microwave power stay constant to hold the mixture at this temperature. The time of the reaction does not include the ramp period.
19. For recent examples of the use of NMP under microwaves see: (a) Lamazzi, C.; Dreau, A.; Bufferne, C.; Flouzat, C.; Patrick Carlier, P.; ter Halle, R.; Besson, T. *Tetrahedron Lett.* **2009**, *50*, 5402–5405; (b) Pereira, M.; De, F.; Thiéry, V.; Besson, T. *Tetrahedron Lett.* **2007**, *48*, 7657–7659.
20. *Typical procedure for the preparation of cycloadduct* **2a**: a mixture of perfluorothioamide **1a** (1.0 mmol) and 2,3-dimethylbutadiene (2.5 mmol) in *N*-methylpyrrolidone (5 mL) in the presence of pieces of Weflon™ (Weflon™ is Teflon™ filled with graphite) was heated 30 min at 180 °C under irradiation (400 W) in a microwave oven. After 30 min of heating, 2,3-dimethylbutadiene (2.5 mmol) was added to the cooled reaction mixture, then the mixture was again heated for 30 min. This procedure was repeated three times (total heating time: 2.5 h, 1,3-diene: 12.5 equiv). After cooling, the reaction mixture was poured into water (50 mL) and extracted three times with dichloromethane (3 × 30 mL). The combined organic phases were washed with water (30 mL), dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with a mixture (9:1) of petroleum ether and ethyl acetate affording 121 mg (yield: 43%) of cycloadduct **2a** (Scheme 3, Table 2).
21. Spectral data of 4-(4,5-dimethyl-2-trifluoromethyl-3,6-dihydro-2*H*-thiopyran-2-yl)morpholine (**2a**). Oil. R_f (petroleum ether/ethyl acetate (9:1)) = 0.37 (TLC-development: ethanolic phosphomolybdic acid solution). ^{1}H NMR ($CDCl_3$, δ ppm): 1.71 (s, 3H, Me), 1.75 (s, 3H, Me), 2.44 (d, $^2J_{H,H}$ = 17.5 Hz, 1H, CH_AH_B), 2.69 (m, 2H, NCH_2), 2.79 (d, $^2J_{H,H}$ = 16.4 Hz, 1H, SCH_AH_B), 2.83 (d, $^2J_{H,H}$ = 17.5 Hz, 1H, CH_AH_B), 3.13 (m, 2H, NCH_2), 3.23 (d, $^2J_{H,H}$ = 16.4 Hz, 1H, SCH_AH_B), 3.59 (m, 4H, $O(CH_2)_2$). ^{19}F NMR ($CDCl_3$, δ ppm): −71.3 (s, 3F, CF_3). ^{13}C NMR ($CDCl_3$, δ ppm): 18.9 (s, CH_3), 20.0 (s, CH_3), 30.4 (s, CH_2S), 35.2 (q, $^3J_{C,F}$ = 1.1 Hz, CH_2), 47.2 (s, CH_2N), 68.1 (s, CH_2O), 71.0 (q, $^2J_{C,F}$ = 24.9 Hz, CCF_3), 122.5 (s, C_q), 123.9 (s, C_q), 126.6 (q, $^1J_{C,F}$ = 293.1 Hz, CF_3). GC–MS: *m/z* = 281 [M^+]. HRMS (ESI$^+$): calcd for $C_{12}H_{18}F_3KNOS$ *m/z* 320.0698, found 320.0692.
22. *Typical procedure for the preparation of ammonium salt* **3a**: a mixture of compound **2a** (1.0 mmol) and trifluoromethanesulfonic acid (1.0 mmol) in *n*-hexane (15 mL) was stirred for 16 h at room temperature. After completion of the reaction, the solution was decanted and the product was dried in vacuo affording 0.40 g (yield: 92%) of ammonium salt **3a** (Scheme 4).
23. Spectral data of (4,5-dimethyl-2-trifluoromethyl-3,6-dihydro-2*H*-thiopyran-2-yl)morpholinium trifluoromethane sulfonate (**3a**). Oil. ^{1}H NMR ($CDCl_3$, δ ppm): 1.84 (s, 3H, Me), 1.87 (s, 3H, Me), 2.76 (d, $^2J_{H,H}$ = 14.5 Hz, 1H, CH_AH_B), 2.95 (d, $^2J_{H,H}$ = 15.5 Hz, 1H, SCH_AH_B), 3.00 (d, $^2J_{H,H}$ = 14.5 Hz, 1H, CH_AH_B), 3.58 (d, $^2J_{H,H}$ = 15.5 Hz, 1H, SCH_AH_B), 3.44 (m, 2H, $NHCH_2$), 3.80 (m, 2H, $NHCH_2$), 4.13 (m, 4H, $O(CH_2)_2$). ^{19}F NMR ($CDCl_3$, δ ppm): −67.9 (s, 3F, CF_3), −79.1 (s, 3F, $CF_3SO_3^{3-}$). Anal. Calcd for $C_{13}H_{19}F_6NO_4S_2$: C, 36.19; H, 4.44; N, 3.25; S, 14.87. Found: C, 35.94; H, 4.65; N, 3.38; S, 17.92.
24. Markovski, L. N.; Shermolovich, Yu. G.; Slusarenko, E. I.; Timoshenko, V. M. Japan Patent 06100555, 1994; *Chem. Abst.* 121: 108523.
25. Spectral data of 3,4-dimethyl-6-(1,1,2,2,3,3,4,4-octafluorobutyl)-*2H*-thiopyran (**4**). This compound was purified by flash column chromatography on silica gel (eluent: petroleum ether). R_f (petroleum ether) = 0.51. Oil. ^{1}H NMR ($CDCl_3$, δ ppm): 1.84 (s, 3H, Me), 1.92 (s, 3H, Me), 3.22 (s, 2H, SCH_2), 6.08 (tt, $^2J_{H,F}$ = 52.2 Hz, $^3J_{H,F}$ = 5.6 Hz, 1H, HCF_2), 6.50 (s, 1H, CH=). ^{19}F NMR ($CDCl_3$, δ

ppm): −111.9 (m, 2F, CF_2), −124.6 (m, 2F, CF_2), −130.7 (m, 2F, CF_2), −138.2 (dm, $^2J_{F,H}$ = 52.2 Hz, 2F, HCF_2). ^{13}C NMR (CD_3COCD_3, δ ppm): 17.5 (s, CH_3), 19.3 (s, CH_3), 31.8 (s, CH_2), 104–122 (m, 3 × CF_2), 115.7 (tt, $^1J_{C,F}$ = 254.4 Hz, $^2J_{C,F}$ = 31.2 Hz, HCF_2), 121.4 (t, $^2J_{C,F}$ = 24.7 Hz, *C*–$(CF_2)_4$H), 126.4 (t, $^4J_{C,F}$ = 2.2 Hz, CH_3–*C*–CH═), 127.3 (s, CH_3–*C*–CH_2), 133.1 (t, $^3J_{C,F}$ = 8.5 Hz, ═CH). MS (ESI+): *m/z* = 327 [M+H]. Anal. Calcd for $C_{11}H_{10}F_8S$: C, 40.50; H, 3.09; S, 9.83. Found: C, 40.12; H, 2.87; S, 9.85.

26. Laganis, E. D.; Lemal, D. M. *J. Am. Chem. Soc.* **1980**, *102*, 6634–6636.