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# Microwave-assisted aliphatic fluorine–chlorine exchange using triethylamine trihydrofluoride (TREAT-HF)

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ABSTRACT

Aliphatic fluorine–chlorine exchange reactions can be performed under microwave conditions using TREAT-HF as a mild and selective fluorination reagent. The highly polar TREAT-HF couples efficiently with microwave irradiation and reaction temperatures of 250 °C can be reached within 30 s. Under these conditions dichloromethyl- and trichloromethyl substrates can be converted into the corresponding fluoro analogs within 5 min. In order to prevent corrosion of borosilicate reaction vessel at high temperatures the use of sintered silicon carbide microwave vials is introduced.



The fluorination of biologically active molecules often results in a profound modification of their biological activity.[1] Fluorine atoms incorporated into bioactive compounds can have major effects on bioavailability and metabolism caused by changes in the lipophilicity and oxidative stability. In many cases the selective installation of fluorine into a molecule leads to compounds with improved binding affinity and/or enhanced physicochemical properties. In the area of agrochemistry the number of disclosed potent crop protection agents containing one or more fluorine atoms is steadily increasing (Fig. 1).

The most widely used technology for introducing fluorine into organic molecules is fluorine–chlorine exchange.[2] While aromatic halogen exchange is commonly performed at elevated temperatures by nucleophilic substitution using alkaline metal salts as a fluoride source (Halex reaction),[3] the most versatile industrial reagent for aliphatic fluorinations is anhydrous hydrogen fluoride.[4] However, the low boiling point and high corrosivity of hydrogen fluoride make it difficult to handle in the laboratory and its high reactivity additionally causes undesired side reactions. Therefore, a number of stable hydrogen fluoride-based reagents have been introduced in recent years in order to overcome the hazards involved in handling hydrogen fluoride.[2] One of these mild fluorination reagents is triethylamine trihydrofluoride (TREAT-HF, $Et_3N{\cdot}3HF$, Franz reagent) which has been widely used for introducing fluorine into organic molecules.[5] TREAT-HF is a commercially available colorless, hygroscopic liquid with a shelf life of at least one year which has been reported not to corrode borosilicate glassware.[5] Although the nucleophilicity of the fluorine ion in TREAT-HF is relatively low compared to other fluoride ion sources it is high enough to permit substitution of activated leaving groups under forcing conditions.[5] In the context of our research on heterocyclic crop protection agents containing *gem*-difluoromethyl groups (e.g., Bixafen[6] and Isopyrazam,[7] Fig. 1) we became interested in applying TREAT-HF as a thermally stable fluorination reagent in microwave-assisted aliphatic fluorine–chlorine exchange reactions. Not unlike ionic liquids,[8] the distinctly polar properties of TREAT-

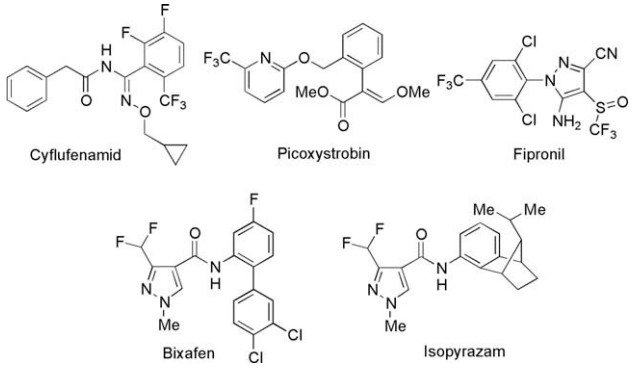


**Figure 1.** Selected fluorine-containing crop protection agents.

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HF appear to make it very suitable as a reagent (and/or solvent) in microwave-heated transformations.[9]

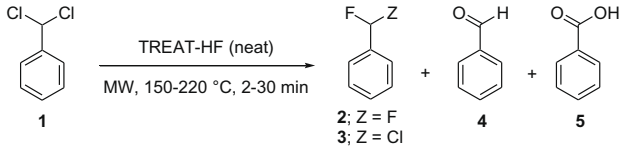
Our initial model reaction to study the feasibility of microwave-assisted aliphatic fluorine–chlorine exchange reactions using TREAT-HF as the reagent involved the fluorination of dichloromethylbenzene (**1**) to difluoromethylbenzene (**2**) (Table 1). The fluorination of **1** applying the more reactive pyridinium poly(hydrogen fluoride) complex (Olah's reagent) was reported in 1997 and required 14 h at room temperature providing a 70% selectivity for difluorination.[10] For the microwave-assisted fluorinations using TREAT-HF as reagent/solvent reactions were performed applying controlled single-mode microwave heating in sealed Pyrex vessels.[11] During our optimization studies it became immediately apparent that the hydrolysis[12] **1**→**4** can be a significant side reaction to the desired fluorination pathway **1**→**3**→**2**. Control experiments established that difluoromethylbenzene (**2**) is stable toward hydrolysis under the reaction conditions and that therefore the formation of benzaldehyde (**4**) together with trace amounts benzoic acid (**5**) is likely to arise from the hydrolysis of dichloromethylbenzene (**1**), as a consequence of adventitious amounts of water being present in the reaction mixture. This hypothesis was substantiated by deliberately adding excess water (7 equiv) to the reaction mixture before microwave irradiation. As expected, under these conditions benzaldehyde (**4**) was the main reaction product. Removal of water from commercial TREAT-HF by azeotropic distillation prior to use with toluene led to significant improvements, in particular for samples of TREAT-HF which had been stored for a long time.

Screening of reaction conditions for the fluorination process next focused on variations in reaction time and temperature and the substrate/reagent ratio. The optimum selectivity for fluorination (vs hydrolysis) was obtained by rapidly heating the reaction mixture to temperatures between 180 and 200 °C. At 150 °C the fluorination was incomplete even after 30 min, with significant amounts of starting material **1** and monofluorination product **3** still being present in the reaction mixture (entries 1 and 2). Increasing the reaction temperature to 180 °C led to a high degree of conversion after 5 min (entry 4), but ultimately 200 °C (1–2 bar) proved to be the optimum temperature for the difluorination of dichloromethylbenzene (**1**) with TREAT-HF. After 5 min full conversion was achieved with no dichloro starting material **1** or monofluoro intermediate **3** being observable by HPLC (entry 6). The selectivity for fluorination was close to 90%, the only remaining product in the crude reaction mixture being benzaldehyde (**4**) resulting from the inadvertent hydrolysis of dichloromethylbenzene (**1**). Extending the reaction time to 10 min at 200 °C did not significantly change the product ratio (entry 7) and a further increase of reaction temperature to 220 °C showed no apparent advantage (entry 8).[13] Changing the substrate/reagent ratio did, however, have a noticeable effect on the product distribution and conversion. While doubling the concentration of **1** led to incomplete conversions, halving the amount of dichloromethylbenzene (**1**) under otherwise identical conditions led to some improvement (compare entries 9 and 10 with entry 4). Since in an industrial context the minimization of reagents and solvents is of considerable importance the chosen reagent/solvent ratio of 3.8/50 (mmol) was not changed. For product isolation the reaction mixture was poured on cold water and was extracted with diethyl ether. Subsequent washing of the organic phase with aqueous sodium carbonate (10%) to remove benzoic acid (**5**) followed by aqueous sodium bisulfite to remove benzaldehyde (**4**) provided pure difluoromethylbenzene (**2**).[14]

As a second example for probing the efficiency of microwave-assisted fluorine–chlorine exchange reactions with TREAT-HF the fluorination of (trichloromethylthio)benzene (**6**) was investigated (Table 2). In 2006, selective mono-, di-, or tri-chlorine–fluorine exchanges on trichloromethyl groups applying TREAT-HF and related reagents were reported, with reaction times of several hours at elevated temperatures not being uncommon.[15] Our optimization studies involving microwave-assisted fluorinations of **6** are summarized in Table 2.

As can be seen from the data presented in Table 2, a careful optimization of the reaction temperature—maintaining the reaction time constant at 5 min—did allow the step-wise generation of monofluoro- (**7**, 70 °C, entry 2), difluoro- (**8**, 160 °C, entry 5),

**Table 1**
Optimization of the fluorination of dichloromethylbenzene (**1**) with TREAT-HF (50 mmol) under controlled microwave conditions.[a]

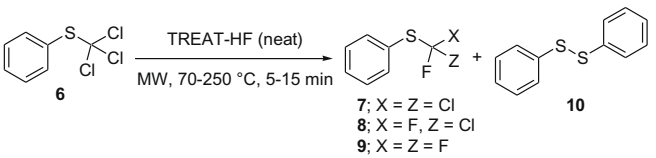



| Entry | **1** (mmol) | Temperature (°C) | Time (min) | Product distribution[b] (%) 1/2/3/4/5 |
|---|---|---|---|---|
| 1 | 3.8 | 150 | 10 | 50/13/32/3/2 |
| 2 | 3.8 | 150 | 30 | 13/44/27/13/2 |
| 3 | 3.8 | 180 | 2 | 6/60/28/4/2 |
| 4 | 3.8 | 180 | 5 | 1/77/9/9/4 |
| 5 | 3.8 | 200 | 3 | 2/82/5/9/2 |
| 6 | 3.8 | 200 | 5 | 0/89/0/11/0 |
| 7 | 3.8 | 200 | 10 | 0/88/0/9/3 |
| 8 | 3.8 | 220 | 3 | 1/85/1/10/3 |
| 9 | 7.6 | 180 | 5 | 12/41/23/22/2 |
| 10 | 1.9 | 180 | 5 | 1/84/4/8/2 |

[a] Reaction conditions: single-mode microwave irradiation (Biotage Initiator 8 EXP 2.0, power setting: very high absorbing = 90 W max Power), 2–5 mL sealed Pyrex microwave vial, 3 mL TREAT-HF (50 mmol), magnetic stirring, external IR temperature monitoring, reaction time refers to fixed hold time at the set temperature, excluding a ramp time of ca. 1 min.

[b] Product distribution refers to relative peak area (%) ratios of crude HPLC–UV (215 nm) traces. The identity of products **2**–**5** was established by GC–MS analysis.

**Table 2**
Optimization of the fluorination of (trichloromethylthio)benzene (**6**) with TREAT-HF (50 mmol) under controlled microwave conditions[a]




| Entry | **6** (mmol) | Temperature (°C) | Time (min) | Product distribution[b] (%) 6/7/8/9/10 |
|---|---|---|---|---|
| 1 | 3.7 | 70 | 5 | 51/48/0/0/1 |
| 2 | 3.7 | 100 | 5 | 1/94/3/0/2 |
| 3 | 3.7 | 130 | 5 | 0/69/28/0/3 |
| 4 | 3.7 | 180 | 5 | 0/0/75/17/8 |
| 5 | 3.7 | 160 | 5 | 0/1/90/3/6 |
| 6 | 3.7 | 200 | 5 | 0/0/51/39/10 |
| 7 | 3.7 | 230 | 5 | 0/0/5/82/13 |
| 8 | 3.7 | 250 | 5 | 0/0/0/91/9 |

[a] Reaction conditions: single-mode microwave irradiation (Biotage Initiator 8 EXP 2.0, power setting: very high absorbing = 90 W max Power), 2–5 mL sealed Pyrex microwave vial, 3 mL TREAT-HF (50 mmol), magnetic stirring, external IR temperature monitoring, reaction time refers to fixed hold time at the set temperature, excluding a ramp time of ca. 1 min.

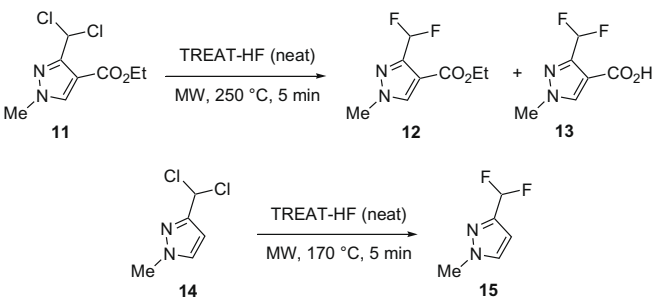
[b] Product distribution refers to relative peak area (%) ratios of crude HPLC–UV (215 nm) traces. The identity of products **7**–**10** was confirmed by GC–MS analysis.

and (trifluoromethylthio)benzene (**9**, 250 °C, entry 8) in remarkably high selectivity.[14] As expected, an increase in reaction temperature led to a higher degree of fluorination. Diphenyl disulfide (**10**) was always present as a by-product in small quantities (1–13%) as a result of hydrolysis of the perchlorinated thioanisoles to thiophenol followed by subsequent oxidation. Similar to the results described in Table 1, (trifluoromethylthio)benzene (**9**) proved to be stable under the reaction conditions and did not undergo hydrolysis once formed.

During the TREAT-HF mediated fluorination of chloro derivatives **1** and **6** at high temperatures (>200 °C), we did notice an apparent corrosion of the Pyrex microwave reaction vials in the vapor space above the liquid's surface. Although generally considered non-corrosive,[5,16] TREAT-HF can release hydrogen fluoride at elevated temperatures and will therefore attack borosilicate glass to some extent. In a control study measuring the weight loss of unused fresh microwave reaction vessels (weight ca. 16.5 g) after exposure to TREAT-HF under microwave conditions we have discovered that corrosion occurs even at comparatively low temperatures (100 °C) and is highly dependent on reaction temperature and time. While at 100 °C the weight loss after 5 min is already measurable but comparatively small (20 mg), significant loss of glass was encountered after a 30 min exposure at 250 °C (500 mg).[17] Hydrogen fluoride-mediated vessel corrosion at these temperatures leads to the formation of gel-type materials, making an extractive work-up of the reaction mixture troublesome. In addition, it became apparent that the undesired hydrolysis phenomena in the fluorinations described above (see Tables 1 and 2) are likely the result of water being formed during the corrosion process ($SiO_2 + 4HF \rightarrow SiF_4 + 2H_2O$ and $SiO_2 + 6HF \rightarrow H_2[SiF_6] + 2H_2O$).

We have therefore repeated the fluorination **1**→**2** in a custom-made microwave vial made out of sintered silicon carbide (SiC).[18,19] Silicon carbide is not only completely resistant to TREAT-HF even at 250 °C for prolonged periods of time, but is also a strong microwave absorber which makes it ideal for performing microwave chemistry.[18] Employing our optimized fluorination conditions (Table 1, entry 6) the degree of hydrolysis **1**→**4** could indeed be reduced from 11% (Pyrex) to 5% (SiC).

Having access to an extensive data set on microwave-assisted controlled fluorine–chlorine exchange reaction using TREAT-HF as comparatively mild fluorination reagent, we subsequently applied this expertise to the preparation of our desired target structure, ethyl 3-difluoromethyl-1-methyl-1*H*-pyrazole-4-carboxylate (**12**) (Scheme 1). This difluoromethyl-substituted heterocycle is a key precursor in the preparation of pyrazolyl-carboxamides such as Bixafen and Isopyrazam which are known to be active fungicidal ingredients (Fig. 1).[6,7] The preparation of **12** by fluorination of the corresponding dichloro derivative **11**[20] with TREAT-HF in an autoclave at 145 °C (8 h) was recently disclosed in the patent literature.[21] Using microwave irradiation the conditions were rapidly optimized on a 2.5 mmol scale (2 mL TREAT-HF) to provide the desired difluoromethyl structure **12** within only 5 min reaction time. At 150 °C (5 min) the crude mixture was still mainly composed of unreacted starting material **11** while at 200 °C (5 min) both the starting material and the monofluoro intermediate where present. Ultimately, reaction temperatures between 230 and 250 °C proved well suited for the efficient generation of the desired difluoro analog **12**. After 5 min full conversion was obtained with minor amounts (ca. 10%) of ester hydrolysis product **13** being identified as the only byproduct by HPLC and GC–MS analysis. From a preparative experiment on a 13.5 mmol scale using a 20 mL microwave vial a 69% isolated yield of **12** was obtained.[22]




**Scheme 1.** Fluorination of ethyl 3-(dichloromethyl)-1-methyl-1*H*-pyrazole-4-carboxylate (**11**) and 3-(dichloromethyl)-1-methyl-1*H*-pyrazole (**14**).

Along similar lines, the fluorination of 3-dichloromethylpyrazole **14** to the corresponding difluoro derivative **15** was investigated (Scheme 1). A recent patent discloses this TREAT-HF mediated fluorination under autoclave conditions (160 °C, 1 h) and the subsequent conversion of pyrazole **15** to pyrazolyl-4-carboxamides using bromination/aminocarbonylation chemistry.[23] Applying sealed vessel microwave heating, optimum conditions for the fluorination **14**→**15** utilized 170 °C for 5 min, with only trace amounts of the corresponding aldehyde hydrolysis product being formed.[24]

In conclusion we have demonstrated that TREAT-HF is a suitable reagent for performing efficient aliphatic fluorine–chlorine exchange reactions under high-temperature microwave conditions. Due to the polar and ionic nature of this ionic liquid-like fluorination reagent high reaction temperatures can be attained rapidly on exposure to microwave irradiation. This allows a selective stepwise fluorine–chlorine exchange under highly controlled reaction conditions. Fluorinations that conventionally require many hours have been performed in less than 5 min reaction time under microwave conditions. For fluorination processes involving exposure to TREAT-HF for prolonged time periods at high temperatures microwave reaction vessels made from highly resistant silicon carbide are a practical alternative.

## Supplementary data

Supplementary data (Experimental procedures) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.03.103.

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9. We are not aware of any publications describing microwave-assisted fluorine-halogen exchange reactions using TREAT-HF. For previous reports on the use of

microwave irradiation in conjunction with this reagent for epoxide ring-opening and C=O to $CHCF_2$ exchange, see: (a) Yu, H-W.; Nakano, Y.; Fukuhara, T.; Hara, S. *J. Fluorine Chem.* **2005**, *126*, 962–966; (b) Akiyama, Y.; Hiramatsu, C.; Fukuhara, T.; Hara, S. *J. Fluorine Chem.* **2006**, *127*, 920–923; (c) Furuya, T.; Fukuhara, T.; Hara, S. *J. Fluorine Chem.* **2005**, *126*, 721–725; (d) Inagaki, T.; Fukuhara, T.; Hara, S. *Synthesis* **2003**, 1157–1159.

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13. It should be noted, however, that extremely rapid fluorinations with similar high selectivities can be achieved by irradiating the reaction mixture with constant 300 W of microwave power for 30 s. This leads to a maximum monitored reaction temperature of 250 °C as a result of the high microwave absorptivity of the polar TREAT-HF reagent/solvent (Refs. 8,9).
14. Isolated yields on experiments carried out on a comparatively small scale were only moderate (50–60%) as a consequence of the high volatility of the fluorinated product. See also: (a) Kitazume, T.; Ebata, T. *J. Fluorine Chem.* **2004**, *125*, 1509–1511 (compound **2**); (b) Pooput, C.; Dolbier, W. R., Jr.; Medebielle, M. *J. Org. Chem.* **2006**, *71*, 3564–3568 (compound **9**).
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17. CAUTION! Corrosion of microwave vials during usage represents a serious safety risk as the pressure rating of the heavy-walled vials (20 bar) will not be maintained. Prolonged exposure of TREAT-HF at high temperatures and pressures (e.g., ca. 10 bar at 250 °C) or repeated vial usage must therefore be strictly avoided.
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19. Microwave experiments in SiC vessels closely simulate oil bath experiments since the penetration of the electromagnetic field into the inner part of the vial is small. Due to the high thermal conductivity of SiC, rapid heating of the reaction mixture can nevertheless be obtained, similar to a standard microwave chemistry experiment. Further details on SiC reaction vessels for use in single-mode microwave reactors will be reported in subsequent publications.
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22. *Representative experimental procedure*: In a 20 mL sealed Biotage microwave vial dichloromethyl–pyrazole **11**[20] (3.200 g, 13.5 mmol) and TREAT-HF (13.9 g, 86 mmol, 14 mL) were heated with stirring to 250 °C for 5 min. After cooling, the content of the reaction vessel was poured on water and the aqueous mixture was extracted with MTBE. The organic phase was washed with water, 1 N HCl, and saturated aqueous NaCl solution and dried over $MgSO_4$. Removal of the solvent provided 1.90 g (69%) of difluoromethyl–pyrazole **12** as a light brown powder (>90% purity by HPLC at 215 nm). $^1$H NMR ($CDCl_3$, 360 MHz): $\delta$ 1.37 (t, $J$ = 7.1 Hz, 3H), 3.98 (s, 3H), 4.33 (q, $J$ = 7.1 Hz, 2H), 7.12 (t, $J$ = 54.0 Hz, 1H), 7.91 (s, 1H), MS (EI, 70 eV): $m/z$ = 204, mp = 58–59 °C.
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24. The fluorination was performed on an unseparable mixture of the 3-dichloromethyl pyrazole **14** and its 5-dichloromethyl isomer. See Supplementary data for more details.