Major advance in the synthesis of fluoroalkyl pyrazoles – Tunable regioselectivity and broad substitution pattern.

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Abstract: A novel approach towards highly functionalized fluoroalkyl pyrazoles was developed using Fluoroalkyl Amino Reagents in combination with a variety of fluorinated ketimines. The tunable introduction of fluoroalkyl groups in position 3 and 5 was allowed by using either 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 as well as 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 either in Agro- or Medicinal chemistry.^[1] The introduction of fluorine has demonstrated high 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 or drugs over the past years, mostly containing trifluoromethyl and/or fluorine substituents.^[2] In the meantime, the difluoromethyl group (-CHF₂) and related emergent fluoroalkyl substituents still remain under-exploited due to a former lack of strategies allowing for their facile introduction into building blocks of interest or more complex structures, in addition with a total absence in naturally-occurring molecules.^[3]

In recent years, the introduction of the -CHF₂ group has been broadly studied.^[4] A common strategy relies on deoxofluorination of aldehydes using DAST and related reagents, but suffers from several difficulties (substrate stability, harsh conditions). The more elegant direct difluoromethylation of (hetero)arenes has been subjected to many studies.^[5] Recently, Mykhailiuk reported on the use of *in situ* generated gaseous and explosive difluoromethyl diazomethane, providing 3-difluoromethyl pyrazoles - a prevalent class of building blocks in agrochemistry, with high yields via a [3+2] cycloaddition.^[6] So far, all these reagent-based approaches were not suitable for industrial application. Our group recently reported on the use of Fluoroalkyl Amino Reagents (FARs) as efficient and versatile reagents for the regioselective introduction of the -CHF₂ group into heterocyclic building blocks (pyrazoles, isoxazoles).^[7] A key intermediate in the preparation of a marketed SDHI fungicide (Bixafen, Bayer CropScience) is prepared by means of FAR which is reacted with amino acrylates.^[8]

Figure 1. Use of FARs for the preparation of a large variety of bis- to tetra-substituted pyrazoles as highly valuable building blocks for Life Science research. Commercially available FARs in their activated form (**1a**, **1b**, **1c**). New facile access to a novel FAR for introduction of the -CHFOCF₃ substituent (**1d**)

Recently, it has been shown that bis(dihaloalkyl)pyrazoles reveal fungicide activity with a new mode of action.^[9] Some process applications to 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, allowing the

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introduction of $-\text{CHF}_2$, $-\text{CHFCI}$ and $-\text{CHF}_2\text{CF}_3$ substituents. This provided highly functionalized pyrazoles with structural diversity, but possessed drawbacks such as atom efficiency, difficult benzophenone removal and limitation to *NH*-pyrazoles.^[11]

Herein we report a facile, robust and scalable strategy to synthesize highly functionalized bis(fluoroalkyl)pyrazoles presenting vast substitution patterns in positions 1, using mild conditions and avoiding the use of difficult-to-remove benzophenone, with tunable introduction of Rf^1/Rf^2 in positions 3 and 5.

Regarding 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 position 3 and 5, with the possibility of controlling the regioselectivity of the hydrazine addition.

Another objective was to synthesize a new FAR for the introduction of challenging emergent fluoroalkyl substituents such as $-\text{CHFOCF}_3$. This new FAR (**1d**, Fig. 1) can be prepared 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 with a lower steric hindrance (in comparison with $-\text{CHF}_2\text{CF}_3$ for example) due to an oxygen-spacer between the CF_3 moiety and the reactive electrophilic centre. It was added to the series of commercially available FARs – TFEDMA, Yarovenko reagent, and Ishikawa reagent, to be reacted in their activated form (**1a**, **1b**, **1c**, Fig. 1) with fluorinated ketimines **2a-c** (for ketimines preparation, see S.I.).

We were pleased to observe that the *in situ* formed (fluoroalkyl)enamine resulting from (fluoroalkyl)ketimine (**2a-c**) reacted smoothly and often quantitatively with activated FARs, providing a vinamidinium moiety at room temperature in dry MeCN. The further hydrolysis of these species afforded the corresponding vinamides (**3**, **4**, Table 1). These vinamides were prepared to obtain precursors of heterocycles with different reactivities.

Table 1. Preparation of bis(fluoroalkyl) vinamides **3/4**. Crystallographic structure of vinamide **3a** (bottom) ^[16].

	2a-b	1a-d							
	Rf^2	Rf^1	NR'_2	BF_4^-	$\text{H}_2\text{O}/\text{H}^+$	Rf^2	Rf^1	Rf^2	Rf^1
	$\text{Ph}-\text{CH}=\text{N}-\text{CH}(\text{Rf}^2)-\text{N}(\text{Rf}^1)-\text{NR}'_2$	F	BF_4^-	$\text{Ph}-\text{CH}=\text{N}-\text{CH}(\text{Rf}^2)-\text{N}(\text{Rf}^1)-\text{NR}'_2$		$\text{Ph}-\text{CH}=\text{N}-\text{CH}(\text{Rf}^2)-\text{N}(\text{Rf}^1)-\text{NR}'_2$	Rf^1	Rf^2	Rf^1
Entry:	Ket.:	Cmpd.:	Rf^1	Rf^2	R'	Conv. (%)	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	CHF_2CF_3	CHF_2	Et	88%	[25% / 18%] ^a		
5	2a	3e / 4e	CHFCI	CHF_2	Et	n.d.	31% / 17%

[a]: 60/40 mixture. [b]: isolated pure after micro-distillation. [c]: isolated pure after chromatography.

Table 2. Synthesis of *NH*-pyrazoles (**5-8**) using hydrazine hydrate

	2a-c	1a-d		
	Rf^2	Rf^1	NR'_2	BF_4^-
	$\text{Ph}-\text{CH}=\text{N}-\text{CH}(\text{Rf}^2)-\text{N}(\text{Rf}^1)-\text{NR}'_2$	F	BF_4^-	$\text{Ph}-\text{CH}=\text{N}-\text{CH}(\text{Rf}^2)-\text{N}(\text{Rf}^1)-\text{NR}'_2$
Entry.	Cmpd.	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}
7	7a	CHFCI	CHF_2	81% ^{a,d}
8	7b	CHFCI	CF_3	30% ^{a,d}
9	8a	CHF_2CF_3	CHF_2	96% ^a
10	8b	CHF_2CF_3	CF_3	27% ^a

Table 3. Synthesis of *NMe*-pyrazoles (**10-13**) using methyl hydrazine

Step 2:
 MeNHNH_2 (1.5 eq.)
 H_2SO_4 (0.5 eq.)
 MeCN , 1h

9 - 12

P¹

P²

Entry	Cmpd.	Rf ¹	Rf ²	Yield:	Ratio P ¹ / P ²
1	9a	CHF₂	CHF₂	90%^a	-
2	9b/9c		CF₃	>99%^{a,c}	85/15
3	9d/9e			From 3b : 96%^b	0/100
4	9d/9e		C₂F₅	>99%^a	87/13
5	10a/10b	CHFOCF₃	CHF₂	99%^{a,e}	71/29
6	10c		CF₃	66%^a	100/0
7	10d		C₂F₅	81%^{a,d}	100/0
8	11a/11b		CHFCI	CHF₂	45%^{a,d}
9	12a/12b	CHFCF₃	CHF₂	84%^{a,e}	31/69

Tables 2 and 3:

[a]: ¹⁹F NMR yield using fluorobenzene as internal standard. [b]: isolated yield. [c]: only 0.1 eq. cc H₂SO₄ used. [d]: after 18h more. [e]: separated by silica gel chromatography. [f]: reproducibility issues (see text).

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

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

As expected, dimethyl iminium salts are more electrophilic than diethyl iminium salts, which are also of lower purity when purchased from commercial sources. Activated FARs **1a** and **1d** indeed provided the best results, while activated Yarovenko and Ishikawa reagents **1b** and **1c** were of lower purity and reactivity (Fig. 1). With **1d**, the reaction proceeded well to the pyrazoles **6a-c** and **10a-d** (Entries 4-6, Table 1 and Entries 5-7, Table 2), the most complex part being the preparation of the FAR itself - avoiding THF polymerization - as commercial dimethylamine solution was available only in this solvent. For these two FARs, the regioselectivity was high to excellent and in favour of P¹ regioisomers (Table 3). The Yarovenko reagent seemed highly incompatible with electron-poor ketimines like **2b,c**. The regioselectivity observed (Entry 8, Table 3) was not reproducible and difficult to control (73/27 to 19/81 for different attempts). The Ishikawa reagent displayed a similar behaviour with no reaction with electron-poor ketimines like **2b** and **2c** and a lower regioselectivity surprisingly reversed in favour of the P² regioisomers (Entry 9, Table 3). This could be explained by the higher steric hindrance of $-\text{CHFCF}_3$ in addition with a 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 -analog, 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, Fig. 2), and a pyrazole ring formation driven by the loss of volatile dialkylamine instead of benzylamine (Path B more favourable). When considering Yarovenko and Ishikawa reagents, the lower reactivity of diethyl iminium salts combined with higher steric hindrance of Rf^1 groups lead to different regioselectivities. We also investigated the introduction of a large diversity of substituents into positions 1 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 presence of hydrazine hydrochloride salts, Et_3N was added to increase hydrazine solubility, and no H_2SO_4 was further needed. However, when we reacted the unsymmetrical vinamide **3b** (Table 1) with methyl hydrazine we successfully reversed the regioselectivity (Entry 3, Table 2).

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

Figure 2. Mechanistic rationalization of the regioselectivity of hydrazine addition onto vinamidinium species (for $\text{R} = \text{Me}$).

Scheme 1. Alternative methods to access *N*-alkyl and *N*-(het)aryl

Method A: hydrazine, cc H_2SO_4 , MeCN, r.t., -50 °C, 1h. **Method B:** hydrazine, cc H_2SO_4 , Toluene / (MeCN), 120-140 °C, microwave, 30min - 2h.

[a]: ^{19}F NMR yield using PhF as internal standard. [b]: isolated yield. [c]: *t*-Bu sensitive to excess of cc H_2SO_4 at 50 °C. NH-pyrazole **5a** partially formed. [d]: Et_3N used instead of H_2SO_4 . [e]: after 18h more.

Several limitations were observed such as non-compatibility with acido-labile groups (BOC, Tosyl, *t*-Bu, Benzoyl under certain conditions, etc.) and sluggish reactions (especially **13f** with heterogeneous mixture). However, a large variety of *N*-substituents could be accessed during the pyrazole ring formation.

As reported by several groups (Fustero et al.^[12], Bonaccorso et al.^[13], 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 hydroxyl-pyrazolines which do not dehydrate in the reaction conditions. In our case, vinamidinium/vinamide moieties can be considered as 1,3-diiminium and 1-keto-3-iminium species with a fluoroalkyl group on each side.

It was observed that in presence of H-bonding *N*-substituents on the pre-formed pyrazolic core, the dehydration/deamination step was disfavoured due to an adjacent highly electron-withdrawing fluoroalkyl group, while H-bonding was stabilizing the pyrazoline form. Several pyrazolines could be isolated (Scheme 2) and provided single crystals for crystallographic analysis (**15a**, **16a/b**, **17b**, Fig. 3)^[16]. BOC and Tosyl groups showed very low thermal stability at >80 °C (**15**, **18**, Scheme 2) under microwave conditions. 2-Pyridinyl and tosyl groups were less able to stabilize pyrazolines **17a** and **18a** via H-bonding and the deamination occurred readily, providing the corresponding pyrazoles **17c** and **18c** with 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 possessed an opposite reactivity. Indeed, in most examples, 5-benzylaminopyrazolines were prepared from the corresponding vinamidinium (Method A), whereas 5-hydroxypyrazolines were prepared from the corresponding vinamides (Method B). Using a fluorinated polar protic solvent like HFIP made a critical improvement in 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, providing excellent yields (**14b**, **16b**, **17b**, Scheme 2).

We extended this reaction to non-symmetrical vinamides (**3b**, **3c**, **3e** and **3d/4d**, Table 1), and observed that whichever **Rf¹/Rf²** couple was used, the reactivity of the *in situ* formed benzyl iminium was always higher than the one of the adjacent fluoroalkyl ketone, providing 5-**Rf¹**-5-OH-pyrazolines (**14d,e,h**) with good to excellent yields. The vinamide mixture **3d/4d** (65/35) provided a mixture of pyrazolines **14f/14g** (68/32) as both vinamides reacted highly regioselectively and efficiently (respectively 93% from **3d** and 71% from **4d**). An interesting example was the use of aqueous hydroxylamine (where nitrogen is more nucleophilic than oxygen) for the cyclization of the bis(CHF₂)vinamidinium derived from **1a** and **2a**, providing regioselectively 5-benzylamino-isoxazoline **19a** with very good yield. A similar result was observed when reacting the corresponding bis(CHF₂)vinamide with hydroxylamine•HCl in HFIP, to access regioselectively 5-hydroxy-isoxazoline **19b** also with good yield (Scheme 2).

Finally, we demonstrated that bis(fluoroalkyl)pyrazolines could be conveniently aromatized under basic conditions using thionyl chloride to access the desired pyrazoles.^[13] *N*-Benzoyl-5-hydroxy-pyrazoline **14b** and *N*-2-pyridinyl-5-hydroxy-pyrazoline

17b were very efficiently dehydrated at room temperature (**14c**, **17c**), while reflux heating was required for *N*-benzoyl-5-benzylamino-pyrazoline **14a** and *N*-BOC-5-benzylamino-pyrazoline **15a**, which provided quantitatively pyrazole **5a** due to the instability of BOC in bis(fluoroalkyl)pyrazoles (Scheme 3).

Scheme 2. Preparation of 2-pyrazolines/pyrazoles **14-18** with tunable fluoroalkyl substitution. Preparation of two isoxazolines **19a,b**.

Method A: hydrazine, cc H₂SO₄, MeCN, 20 °C, 1-18h. **Method B:** hydrazine, cc H₂SO₄, Toluene / (MeCN), 120-140 °C, microwave, 30min-2h. **Method C:** hydrazine, HFIP, 100-140 °C, 30 min-5 h. [a]: ¹⁹F NMR yield using PhF as internal standard. [b]: isolated yield. [c]: R group cleaved between 120 and 150 °C. NH-pyrazole **5a** formed. [d]: R group cleaved between 80 and 120 °C. NH-pyrazole **5a** formed. [e]: Et₃N used to enhance hydrazine solubility, no H₂SO₄ further added. [f]: **18c** was isolated directly. [g]: No cc H₂SO₄ 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 (50wt.% aq.) used instead of hydrazine. [k]: hydroxylamine•HCl used instead of hydrazine. *: Mixture of diastereoisomers formed.

Figure 3. Crystallographic structures of (±)-5-benzylamino-pyrazolines **15a** (left), **16a** (center-left), (±)-5-hydroxy-pyrazoline **16b** (center-right) and **17b** (right) (protons not shown)^[16].

Scheme 3. Dehydration/Debenzylamination of pyrazolines **14**, **15** and **17**.

[a]: ¹⁹F NMR yield using PhF as internal standard. [b]: isolated yield. [c]: NH-pyrazole **5a** isolated instead of **15c**.

To complete the investigation, we introduced a variety of functionalities into position 4 of the model 3,5-bis(CHF₂)-NH-pyrazole **5a**, in order to further improve the applicability of our building-blocks. This was achieved via electrophilic aromatic substitution reactions followed by further transformations. Common halogens were readily introduced as well as the nitro group, and further pyrazole protection was achieved by introducing THP. Interestingly, 4-NO₂-pyrazole **23d** was crystalline as the hydrate, but amorphous after chromatography, while *N*-THP-4-NO₂-pyrazole **22c** was also crystalline. *N*-methyl pyrazoles **21a-c** were accessed via methylation reactions. The use of the turbo Grignard reagent was found to be the most efficient route towards compounds **23a-e** starting from THP-iodo-pyrazole **22b**. The conversion of the pinacol boronic ester **23a** to the potassium trifluoroborate **23b** was quantitatively achieved using described conditions.^[15] Despite numerous efforts, it was not possible to introduce fluorine in position 4 between two fluoroalkyl groups using electrophilic fluorinating reagents such as Selectfluor®, NFSI or 1-fluoropyridinium triflate, starting from THP-iodo-pyrazole **22b**. Instead, fluorination of the THP group was observed, mainly in position 6.

Figure 4. Crystallographic structures of 4-NO₂-NH-pyrazole•½H₂O (**20d**, left) and *N*-THP-4-NO₂-pyrazole (**22c**, right)^[16]. **Scheme 4.** Introduction of various functional groups into position 4 of bis(CHF₂)pyrazole **5a**.

i : aq. NaOCl, AcOH, rt, 18h. 82%. *ii* : cat. Fe, Br₂, 100 °C, 1h. 90%. *iii* : I₂, CF₃COOAg, DCM, -15 °C to rt, 4h. 98%. *iv* : HNO₃, H₂SO₄, 115 °C, 15min, microwave. 99%. *v* : **20c**, Mel, Et₃N, DCM, rt. 52%. *vi* : **20d**, Mel, Et₃N, DCM, rt, 18h. 99%. *vii* : **21b**, cat. Pd/C, H₂, EtOH, rt, 1h. 86%. *viii* : **20b**, DHP, cat. TsOH, DCM, 50 °C, 18h. 95%. *ix* : **20c**, DHP, cat. TsOH, DCM, rt, 18h. 89%. *x* : **20d**, DHP, cat. TsOH, DCM, rt, 18h. 45%. *xi* : **22c**, cat. Pd/C, H₂, EtOH, 50 °C, 18h. 86%. *xii* : 1) **22b**, *i*PrMgCl•LiCl solution in THF, -30 °C, 1h. 2) *i*PrO-B(pin), -30 °C to rt, 1h. 99%. *xiii* : **23a**, aq. KHF₂, MeOH, rt, 30min. 99%. *xiv* : 1) **22b**, *i*PrMgCl•LiCl solution in THF, -30 °C, 1h. 2) DMF, -30 °C to rt, 1h. 3) cc HCl, EtOH, rt, 72h. 54%. *xv* : 1) **22b**, *i*PrMgCl•LiCl solution in THF, -30 °C, 1h. 2) dry CO₂, -30 °C to rt, 1h. 3) 1N HCl. 60%. Then rapidly 3) cat. cc HCl, MeOH, rt, 1h. 39%. *xvi* : **22d**, 2N HCl in Et₂O, rt, 30min. 46%.

In conclusion, we have developed an elegant method to access 3,5-bis(fluoroalkyl)pyrazoles with tunable regioselectivity, based on the use of fluorinated ketimines, activated FARs and hydrazines. These pyrazoles are highly valuable building-blocks for agrochemical ingredients revealing a novel mode of action. A new FAR has been employed allowing the introduction of a very novel fluoroalkyl moiety (-CHFOCF₃), prepared by hydroamination of trifluoromethyl trifluorovinyl ether and *in situ* activation. The opposed reactivity of vinamidinium and vinamide species was found to be of great value to tune the regioselectivity of the hydrazine addition. We demonstrated the feasibility of further functionalization of position 4 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 upon Agro/Medicinal chemistry and related.

Experimental section

General procedure for the preparation of bis(fluoroalkyl)vinamides (3-4):

To a solution of activated FAR **1a-d** (1.2 eq., 1.95 mmol) in dry MeCN (2 mL) was added a solution of fluorinated ketimine **2** (1 eq., 300 mg, 1.64 mmol) in dry MeCN (2 mL). The mixture was stirred at the defined temperature (20-50 °C) for 15min-1h. The mixture was diluted with CH₂Cl₂ (10 mL) and hydrolysed with

HCl 1N (10 mL) under vigorous stirring for 1h. When the crude's purity was not sufficient, flash chromatography or distillation under reduced pressure were achieved.

General procedure for the preparation of bis(fluoroalkyl)pyrazoles (5-12):

To a solution of activated FAR **1a-d** (1.2 eq., 1.95 mmol) in dry MeCN (2 mL) was added a solution of fluorinated ketimine **2** (300 mg, 1.64 mmol) in dry MeCN (2 mL). The mixture was stirred at the defined temperature (20-50 °C) for 15min-1h. Hydrazine hydrate (1.51 eq., 123 mg, 0.12 mL, 2.47 mmol) or Methyl hydrazine (1.51 eq., 123 mg, 0.12 mL, 2.47 mmol) were respectively added via syringe at the described temperature (20-50 °C), rapidly followed by cc H₂SO₄ (0.56 eq., 92 mg, 0.05 mL, 0.91 mmol). The mixture was stirred at described temperature for 1-18h.

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 occurred under classical heating conditions (20-50 °C, 1-18h). 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 eq., 569 mg, 2.87 mmol) and cc H₂SO₄ (2.1 eq., 404 mg, 0.22 mL, 4.0 mmol) in Toluene (8 mL). The mixture was heated 30min-2h at 120-140 °C under microwave irradiation into 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 than Method A in previous paragraph using corresponding vinamides and hydrazines (for details see S.I.).

Method B: Similar conditions than Method B in previous paragraph using corresponding vinamides and hydrazines (for details see S.I.).

Method C:

Corresponding vinamide (1.7 mmol) was treated with corresponding hydrazines (1.9 eq., 3.2 mmol) in HFIP (5 mL). The mixture was heated 30min-5h at 100-140 °C under microwave irradiation into a sealed vial. After concentration *in vacuo*, crude materials were purified by flash chromatography.

Typical procedure for the preparation of 3,5(bis)fluoroalkylpyrazoles from pyrazolines.:

A solution of SOCl₂ (2.09 eq., 65.6 mg, 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 eq., 166 mg, 0.17 mL, 2.1 mmol) in toluene (2 mL) at 0 °C. After raising the temperature to room temperature, the mixture was refluxed for 3h (no reflux was required for hydroxyl-pyrazolines).

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obtained free of charge from the Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif, 2016.

FULL PAPER

An efficient method to access fluoroalkyl pyrazoles based on the use of Fluoroalkyl Amino Reagents (FARs) is reported.

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Major advance in the synthesis of 3,5-bis(fluoroalkyl)pyrazoles – Tunable regioselectivity and broad substitution pattern.