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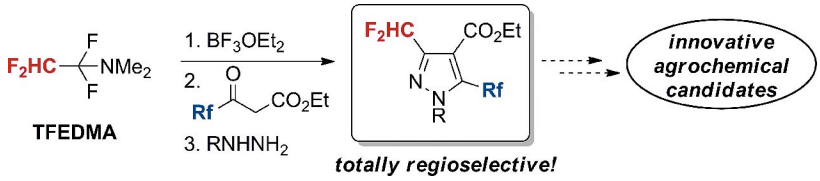
SHORT COMMUNICATION

Organofluorine Compounds



FAR out! Unsymmetrical 3,5-bis(fluoroalkyl)pyrazoles are regioselectively synthesized by a straightforward one-pot sequence. Treatment of fluorinated β-keto esters with (tetrafluoroethyl)dimethylamine (TFEDMA) as a practical CF_2H transfer reagent and subsequent cyclocondensation with hydrazine derivatives affords 3-(difluoromethyl)-5-(fluoroalkyl)pyrazoles as single isomers. Rf = fluorinated alkyl group.

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A New Life for an Old Reagent: Fluoroalkyl Amino Reagents as Efficient Tools for the Synthesis of Diversely Fluorinated Pyrazoles

Keywords: Fungicides / Agrochemistry / Regioselectivity / Nitrogen heterocycles / Fluorine

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A New Life for an Old Reagent: Fluoroalkyl Amino Reagents as Efficient Tools for the Synthesis of Diversely Fluorinated Pyrazoles

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Dedicated to the 150th anniversary of Bayer

Keywords: Fungicides / Agrochemistry / Regioselectivity / Nitrogen heterocycles / Fluorine

Herein we describe the first practical method for the regioselective preparation of 3,5-bis(fluoroalkyl)pyrazoles. Starting from commercially available fluoroacetoacetates and by using (tetrafluoroethyl)dimethylamine as a convenient CF_2H transfer reagent, this straightforward one-pot sequence affords highly substituted pyrazoles in good yields and excellent regioselectivity. Furthermore, these carboxylate intermediates were converted into the corresponding pyrazolic acids, which are valuable building blocks for the design of novel bioactive ingredients.

Introduction

The introduction of fluorine atoms into lead structures is a powerful strategy to optimize the properties of agricultural and pharmaceutical products.[1] Hence, a significant rise in the number of active ingredients containing at least one fluorine atom has been observed over the last decades,[2] and a recent survey estimated that as many as 18% of the pesticides on the market are fluorinated compounds.[3] Among the vast array of fluorine-containing functionalities, (fluoroalkyl)pyrazoles have attracted considerable attention because of their potentially enhanced biological properties.[4] In particular, huge interest was accorded to (difluoromethyl)pyrazolecarboxamides, which belong to the class of succinate-dehydrogenase inhibitor (SDHI) fungicides. At least four different compounds of this class were recently introduced to the crop-protection market (Figure 1).

α-Fluoroalkyl amino reagents (FARs) are selective fluorinating agents commonly used for the synthesis of alkyl fluorides and *gem*-difluorides by reaction with alcohols and activated carbonyl groups.[5,6] Among them, (tetrafluoroethyl)dimethylamine (TFEDMA, **1**) is also considered as a difluoroacetyl transfer reagent if it is activated in the presence of a Lewis acid and subsequently treated with carbon nucleophiles.[7] Its facile and low-cost preparation from tetrafluoroethylene makes it a reagent of choice for industrial applications. In 2006, Pazenok et al. discovered that TFEDMA can be used in the preparation of (difluoromethyl)pyrazoles. After activation with boron trifluoride and reaction with (dimethylamino)acrylate, the cyclocondensation of intermediate **4** with methylhydrazine furnished desired mono(fluoroalkyl)pyrazole **5** with good regioselectivity (Scheme 1).[8] This approach is very versatile, as other FARs can be used to either introduce a 1,2,2,2-tetrafluoroethyl substituent (by using the Ishikawa reagent, **2**) or a chlorofluoromethyl group (by using the Yarovenko reagent, **3**) at the 3-position of the pyrazole.

Despite recent advances in the synthesis of fluorinated pyrazoles,[9] the preparation of pyrazoles bearing two fluorinated groups remains scarcely depicted in the literature,[10] even if 3,5-bis(fluoroalkyl)pyrazoles are an important class of bioactive molecules.[11] The reported methods often describe symmetrical fluorinated pyrazoles [Scheme 2, Equation (1)], involve tedious multistep synthesis with restrictive stages [Scheme 2, Equation (2)], and only allow access to 4-unsubstitued pyrazoles.[12] Consequently, the development of efficient approaches to generate diversely fluoroalkyl-substituted pyrazoles should open a new entry to innovative agrochemical and pharmaceutical candidates. Thus, we thought that fluorinated β-keto esters could react as nucleophiles with TFEDMA to afford adduct **6** bearing two fluoroalkyl substituents and provide access to 3,5-bis-

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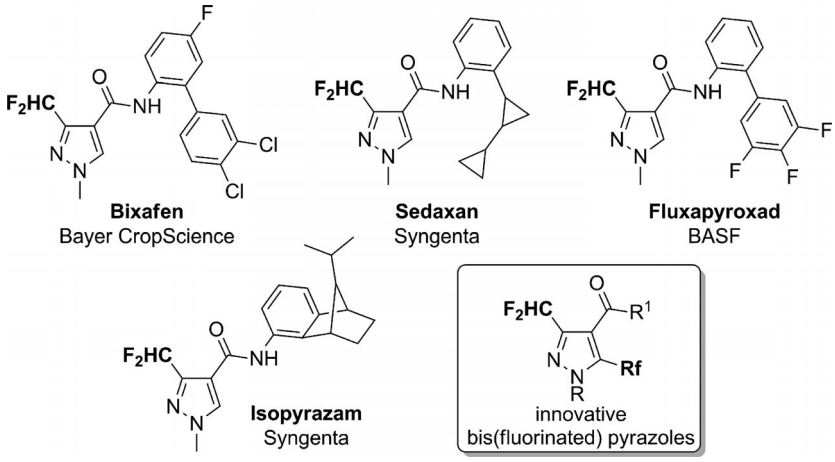
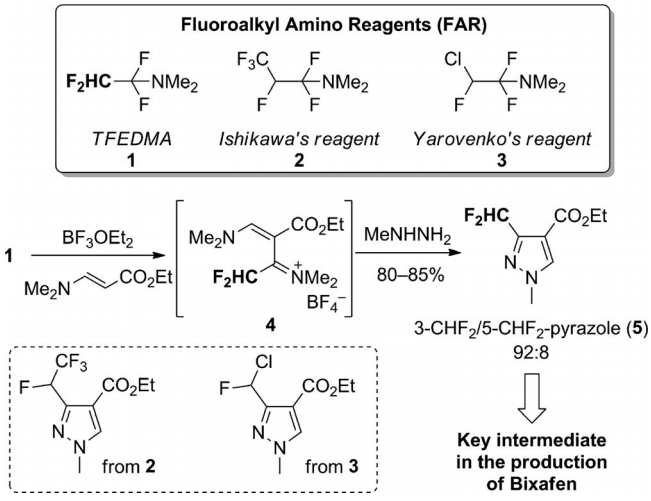


Figure 1. Second-generation broad-spectrum fungicides containing difluoromethylated pyrazoles. Rf = fluorinated alkyl group.



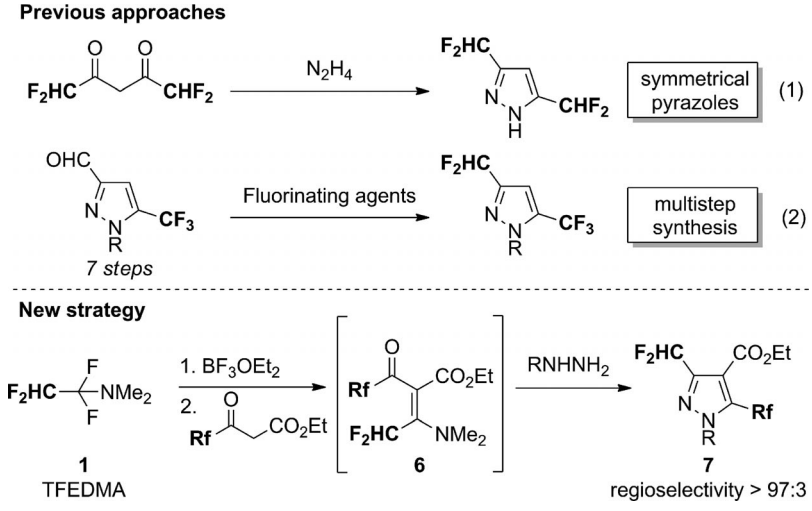
Scheme 1. Utilization of FARs for the synthesis of mono(fluoroalkyl)pyrazole carboxylates.

(fluoroalkyl)pyrazoles **7** after a cyclocondensation step with hydrazine (Scheme 2).

Herein we document the first practical method for the regioselective preparation of 3,5-bis(fluoroalkyl)pyrazoles **7**. Starting from commercially available fluoroacetoacetates and by using TFEDMA as a convenient CF_2H transfer reagent, this straightforward one-pot sequence affords highly substituted pyrazoles in good yields and excellent regioselectivity (>97:3, Scheme 2). Furthermore, these carboxylate intermediates were converted into the corresponding pyrazolic acids, which are valuable building blocks for the design of novel bioactive ingredients.

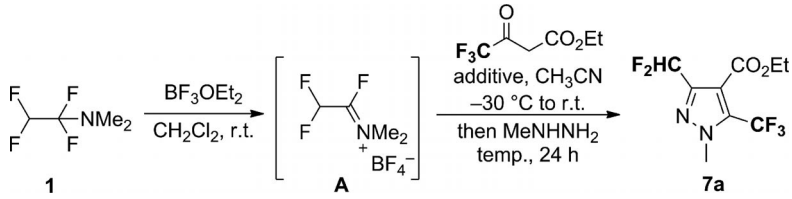
Results and Discussion

According to the procedure developed by Wakselman et al.,[7a] TFEDMA was activated with $BF_3{\cdot}OEt_2$ (1 equiv.) in CH_2Cl_2 at room temperature. Under these conditions, the



Scheme 2. Regioselective one-pot preparation of 3,5-bis(fluoroalkyl)pyrazoles.

Table 1. Optimization of the reaction conditions.



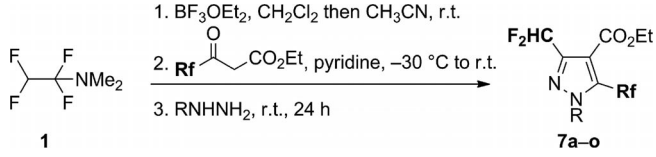
Entry	Additive	Temp. [°C]	Yield [%][a]
1	Cs_2CO_3 (3 equiv.)	r.t.	n.r.
2	KF (3 equiv.)	r.t.	20
3	KF (3 equiv.)	0	16
4	KF (3 equiv.)	–30	9
5	KF (3 equiv.), $FeCl_3$ (1 equiv.)	r.t.	n.r.[b]
6	KF (3 equiv.), $TiCl_4$ (1 equiv.)	r.t.	n.r.[b]
7	KF (3 equiv.), $Yb(OTf)_2$ (0.2 equiv.)	r.t.	13[b]
8	KF (3 equiv.), $Cu(OTf)_2$ (0.2 equiv.)	r.t.	22[b]
9	KF (3 equiv.), $CuCl_2$ (0.2 equiv.)	r.t.	16[b]
10	KF (3 equiv.), $CuCl_2$ (1 equiv.)	r.t.	27[b]
11	pyridine (3 equiv.)	r.t.	63

[a] Isolated yield. n.r. = no reaction. [b] The Lewis acids was introduced prior to the addition of hydrazine at the indicated temperature.

electrophilic character of TFEDMA is enhanced, and iminium salt **A** can undergo nucleophilic attack with various β-keto esters. Ethyl trifluoroacetoacetate was then added in the presence of an inorganic base in CH_3CN at –30 °C, and after 12 h at room temperature, methylhydrazine was added at the same temperature. No reaction was observed with the use of cesium carbonate, and a poor yield was obtained with potassium fluoride (Table 1, Entries 1 and 2). Decreasing the temperature during the addition of hydrazine did not improve the outcome of the reaction (Table 1, Entries 2–4). At this point, we thought that the low yields could be due to a lack of reactivity of adduct **6**. It was thought that the addition of an azaphilic Lewis acid would increase the electrophilicity of the carbon atom adjacent to the NMe_2 group. We therefore decided to examine various additives with the hope of finding a Lewis acid that would facilitate the 1,4-addition of hydrazine to the adduct (Table 1, Entries 5–10).[13] When either iron(III) or titanium(IV) chloride (1 equiv.) was added to the reaction mixture, no desired product was detected (Table 1, Entries 5 and 6), whereas catalytic amounts of ytterbium(III) and copper(II) triflate did not improve the yield of the reaction (Table 1, Entries 7 and 8). An unsatisfactory yield of 27% was reached in the presence of stoichiometric copper(II) chloride (Table 1, Entry 10), and this led us to reconsider the choice of the base. Finally, the reaction was carried out with pyridine as the organic base, and desired 3-(difluoromethyl)-5-(trifluoromethyl)pyrazole **7a** was obtained in a fair 63% yield (Table 1, Entry 11).

Having optimized the conditions for the one-pot sequence, we next decided to perform the reaction on several fluorinated β-keto esters to determine the scope of the methodology. The sequence was carried out with commercially available ethyl difluoro-, ethyl trifluoro-, and ethyl pentafluoroethylacetoacetates, whereas ethyl chlorodifluoroacetoacetate was synthesized by Claisen condensation.[14] Different hydrazines (i.e., hydrazine hydrate and methyl-, phenyl-, and *tert*-butylhydrazine) were also used for the cyclocondensation, and the results are summarized in Table 2.

Table 2. Scope of the reaction.



Entry	Rf	R	Compound	Yield [%][a]
1	CF_3	CH_3	**7a**	73
2	CF_3	H	**7b**[b]	75
3	CF_3	Ph	**7c**	67
4	CF_3	*t*Bu	**7d**[c]	53
5	CF_2H	CH_3	**7e**	69
6	CF_2H	H	**7f**[b]	56
7	CF_2H	Ph	**7g**	43
8	CF_2H	*t*Bu	**7h**[c]	30
9	C_2F_5	CH_3	**7i**	75
10	C_2F_5	H	**7j**[b]	67
11	C_2F_5	Ph	**7k**	85
12	C_2F_5	*t*Bu	**7l**[c]	33
13	CF_2Cl	CH_3	**7m**	72
14	CF_2Cl	H	**7n**[b]	72
15	CF_2Cl	Ph	**7o**	53

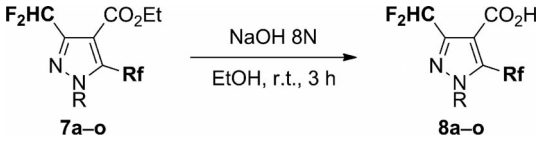
[a] Isolated yield. [b] Hydrazine hydrate was used for the cyclocondensation step. [c] *t*BuNHNH$_2$·HCl was used for the cyclocondensation step.

3,5-Bis(fluoroalkyl)pyrazoles **7a–o** were obtained in moderate to good yields depending on the fluoroalkyl group on the β-keto ester and the hydrazine employed. Ethyl trifluoroacetoacetate provided the most consistent results with yields between 53 and 75% (Table 2, Entries 1–4). Electronic effects appear to have a small influence on the reaction, as the yields increased with the electron-with-

drawing character of the Rf substituent on the β-keto ester (Table 2, Entries 5–8 vs. Entries 9–12). The nucleophilicity and the steric demand of the hydrazine have pronounced effects on the outcome of the cyclocondensation. Methyl- and phenylhydrazines led to higher yields than *tert*-butylhydrazine and hydrazine hydrate. Fortunately, in all cases 3,5-bis(fluoroalkyl)pyrazoles **7** were formed as single regioisomers, which were easily isolated by simple flash chromatography.

We next investigated further transformations of these versatile pyrazole building blocks. Saponification of the ester group in these products would allow access to attractive (difluoromethyl)pyrazolecarboxamides through peptide coupling. To this end, carboxy esters **7** were treated with aqueous sodium hydroxide in ethanol at room temperature. Although N–H pyrazoles **7b**, **7f**, **7j**, and **7n** returned only starting material under these conditions, the *N*-substituted pyrazoles were readily hydrolyzed to corresponding carboxylic acids **8** (Table 3). These acids were obtained in high yields and in analytically pure form after aqueous workup.

Table 3. Saponification of 3,5-bis(fluoroalkyl)pyrazoles **7**.



7a–o **8a–o**

Entry	Rf	R	Compound	Yield [%][a]
1	CF_3	CH_3	**8a**	98
2	CF_3	Ph	**8c**	94
3	CF_3	*t*Bu	**8d**	94
4	CF_2H	CH_3	**8e**	97
5	CF_2H	Ph	**8g**	98
6	CF_2H	*t*Bu	**8h**	97
7	C_2F_5	CH_3	**8i**	97
8	C_2F_5	Ph	**8k**	98
9	C_2F_5	*t*Bu	**8l**	99
10	CF_2Cl	CH_3	**8m**	80
11	CF_2Cl	Ph	**8o**	99

[a] Isolated yield.

The cyclization step towards ethyl 3,5-bis(fluoroalkyl)-pyrazole-4-carboxylates **7** was completely regioselective. Indeed, with every hydrazine used (i.e., methyl-, phenyl-, and *tert*-butylhydrazine) and every fluorinated β-keto ester, only one regioisomer was observed by $^1H/^{19}F$ NMR spectroscopy. Furthermore, careful interpretation of the ^{13}C NMR spectra of compounds **7** showed a coupling constant between the carbon atom of the *N*-alkyl group and the fluorine atoms of the substituent at the 5-position of the pyrazole ring (e.g., in **7a**: q, $^4J_{C,F}$ = 3.3 Hz; Figure 2). This clear evidence reveals that the unique isomer prepared in these reactions was always the 3-(difluoromethyl)-5-(fluoroalkyl)pyrazole. In addition, we were able to perform a single-crystal X-ray analysis of carboxylic acid **8a** to confirm unambiguously the regioselectivity of the reaction (Figure 2).[15]

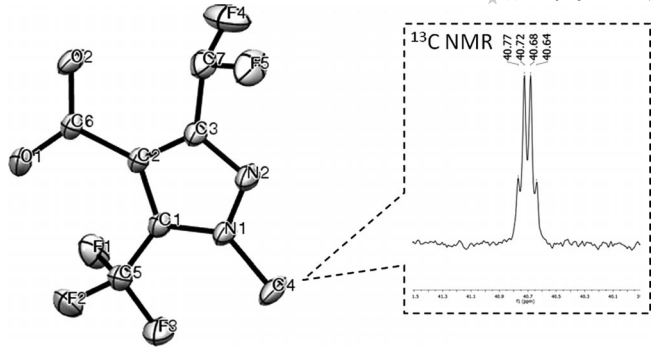


Figure 2. Evidence for the regioselectivity of the reaction: ^{13}C NMR analysis of the signal for the NMe group of **7a** (right), and ORTEP diagram of compound **8a** (left).[15]

Conclusions

We have developed a straightforward method for the synthesis of unsymmetrical 3,5-bis(fluoroalkyl)pyrazoles. This innovative one-pot sequence provides ethyl 3,5-bis(fluoroalkyl)pyrazole-4-carboxylates as single isomers from commercially available β-keto esters and hydrazines by using TFEDMA as a CF_2H transfer reagent. This robust process is suitable for multigram-scale synthesis and allows potential access to pyrazolecarboxamides after a simple saponification step towards pyrazolic acids en route to promising bioactive ingredients.

Experimental Section

General Procedure for the Preparation of Pyrazoles 7a–o: $BF_3{\cdot}OEt_2$ (50 mmol, 1 equiv.) was added to a solution of TFEDMA (50 mmol, 1 equiv.) in dry CH_2Cl_2 (50 mL) under argon in a Teflon flask. The solution was stirred at room temperature for 15 min, and CH_2Cl_2 was removed under reduced pressure. The mixture was taken up in dry CH_3CN (50 mL). In another Teflon flask, the fluoroacetoacetate (50 mmol, 1 equiv.) was added to a solution of pyridine (150 mmol, 3 equiv.) in dry CH_3CN (100 mL), and the mixture was stirred at room temperature for 15 min. At –30 °C, the contents of the first flask was added dropwise to the second flask, and the reaction mixture was stirred at –30 °C for 2 h and allowed to reach room temperature overnight. The desired hydrazine (75 mmol, 1.5 equiv.) was added dropwise at room temperature, and the reaction mixture was stirred for 24 h. The solution was concentrated under reduced pressure and taken up in Et_2O (100 mL). The organic phase was washed with 1 M HCl (3 × 50 mL) and brine (50 mL), dried with sodium sulfate, and concentrated at atmospheric pressure. The crude material was purified by column chromatography on silica gel to afford the expected 3,5-bis(fluoroalkyl)pyrazole.

Supporting Information (see footnote on the first page of this article): Experimental procedures, spectroscopic data, and copies of the ^1H, ^{13}C, and ^{19}F NMR spectra.

Acknowledgments

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[15] CCDC-928227 (for **8a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.

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