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Fluoroalkyl Amino Reagents

A Major Advance in the Synthesis of Fluoroalkyl Pyrazoles: Tuneable Regioselectivity and Broad Substitution Patterns

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Abstract: A novel approach towards highly functionalized fluoroalkyl pyrazoles was developed by using fluoroalkyl amino reagents in combination with a variety of fluorinated ketimines. Tuneable introduction of fluoroalkyl groups in the 3- and 5-positions was possible by using vinamidinium intermediates or the corresponding enamino ketones after hydrolysis. These high-value building blocks can give rise to a large number of analogues for bioactivity screening and discovering new heterocyclic bioactive ingredients in various life science fields.

Introduction

The introduction of emergent fluorinated substituents has become a new challenge in the context of small-molecule research in agro- and medicinal chemistry.[1] The introduction of fluorine has demonstrated great potential in the discovery of analogues of active ingredients and represents a great opportunity to light upon new bioactive molecules with new modes of action. This growing interest is due to the occurrence of fluorinated active ingredients in recently marketed agrochemicals and drugs over the past years, most of which contain trifluoromethyl and/or fluoro substituents.[2] However, the difluoromethyl group (CHF_2) and related emergent fluoroalkyl substituents still remain under-exploited due to a lack of strategies for their facile introduction into building blocks or more complex structures and their total absence in naturally occurring compounds.[3]

In recent years, introduction of the CHF_2 group has been broadly studied.[4] A common strategy relies on deoxofluorination of aldehydes with diethylaminosulfur trifluoride and related reagents, but suffers from several difficulties (substrate stability, harsh conditions). The more elegant direct difluoromethylation of (hetero)arenes has been the subject of many studies.[5] Recently, Mykhailiuk reported on the use of gaseous and explosive difluoromethyl diazomethane generated in situ to prepare 3-difluoromethyl pyrazoles, which are a prevalent class of building blocks in agrochemistry, in high yields through [3+2] cycloaddition.[6] So far, all these reagent-based approaches were not suitable for industrial application. We recently reported on the use of fluoroalkyl amino reagents (FARs) as efficient and versatile reagents for the regioselective introduction of the CHF_2 group into heterocyclic building blocks (pyrazoles, isoxazoles).[7] A key intermediate in the preparation of a commercial SDHI fungicide (Bixafen, Bayer Crop Science) is prepared by reaction of an FAR with amino acrylates.[8]

Recently, it has been shown that bis(dihaloalkyl)pyrazoles show fungicidal activity with a new mode of action.[9] Some process applications of bis(dihaloalkyl)pyrazoles have been described.[10] We developed a general approach towards bis(fluoroalkyl)pyrazoles based on the use of FARs and fluorinated azines derived from benzophenone to introduce CHF_2, CHFCl and $CHFCF_3$ substituents. This provided highly functionalized pyrazoles with structural diversity, but had drawbacks such as low atom efficiency, difficult removal of benzophenone and limitation to *N*-H pyrazoles.[11]

Herein, we report a facile, robust and scalable strategy to synthesize highly functionalized bis(fluoroalkyl)pyrazoles showing diverse substitution patterns at the 1-position under mild conditions without the use of difficult-to-remove benzophenone, which allows tunable introduction of fluorinated groups Rf^1/Rf^2 in the 3- and 5-positions.

Results and Discussion

Considering the limitations and drawbacks of the previous method, the objective of this project was to design a novel strategy to easily prepare highly substituted pyrazoles containing two fluoroalkyl substituents in the 3- and 5-positions, with the possibility of controlling the regioselectivity of the hydrazine addition. Another objective was to synthesize a new FAR

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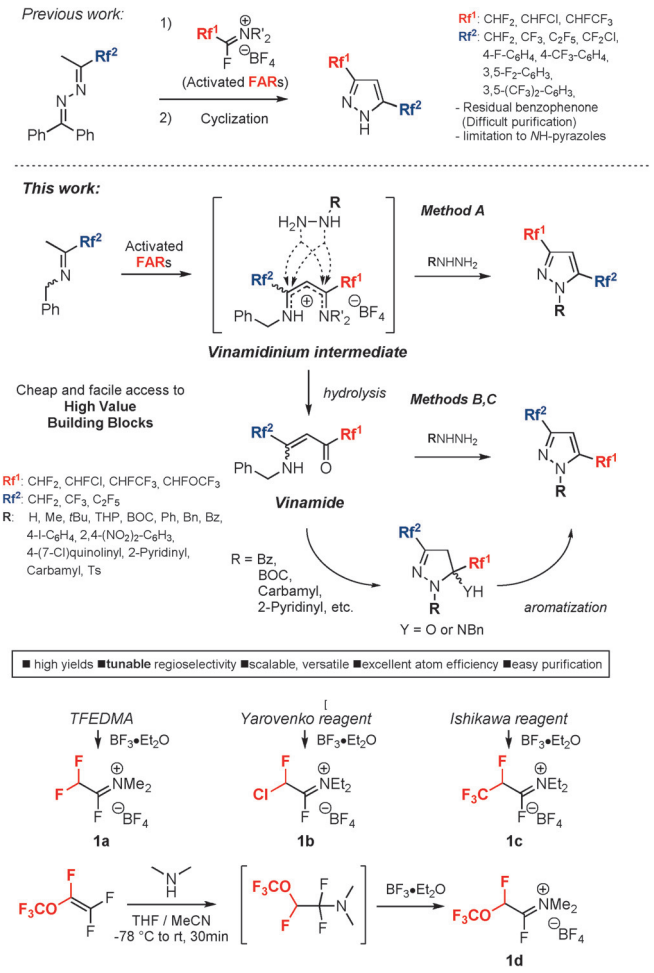
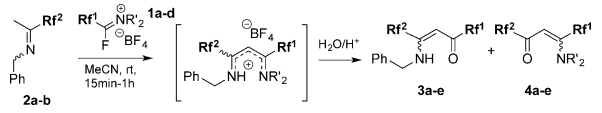


Figure 1. Use of FARs for the preparation of a variety of bis- to tetrasubstituted pyrazoles as highly valuable building blocks for life science research. Commercially available FARs in their activated form (**1a**, **1b**, **1c**). New facile access to novel FAR **1d** for introduction of the $CHFOCF_3$ substituent.

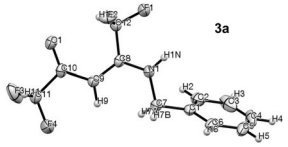
for the introduction of challenging emergent fluoroalkyl substituents such as $CHFOCF_3$. This new FAR can be prepared as its activated form (**1d**, Figure 1) from commercially available gaseous trifluoromethyl trifluorovinyl ether by liquefaction and condensation with dimethylamine, followed by in situ activation with boron trifluoride etherate. The new fluoroalkoxy fluoroalkyl group is highly electron withdrawing and has lower steric hindrance (for example, in comparison with $CHFCF_3$) due to the oxygen spacer between the CF_3 moiety and the reactive electrophilic centre. Together with a series of commercially available FARs (TFEDMA, Yarovenko reagent and Ishikawa reagent) in their activated forms (**1a**, **1b** and **1c**; Figure 1), **1d** was treated with fluorinated ketimines **2a–c** (for preparation of ketimines, see the Supporting Information).

The (fluoroalkyl)enamine resulting from (fluoroalkyl)ketimines **2a–c** reacted smoothly and often quantitatively in situ with activated FARs to produce a vinamidinium moiety at room temperature in dry MeCN. The hydrolysis of these species afforded the corresponding vinamides **3** and **4** (Table 1). These vinamides were prepared to obtain precursors of heterocycles with different reactivities.

Table 1. Preparation of bis(fluoroalkyl) vinamides **3** and **4** and crystallographic structure of vinamide **3a**.[16]



Entry	2	3/4	Rf^1	Rf^2	R′	Conversion [%]	Yield (3/4) [%]
1	**2a**	**3a/4a**	CHF_2	CHF_2	Me	99	79/0
2	**2b**	**3b/4b**	CHF_2	CF_3	Me	99	74/0
3	**2a**	**3c/4c**	$CHFOCF_3$	CHF_2	Me	92	83/0
4	**2a**	**3d/4d**	$CHFCF_3$	CHF_2	Et	88	(25/18[b])[a]
5	**2a**	**3e/4e**	CHFCl	CHF_2	Et	n.d.	31[c]/17



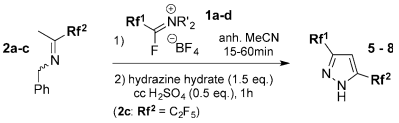
[a] Isolated as a mixture. [b] Isolated in pure form after microdistillation. [c] Isolated in pure form after chromatography.

Vinamidinium salts prepared from Ishikawa and Yarovenko reagents were less efficiently hydrolyzed due to increased stabilization and more sterically hindered *N*-diethyl iminium moieties, and provided a mixture of secondary vinamides **3** and tertiary vinamides **4**, which could be separated by distillation after prior chromatography (Table 1, entries 4, and 5).

Further treatment of the vinamidinium species with hydrazine hydrate or methyl hydrazine and subsequent addition of concentrated H_2SO_4 (0.5 equiv) rapidly afforded the corresponding *N*-H and *N*-Me pyrazoles **5–8** (Table 2) and **9–12** (Table 3). Various parameters influenced the reaction, especially the nature of both fluoroalkyl groups of the vinamidinium species, the *N*-alkyl chains of each FAR, concentration of H_2SO_4, and temperature.

As expected, dimethyl iminium salts are more electrophilic than diethyl iminium salts, which are also of lower purity when

Table 2. Synthesis of *N*-H pyrazoles **5–8** by using hydrazine hydrate.



Entry	Compound	Rf^1	Rf^2	Yield [%]
1	**5a**	CHF_2	CHF_2	99[a]
2	**5b**	CHF_2	CF_3	99[a]
3	**5c**	CHF_2	C_2F_5	99[a]
4	**6a**	$CHFOCF_3$	CHF_2	85[b]
5	**6b**	$CHFOCF_3$	CF_3	81[a]
6	**6c**	$CHFOCF_3$	C_2F_5	99[a,d], 38[a,c]
7	**7a**	CHFCl	CHF_2	81[a,d]
8	**7b**	CHFCl	CF_3	30[a,d]
9	**8a**	$CHFCF_3$	CHF_2	96[a]
10	**8b**	$CHFCF_3$	CF_3	27[a]

[a] ^{19}F NMR yield with fluorobenzene as internal standard. [b] Yield of isolated product. [c] Only 0.1 equiv conc. H_2SO_4 used. [d] After a further 18 h.

Table 3. Synthesis of *N*-Me pyrazoles **9**–**12** by using methyl hydrazine.

Entry	Compound	Rf^1	Rf^2	Yield	Ratio P^1/P^2
1	**9a**	CHF_2	CHF_2	90[a]	–
2	**9b/9c**	CHF_2	CF_3	>99[a,c]	85:15
3	**9b/9c**	CHF_2	CF_3	96[b]	0:100
4	**9d/9e**	CHF_2	C_2F_5	>99[a]	87:13
5	**10a/10b**	$CHFOCF_3$	CHF_2	99[a,e]	71:29
6	**10c**	$CHFOCF_3$	CF_3	66[a]	100:0
7	**10d**	$CHFOCF_3$	C_2F_5	81[a,d]	100:0
8	**11a/11b**	CHFCl	CHF_2	45[a,d]	73:27[f]
9	**12a/12b**	$CHFCF_3$	CHF_2	84[a,e]	31:69

[a] Yield determined from ^{19}F NMR spectroscopy with fluorobenzene as internal standard. [b] From **3b**, yield of isolated product. [c] Only 0.1 equiv conc. H_2SO_4 used. [d] after a further 18 h. [e] Separated by silica-gel chromatography. [f] Reproducibility issues (see text).

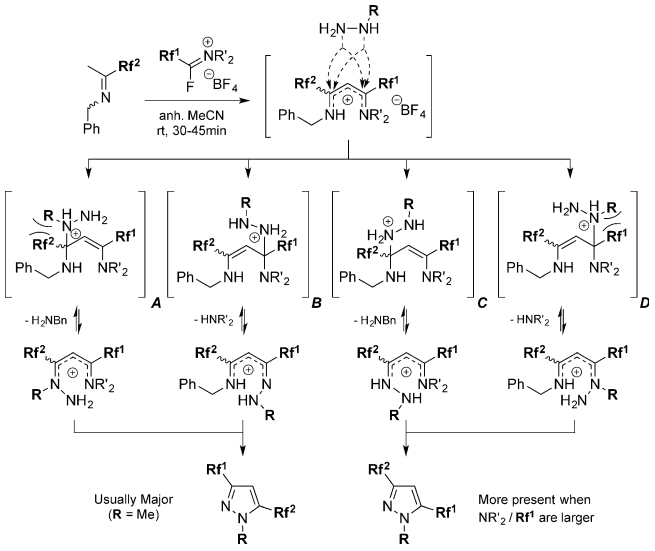
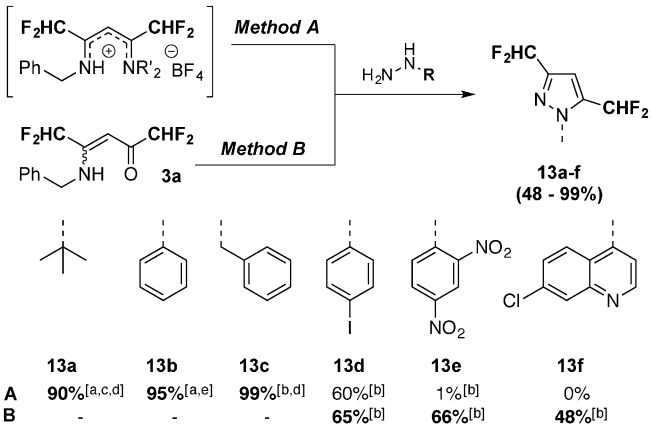


Figure 2. Mechanistic rationalization of the regioselectivity of hydrazine addition to vinamidinium species (for R = Me).

prepared from commercial sources. Activated FARs **1a** and **1d** indeed gave the best results, whereas activated Yarovenko and Ishikawa reagents **1b** and **1c** (Figure 1) were of lower purity and reactivity. With **1d**, the reaction proceeded well to give pyrazoles **6a**–**c** and **10a**–**d** (Table 1, entries 4–6 and Table 2, entries 5–7), and the most difficult part was preparation of the FAR while avoiding THF polymerization, as commercial dimethylamine solution was available only in this solvent. For **1a** and **1d**, the regioselectivity was high to excellent and in favour of P^1 regioisomers (Table 3). The Yarovenko reagent seemed highly incompatible with electron-poor ketimines such as **2b**,**c**. The observed regioselectivity (Table 3, entry 8) was not reproducible and difficult to control (73:27 to 19:81 for different attempts). The Ishikawa reagent showed similar behaviour: no reaction with electron-poor ketimines such as **2b** and **2c** and lower regioselectivity, which surprisingly was reversed in favour of the P^2 regioisomers (Table 3, entry 9). This could be explained by the greater steric hindrance of $CHFCF_3$ and the less reactive iminium species.

Inspired by the work of Fustero and co-workers,[12] we hypothesized in the case of TFEDMA and its OCF_3 analogue a more favourable attack of the NH_2 group of methyl hydrazine to lower the steric clash between CH_3 and Rf^1/Rf^2 (paths B and C, Figure 2) and pyrazole ring formation driven by the loss of volatile dialkyl amine instead of benzylamine (path B more favourable). With the Yarovenko and Ishikawa reagents, the lower reactivity of diethyl iminium salts combined with higher steric hindrance of Rf^1 groups led to different regioselectivities. We also investigated the introduction of a wide diversity of substituents into the 1-positions of bis(fluoroalkyl) pyrazoles using a variety of commercially available hydrazines (Scheme 1). Conveniently, bis(CHF_2) pyrazoles were prepared to avoid the preparation of numerous pairs of regioisomers. In the presence of hydrazine hydrochloride salts, Et_3N was added to increase hydrazine solubility, and no further H_2SO_4 was needed. By treating unsymmetrical vinamide **3b** (Table 1) with

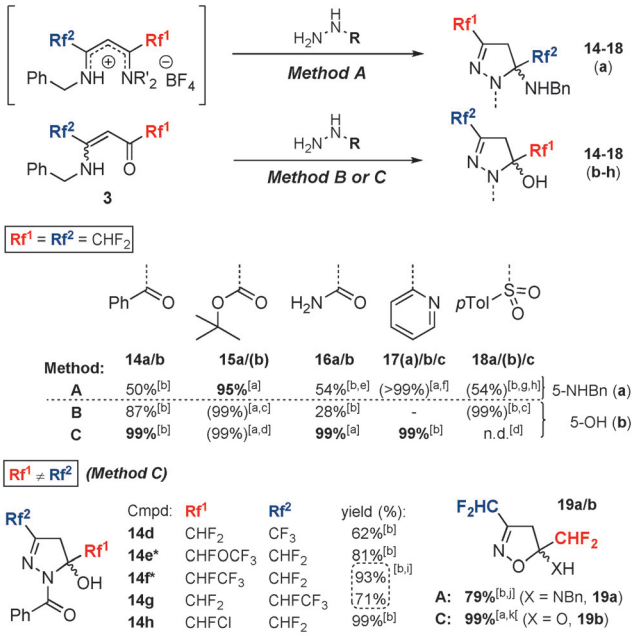


Scheme 1. Alternative methods to access *N*-alkyl and *N*-(het)aryl bis(difluoromethyl)pyrazoles **13a**–**f**. Method A: hydrazine, conc. H_2SO_4, MeCN, RT → 50 °C, 1 h. Method B: hydrazine, conc. H_2SO_4, toluene/MeCN, 120–140 °C, microwave, 0.5–2 h. [a] ^{19}F NMR yield with PhF as internal standard. [b] Yield of isolated product. [c] *t*Bu sensitive to excess of conc. H_2SO_4 at 50 °C. *N*-H pyrazole **5a** partially formed. [d] Et_3N used instead of H_2SO_4. [e] After a further 18 h.

methyl hydrazine, we successfully reversed the regioselectivity (Entry 3, Table 2).

Initially, in situ cyclization of vinamidinium species in the presence of H_2SO_4 (Scheme 2, method A) provided efficiently pyrazoles **13a**–**d**, but for both more sterically hindered hydrazines and electron-poor hydrazines, no reaction was observed under our conditions. To circumvent this issue, microwave reaction conditions were developed starting from vinamides **3/4** (Scheme 2, method B), and thus compounds **13e,f** were obtained in moderate to good yields.

Several limitations were observed, such as non-compatibility with acid-labile groups (Boc, tosyl, *t*Bu, benzoyl under certain conditions, and so on) and sluggish reactions (especially **13f**



Scheme 2. Preparation of 2-pyrazolines/pyrazoles **14**–**18** with tunable fluoroalkyl substitution. Preparation of two isoxazolines **19a**,**b**. Method A: hydrazine, conc. H_2SO_4, MeCN, 20 °C, 1–18 h. Method B: hydrazine, conc. H_2SO_4, toluene/MeCN, 120–140 °C, microwave, 0.5–2 h. Method C: hydrazine, HFIP, 100–140 °C, 0.5–5 h. [a] ^{19}F NMR yield with PhF as internal standard. [b] Yield of isolated product. [c] R group cleaved between 120 and 150 °C. *N*-H pyrazole **5a** formed. [d] R group cleaved between 80 and 120 °C. *N*-H pyrazole **5a** formed. [e] Et_3N used to enhance hydrazine solubility, no further H_2SO_4 added. [f] **18c** was isolated directly. [g] No conc. H_2SO_4 used. [h] pyrazole **18c** was separated by chromatography from pyrazoline **18a** (29% isolated). [i] **14f** and **14g** prepared from a 65/35 mixture of **3d**/**4d** (Method C) and separated by chromatography. [j] Hydroxylamine (50 wt% aq.) used instead of hydrazine. [k] Hydroxylamine·HCl used instead of hydrazine. ⋆ Mixture of diastereoisomers formed.

with heterogeneous mixture). However, a large variety of *N*-substituents could be accessed in pyrazole ring formation.

As reported by Fustero et al.,[12] Bonacorso et al.,[13] and Norris et al.,[14] the synthesis of fluoroalkyl pyrazoles from fluorinated 1,3-diketones or analogues and hydrazines can lead to regioisomeric pairs of pyrazoles, but also to hydroxypyrazoline which are not dehydrated under the reaction conditions. In our case, vinamidinium/vinamide moieties can be regarded as 1,3-diiminium and 1-keto-3-iminium species with a fluoroalkyl group on each side.

It was observed that, in the presence of H-bonding *N*-substituents on the preformed pyrazolic core, the dehydration/deamination step was disfavoured due to an adjacent highly electron-withdrawing fluoroalkyl group, whereas H-bonding stabilizes the pyrazoline form. Several pyrazolines could be isolated (Scheme 2) and provided single crystals for crystallographic analysis (**15a**, **16a**,**b**, **17b**; Figure 3).[16] Boc and tosyl groups showed very low thermal stability above 80 °C under microwave conditions (**15**, **18**; Scheme 2). 2-Pyridinyl and tosyl groups were less able to stabilize pyrazolines **17a** and **18a** by H-bonding, and deamination occurred readily to provide the corresponding pyrazoles **17c** and **18c** in good to excellent yield. By considering that hydrazines were preferentially achieving nucleophilic attack via the less hindered primary amine (followed by further ring formation), we demonstrated that vinamidinium and vinamides have opposite reactivities. Indeed, in most cases, 5-benzylaminopyrazolines were prepared from the corresponding vinamidinium species (method A), whereas 5-hydroxypyrazolines were prepared from the corresponding vinamides (method B). Using a fluorinated polar protic solvent such as hexafluoropropan-2-ol (HFIP) made a critical improvement to this reaction (method C).[12] This type of non-nucleophilic and highly H-bonding solvent showed high compatibility with the synthesis of 5-hydroxypyrazolines without any acidic assistance and provided excellent yields (**14b**, **16b**, **17b**; Scheme 2).

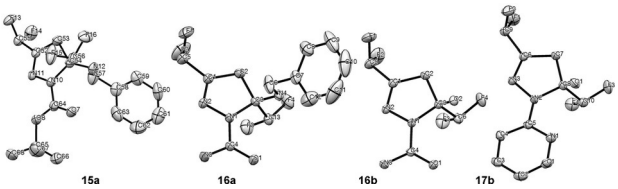
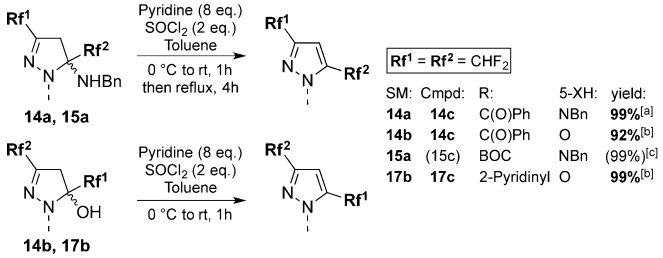


Figure 3. Crystallographic structures of (±)-5-benzylaminopyrazolines **15a** (left), **16a** (centre left), (±)-5-hydroxypyrazoline **16b** (centre right), and **17b** (right). Ellipsoids set at 50% probability; hydrogen atoms omitted.[16]

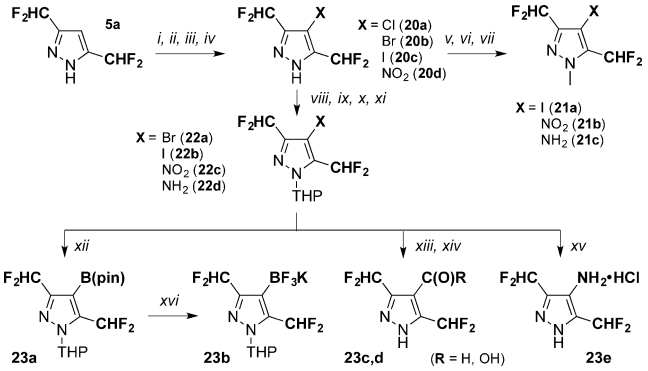
We extended this reaction to non-symmetrical vinamides (**3b**, **3c**, **3e** and **3d**/**4d**; Table 1) and observed that whichever Rf^1/Rf^2 couple was used, the reactivity of the benzyl iminium species formed in situ was always higher than that of the adjacent fluoroalkyl ketone, and 5-Rf^1,5-OH pyrazolines (**14d**,**e**,**h**) were obtained in good to excellent yields. The mixture of vinamides **3d**/**4d** (65:35) provided a mixture of pyrazolines **14f**/**14g** (68:32), as both vinamides reacted highly regioselectively and efficiently (93% from **3d** and 71% from **4d**). An interesting example was the use of aqueous hydroxylamine, in which nitrogen is more nucleophilic than oxygen, for the cyclization of the bis(CHF_2) vinamidinium species derived from **1a** and **2a**, providing regioselectively 5-benzylamino isoxazoline **19a** in very good yield. A similar result was observed when the corresponding bis(difluoromethyl)vinamide was treated with hydroxylamine·HCl in HFIP to access regioselectively 5-hydroxyisoxazoline **19b**, also in good yield (Scheme 2).

Finally, we demonstrated that bis(fluoroalkyl) pyrazolines could be conveniently aromatized under basic conditions by using thionyl chloride to access the desired pyrazoles.[13] *N*-Benzoyl-5-hydroxypyrazoline **14b** and *N*-2-pyridinyl-5-hydroxypyrazoline **17b** were very efficiently dehydrated at room temperature (**14c**, **17c**), whereas heating to reflux was required for *N*-benzoyl-5-benzylaminopyrazoline **14a** and *N*-Boc-5-benzylaminopyrazoline **15a**, which provided quantitatively pyrazole **5a** due to the instability of BOC in bis(fluoroalkyl)pyrazoles (Scheme 3).

To complete the investigation, we introduced a variety of functional groups into the 4-position of model 3,5-bis(CHF_2)-NH-pyrazole **5a**, in order to further improve the applicability of our building blocks (Scheme 4). This was achieved by electrophilic aromatic substitution reactions followed by further transformations. Halo and nitro groups were readily introduced, and further pyrazole protection was achieved by introducing



Scheme 3. Dehydration/debenzylamination of pyrazolines **14**, **15**, and **17**. [a] ^{19}F NMR yield with PhF as internal standard. [b] Yield of isolated product. [c] *N*-H pyrazole **5a** isolated instead of **15c**.



Scheme 4. Introduction of various functional groups into the 4-position of bis(CHF_2) pyrazole **5a**. i) aq. NaOCl, AcOH, RT, 18 h. 82%; ii) cat. Fe, Br_2, 100 °C, 1 h, 90%; iii) I_2, CF_3COOAg, CH_2Cl_2, −15 °C→RT, 4 h, 98%; iv) HNO_3, H_2SO_4, 115 °C, 15 min, microwave, 99%; v) **20c**, MeI, Et_3N, CH_2Cl_2, RT, 52%; vi) **20d**, MeI, Et_3N, CH_2Cl_2, RT, 18 h, 99%; vii) **21b**, cat. Pd/C, H_2, EtOH, RT, 1 h, 86%; viii) **20b**, 3,4-dihydropyran (DHP), cat. TsOH, CH_2Cl_2, 50 °C, 18 h, 95%; ix) **20c**, DHP, cat. TsOH, CH_2Cl_2, RT, 18 h, 89%; x) **20d**, DHP, cat. TsOH, CH_2Cl_2, RT, 18 h, 45%; xi) **22c**, cat. Pd/C, H_2, EtOH, 50 °C, 18 h, 86%; xii) 1) **22b**, *i*PrMgCl·LiCl solution in THF, −30 °C, 1 h; 2) *i*PrOB(pin), −30 °C→RT, 1 h, 99%; xiii) 1) **22b**, *i*PrMgCl·LiCl solution in THF, −30 °C, 1 h; 2) DMF, −30 °C→RT, 1 h; 3) conc. HCl, EtOH, RT, 72 h, 54%; xiv) 1) **22b**, *i*PrMgCl·LiCl solution in THF, −30 °C, 1 h; 2) Dry $CO_{2(s)}$, −30 °C→RT, 1 h. 3) 1 M HCl, 60%, then rapidly 3) cat. conc. HCl, MeOH, RT, 1 h, 39%; xv) **22d**, 2 M HCl in Et_2O, RT, 30 min, 46%; xvi) **23a**, aq. KHF_2, MeOH, RT, 30 min, 99%.

a 2-tetrahydropyranyl (THP) group. Interestingly, 4-NO_2-pyrazole **20d** was crystalline as the hydrate, but amorphous after chromatography, and *N*-THP-4-NO_2-pyrazole **22c** was also crystalline (Figure 4). *N*-Methyl pyrazoles **21a–c** were accessed by methylation reactions. The use of the turbo Grignard reagent was found to be the most efficient route to compounds **23a–d** starting from THP-iodo-pyrazole **22b**. The conversion of the pinacol boronic ester **23a** to the potassium trifluoroborate **23b** was quantitatively achieved under the described conditions.[15] Despite numerous efforts, it was not possible to introduce fluorine in the 4-position between two fluoroalkyl groups by using electrophilic fluorinating reagents such as Selectfluor, *N*-fluorodibenzene sulfonimide and 1-fluoropyridinium triflate, starting from THP-iodo-pyrazole **22b**. Instead, fluorination of the THP group was observed, mainly in the 6-position.

Conclusion

We have developed an elegant method to access 3,5-bis(fluoroalkyl)pyrazoles with tuneable regioselectivity, based on the use of fluorinated ketimines, activated FARs and hydrazines. These pyrazoles are highly valuable building blocks for agrochemical ingredients showing a novel mode of action. A new FAR has been employed to introduce a novel fluoroalkyl moiety ($CHFOCF_3$), prepared by hydroamination of trifluoromethyl trifluorovinyl ether and in situ activation. The opposite reactivity of vinamidinium and vinamide species was found to be of great value to tune the regioselectivity of hydrazine addition. We demonstrated the feasibility of further functionalization of the 4-position of such building blocks to introduce various functional groups for later coupling reactions. We expect these studies to provide facile access to bis-fluorinated pyrazoles and to have a significant impact on agrochemistry, medicinal chemistry and related fields.

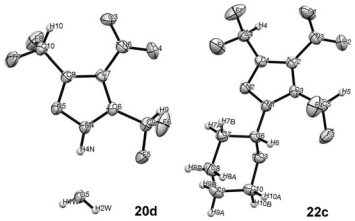


Figure 4. Crystallographic structures of 4-NO_2-NH-pyrazole·0.5 H_2O **20d** (left) and *N*-THP-4-NO_2-pyrazole **22c** (right). Ellipsoids set at 50% probability.[16]

Experimental Section

General procedure for the preparation of bis(fluoroalkyl)vinamides 3 and 4: A solution of fluorinated ketimine **2** (1 equiv, 1.64 mmol) in dry MeCN (2 mL) was added to a solution of activated FAR **1a–d** (1.2 equiv, 1.95 mmol) in dry MeCN (2 mL). The mixture was stirred at the given temperature (20–50 °C) for 15–60 min. The mixture was diluted with CH_2Cl_2 (10 mL) and hydrolyzed with 1 M HCl (10 mL) with vigorous stirring for 1 h. If the purity of the crude product was not sufficient, flash chromatography or distillation under reduced pressure was performed.

General procedure for the preparation of bis(fluoroalkyl)pyrazoles 5–12: A solution of fluorinated ketimine **2** (1.64 mmol) in dry MeCN (2 mL) was added to a solution of activated FAR **1a–d** (1.2 equiv, 1.95 mmol) in dry MeCN (2 mL). The mixture was stirred at the given temperature (20–50 °C) for 15–60 min. Hydrazine hydrate (1.51 equiv, 123 mg, 0.12 mL, 2.47 mmol) or methylhydrazine (1.51 equiv, 123 mg, 0.12 mL, 2.47 mmol) was added by syringe at the given temperature (20–50 °C), rapidly followed by conc. H_2SO_4 (0.56 equiv, 0.05 mL, 0.91 mmol). The mixture was stirred at the given temperature for 1–18 h.

Preparation of *N*-alkyl/aryl 3,5-bis(fluoroalkyl) pyrazoles 13a–f: Method A: Corresponding vinamidinium intermediates were treated with corresponding hydrazines, and cyclization/aromatization was carried out under classical heating conditions (20–50 °C, 1–18 h). Reaction mixtures were concentrated in vacuo and purified by flash chromatography.

Method B: Vinamide **3a** (500 mg, 1.91 mmol) was treated with the corresponding hydrazine (1.5 equiv, 2.87 mmol) and conc. H_2SO_4 (2.1 equiv, 0.22 mL, 4.0 mmol) in toluene (8 mL). The mixture was heated for 0.5–2 h at 120–140 °C under microwave irradiation in a sealed vial. Crude materials were purified by flash chromatography.

Typical procedure for the preparation of *N*-substituted 3,5-bis-(fluoroalkyl) pyrazolines 14–18 and 3,5-bis(fluoroalkyl)isoxazolines 19a,b: Method A: Similar conditions to Method A above with the corresponding vinamides and hydrazines (for details, see Supporting Information).

Method B: Similar conditions to Method B above with vinamides and hydrazines (for details, see Supporting Information).

Method C: The corresponding vinamide (1.7 mmol) was treated with the corresponding hydrazines (1.9 equiv, 3.2 mmol) in HFIP (5 mL). The mixture was heated for 0.5–5 h at 100–140 °C under microwave irradiation in a sealed vial. After concentration in vacuo, crude materials were purified by flash chromatography.

Typical procedure for the preparation of 3,5-bis(fluoroalkyl) pyrazoles from pyrazolines: A solution of $SOCl_2$ (2.09 equiv, 0.04 mL, 0.551 mmol) in toluene (1 mL) was added to a solution of *N*-benzyl pyrazoline (0.264 mmol) and dry pyridine (8.0 equiv, 0.17 mL, 2.1 mmol) in toluene (2 mL) at 0 °C. After raising the temperature to room temperature, the mixture was heated to reflux for 3 h (refluxing was not required for hydroxypyrazolines).

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[16] CCDC 1472446 (**3a**), 1472449 (**15a**), 1472448 (**16a**), 1472445 (**16b**), 1472447 (**17b**), 1472451 (**20d**), and 1472450 (**22c**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

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