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Synthesis of mono- and bis(fluoroalkyl)-pyrimidines from FARs, fluorinated acetoacetates and malononitrile – Easy access to novel high value pyrimidine scaffolds

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Abstract: A new strategy was developed using fluorinated acetoacetates, malononitrile and Fluoroalkyl Amino Reagents (FARs) in order to access unprecedented 4,6-bis(fluoroalkyl)-pyrimidine-5-carboxylates, their carboxylic acid analogues and 4-amino-6-(fluoroalkyl)-pyrimidine-5-carbonitriles. An efficient cyclization step using suitable amidines was developed under microwave irradiation, providing rapidly and efficiently the desired pyrimidines. Standard saponification conditions were applied from carboxylate derivatives to access to the corresponding carboxylic acids. These new valuable building blocks bearing a single or two emergent fluorinated substituents hold strong potential for medicinal and agrochemical research.

Introduction

The pyrimidine system is highly relevant in the discovery of new bioactive molecules, as this nitrogen-based heterocycle is a pharmacophore broadly present in the metabolism of living organism metabolisms.^[1] Many active compounds containing a pyrimidine core have demonstrated interesting activity in a variety of diseases, e.g. the treatment of cancers (Imatinib), high cholesterol (Rosuvastatin), or HIV (Zidovudin).^[2] The synthesis and transformations of pyrimidines have been the object of several reports,^[1, 3a, 2, 3b-d] mostly dealing with non-fluorinated examples. However, a great interest recently emerged in introducing fluorinated substituents onto key pharmacophores, such as pyrimidines, in order to exploit the valuable properties of fluorine (such as increased binding affinity, physicochemical properties and metabolic stability with minor spatial alteration).^[4]

Indeed, several trifluoromethylated pyrimidines already displayed interesting biological activities as well as new biological functions, and innovative methods were recently developed to more easily access these types of structures.^[5] Concerning pyrimidines bearing emergent fluorinated substituents, despite the classical Michael addition-type approach using difficult-to-access fluorinated enones,^[6] the use of 3-(polyfluoroacyl)chromones,^[7] the acid-catalyzed condensation of fluorinated 1,3-diketones with

guanidine^[8] or other multi-step reactions with moderate efficiency, there is still a need to develop robust methods to prepare these building blocks reliably. Even though the introduction of a perfluoroalkyl group onto pre-existing pyrimidines has been recently reported,^[9] the construction of pyrimidines bearing fluorinated substituents remains scarcely described.^[10] Our group recently reported the use of Fluoroalkyl Amino Reagents (FARs) for the facile introduction of emergent fluorinated substituents onto various building blocks such as electron-rich arenes and heteroarenes, pyrazoles and isoxazoles. We also described the preparation of 3,5-bis(fluoroalkyl)pyrazoles and -pyrazolecarboxylates using FARs.^[11] Enriched by this experience, we decided to investigate the preparation of 6-membered heterocycles and more specifically pyrimidines using FARs.

Herein, we report an efficient method for the preparation of alkyl 4,6-bis(fluoroalkyl)-pyrimidine-5-carboxylates and their carboxylic acid analogues, starting from α -fluorinated acetoacetates and FARs activated *in situ* by a Lewis acid. Additionally, a series of 4-amino-6-(fluoroalkyl)-pyrimidine-5-carbonitriles was prepared using the same method, starting from malononitrile.

Results and Discussion

Following recent work achieved in our group,^[11b, 11c] we investigated the possibility of isolating the postulated key intermediates **3a-d** formed during the one-pot synthesis of 3,5-bis(fluoroalkyl)pyrazole-4-carboxylates (Scheme 1). Indeed, they could be isolated neither after standard aqueous work-up, nor after silica gel chromatography. Moreover, intermediates **3a-d** seemed underexploited while they represent valuable analogues of 1,3-diketones bearing two similar or different fluorinated groups. In particular, such 2-carboxy-substituted vinamides bearing fluoroalkyl groups in both positions 1 and 3 are scarcely encountered.^[12] Consequently, we placed more efforts into their isolation. These intermediates were prepared (Table 1) using the conditions previously reported in our group, and were isolated after precipitation of suspected pyridinium borate salts in DCM and filtration through Celite®. After concentration of the filtrate under high vacuum, the crude compound was taken up in toluene for a second filtration through Celite®, followed by a simple azeotropic distillation of the residual pyridine under vacuum. A series of variously substituted α -aminoalkylidene- β -ketoesters **3a-f** was thus prepared from α -fluorinated acetoacetates **2a-d** and activated FARs **1a-c** (Table 1).

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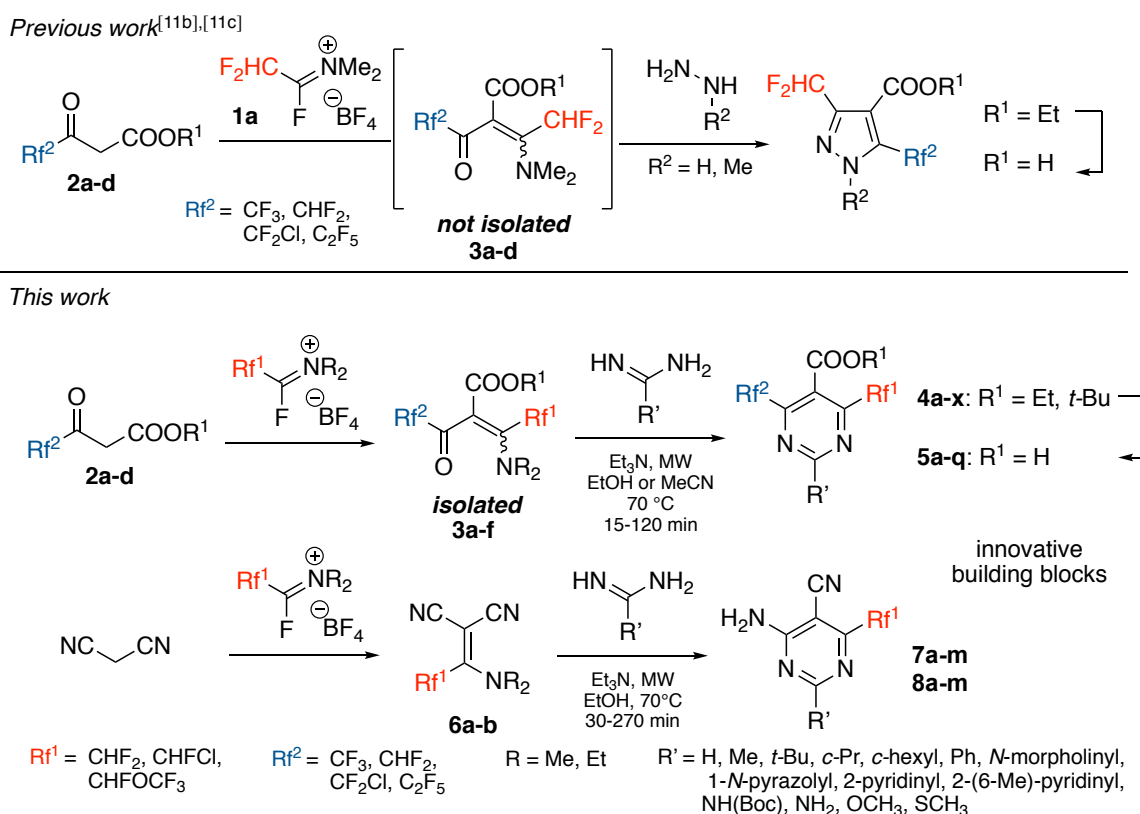
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Scheme 1. *In situ* formation of intermediates **3a-d** during the one-pot synthesis of 3,5-bis(fluoroalkyl)pyrazole-4-carboxylates (top). Synthesis of mono- and bis(fluoroalkyl)-pyrimidines from FARs, fluorinated acetoacetates and malononitrile (bottom)

The resulting oils were isolated with high purity (from 75 up to >95wt.%) and high to excellent yields. Moreover, they are shelf-stable under inert atmosphere (preferably below 20 °C), and can be prepared on large amount (up to 25 g). The α -aminoalkylidene- β -ketoester **3e** provided single-crystals suitable for crystallographic analysis (Figure 1). Once α -aminoalkylidene- β -ketoesters **3a-f** were available, a screening of the most suitable reaction conditions was achieved to afford a model pyrimidine (**4a**, Table 2) upon cyclization with acetamidine hydrochloride. A protic solvent was initially chosen (EtOH), as proton transfer is probably required in the desired ring formation step. After a first attempt under thermal conditions (Table 2, entry 1) with sodium methoxide as a base, microwave irradiation gave dramatic acceleration and yield improvement in the desired transformation (Table 2, entries 2-16). Changing the amount of amidine and base at constant amidine/base ratio showed no positive influence (Table 2, entries 4 vs. 2). The further addition of reagents (Table 2, entry 3) or a longer reaction time (Table 2, entry 5) could not improve the conversion. Several organic bases were tested, and unlike pyridine, which fully inhibited the reaction (Table 2, entry 8), Hünig's base (Table 2, entries 9-12) and even more trimethylamine (Table 2, entries 13-16) gave rather better results. Other protic solvents (*i*PrOH, *t*BuOH) were proven to be compatible with the reaction.

Table 1. Preparation of key α -aminoalkylidene- β -ketoesters **3a-f**.

Entry	act. FAR	R ¹	R	R ^{f1}	R ^{f2}	Pdt	Yield	Purity
1	1a	Et	Me	CHF ₂	CF ₃	3a	92%	95%
2	1a	Et	Me	CHF ₂	CHF ₂	3b	72%	60% ^[a]
3	1a	Et	Me	CHF ₂	C ₂ F ₅	3c	89%	95%
4	1a	<i>t</i> Bu	Me	CHF ₂	CF ₂ Cl	3d	99%	93%
5	1b	Et	Et	CHFCl	CF ₃	3e	93%	75%
6	1c	Et	Me	CHFOCF ₃	CF ₃	3f	80%	95%

[a] **3b** was not characterized due to its low purity

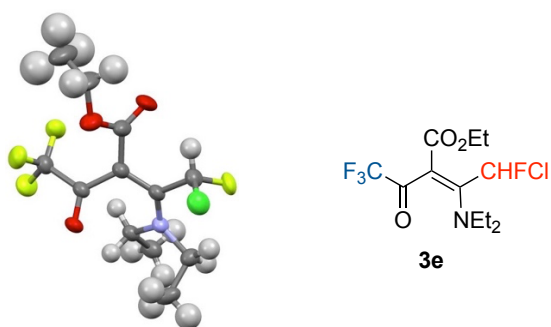


Figure 1. Crystallographic structure of **3e**.^[13]

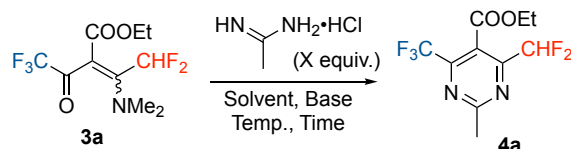
Finally, MeCN was the most efficient solvent in the case of triethylamine as base, affording 91% yield. With efficient reaction conditions in hand, we employed intermediates **3a-f** to prepare a large variety of 4,6-bis(fluoroalkyl)pyrimidine-5-carboxylates **4a-x** (Table 3). Upon reaction with acetamidine hydrochloride, most α -aminoalkylidene- β -ketoesters **3a-f** were efficiently converted into the corresponding pyrimidines **4a-f** (Table 3, entries 1-6), except **3b** (probably due to its lower purity) and **3e**. Beside its lower purity, *N,N*-diethyl intermediate **3e** is also less reactive than *N,N*-dimethyl analogues **3a-d** and **3f**. Indeed, the iminium involved in the transformation is both more stabilized and more congested by ethyl chains, and appears less reactive towards nucleophiles (amidines in this case), as previously reported by our group.^[11f] Once the 2-methyl series completed (Table 3, entries 1-6), the 2-H analogue **4g** (Table 3, entry 7) was difficultly prepared. Side-products resulting from hydrolysis of a key open-chain intermediate were repeatedly isolated, presumably ascribed to the hygroscopic character of formamidine hydrochloride. Changing the formamidine source (from its hydrochloride to its acetic acid salt), the solvent, or drying the hygroscopic amidine did not improve the initial result. The use of DMSO was reported as favouring fast aromatization during the pyrimidine core formation,^[10a] but was not employed since not being the most popular solvent for industrial processes.^[14]

Phenyl analogues **4h-j** were efficiently prepared using benzamidine (Table 3, entries 8-10). For more diverse substituents in position 2, commercially available amidines were used, mostly as hydrochlorides; hydroiodides or sulphates were also employed, but provided poorer results. Amidines (derived from cyclohexyl (**F**), 2-pyrimidinyl (**H**), 2-(6-methyl)-pyridinyl (**I**) chains) were prepared as hydrochloride salts from the corresponding carbonitriles according to literature procedures.^[15] The purity of amidine salt **F** was low, explaining the poor conversion during the pyrimidine synthesis (Table 3, entry 13), similarly to the 2-H example (Table 3, entry 7). Pyrimidines **4k-r** were prepared with modest to excellent yields (Table 3, entries 11-18), with a significant dependence on the quality of both α -aminoalkylidene- β -ketoester and amidine source.

Most alkyl pyrimidine-5-carboxylates were very efficiently converted into the carboxylic acid analogues **5a-q** (except **5d**) using standard basic aqueous conditions after overnight stirring and acidic work-up. No further purification was required and a simple trituration in pentane was sufficient to access highly pure

material. In the case of *tert*-butyl ester **5j** (Table 3, entry 10), acidic conditions were preferred to the basic ones. Additionally, the saponification of compound **4r** led to pyrazole degradation instead of ester hydrolysis (Table 3, entry 18). However, two examples (**5c** and **5q**) provided single crystals and crystallographic structure were determined (Figure 2).

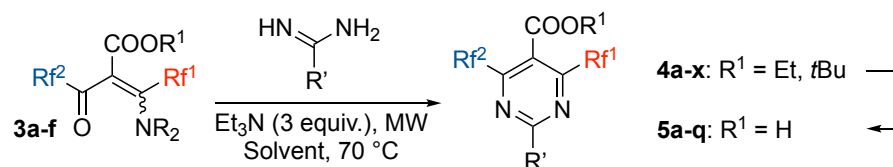
Table 2. Optimization of the conditions for the pyrimidine ring formation step – example of **4a**.



Entry	Solvent	X	Base (equiv.)	Temp. (°C)	Time	Yield
1	EtOH	1.5	NaOMe (3)	80 ^[b]	18 h	33%
2	EtOH	2	NaOMe (3)	70 ^[c]	30 min	57%
3	EtOH	1 + 1	NaOMe (1.5 + 1.5) ^[d]	80 ^[c]	30 + 30 + 60 min	44% ^[a]
4	EtOH	4	NaOMe (6)	80 ^[c]	15 min	40% ^[a]
5	EtOH	2	NaOMe (3)	80 ^[c]	60 min	51% ^[a]
6	EtOH	1.5	NaOMe (3)	80 ^[c]	75 min ^[e]	50% ^[a]
7	EtOH	1.5	NaOMe (3)	80 ^[c]	15 min ^[a]	0% ^[a]
8	EtOH	2	Pyridine (3)	70 ^[c]	30 min	0% ^[a]
9	EtOH	4	DIPEA (6)	70 ^[c]	30 min	60% ^[a]
10	EtOH	2.5	DIPEA (3)	70 ^[c]	30 min	64% ^[a]
11	EtOH	1.2	DIPEA (1.5)	70 ^[c]	30 min	55% ^[a]
12	EtOH	2 + 2	DIPEA (3 + 3)	70 ^[c]	30 + 30 min	75% ^[a]
13	EtOH	2	Et ₃ N (3)	70 ^[c]	30 min	86% ^[a]
14	<i>t</i> BuOH	2	Et ₃ N (3)	70 ^[c]	30 min	58% ^[a]
15	<i>i</i> PrOH	2	Et ₃ N (3)	70 ^[c]	30 min	87% ^[a]
16	MeCN	2	Et ₃ N (3)	70 ^[c]	30 min	91% ^[a]

[a] ¹⁹F NMR yield using PhF as internal standard. [b] Thermal conditions in a sealed tube. [c] Under microwave irradiation. [d] Additional amounts of amidine and base were introduced after 60 min. [e] Use of an excess of 4Å molecular sieves as additive. [f] Use of Amberlyst H15 resin as additive.

Table 3. Preparation of diversely substituted pyrimidine-5-carboxylates **4** and their carboxylic acid analogues **5**.



Entry	Substrate	Solvent	Amidine (equiv.)	R ^{f1}	R ^{f2}	Time	R'	Cmpd.	Yield	Cmpd.	Yield
1	3a	MeCN	A (2)	CHF ₂	CF ₃	15 min	Me	4a	91% ^[a]	5a	93%
2	3b^b	MeCN	A (2)	CHF ₂	CHF ₂	120 min	Me	4b	12%	5b	99%
3	3c	MeCN	A (2)	CHF ₂	C ₂ F ₅	15 min	Me	4c	63%	5c	99%
4	3d	MeCN	A (2)	CHF ₂	CF ₂ Cl	120 min	Me	4d	31%	5d	n.d.
5	3e	MeCN	A (2)	CHFCl	CF ₃	30 min ^[c]	Me	4e	36%	5e	55%
6	3f	MeCN	A (2)	CHFOCF ₃	CF ₃	15 min	Me	4f	49%	5f	89%
7	3a	EtOH	B (2)	CHF ₂	CF ₃	30 min	H	4g	32%	5g	94%
8	3a	EtOH	C (2)	CHF ₂	CF ₃	30 min	Ph	4h	78%	5h	97%
9	3c	MeCN	C (2)	CHF ₂	C ₂ F ₅	15 min	Ph	4i	87%	5i	77%
10	3d	MeCN	C (2)	CHF ₂	CF ₂ Cl	15 min	Ph	4j	93%	5j	62% ^[d]
11	3a	MeCN	D (2.1)	CHF ₂	CF ₃	15 min	<i>t</i> -Bu	4k	79%	5k	92%
12	3a	EtOH	E (2)	CHF ₂	CF ₃	15 min	<i>c</i> -Pr	4l	60%	5l	99%
13	3a	EtOH	F (2)	CHF ₂	CF ₃	15 min	<i>c</i> -Hex	4m	15%	5m	98%
14	3a	EtOH	G (1.2)	CHF ₂	CF ₃	45 min	<i>N</i> -morpholinyl	4n	30%	5n	99%
15	3a	EtOH	H (1.2)	CHF ₂	CF ₃	15 min	2-pyridinyl	4o	82%	5o	99%
16	3a	EtOH	I (1.1)	CHF ₂	CF ₃	15 min	2-(6-Me)pyridinyl	4p	95%	5p	96%
17	3a	EtOH	J (2)	CHF ₂	CF ₃	15 min	2-pyrimidinyl	4q	66%	5q	99%
18	3a	EtOH	K (2)	CHF ₂	CF ₃	15 min	1- <i>N</i> -pyrazolyl	4r	25%	5r	n.d. ^[f]
19	3a	EtOH	L (2)	CHF ₂	CF ₃	15 min	NH(Boc)	4s	56%	5s	n.d. ^[g]
20	3a	<i>i</i> PrOH	L' (2)	CHF ₂	CF ₃	45 min	NH ₂	4t	0%	none	
21	From 4s ^[e]			CHF ₂	CF ₃		NH ₂	4t	99%	none	
22	3a	MeCN	M (1.8)	CHF ₂	CF ₃	15 min	OMe	4u	77%	none	

23	3a	EtOH	N (1.2)	CHF ₂	CF ₃	30 min	SMe	4v	32%	none
24	From 4v			CHF ₂	CF ₃		NMe ₂	4w	20%	none
25	3a	MeCN	P (2)	CHF ₂	CF ₃	90 min ^c	SH	4x	7%	none

A: acetamide hydrochloride; **B**: formamide hydrochloride; **C**: benzamide; **D**: *tert*-butyl carbamide hydrochloride; **E**: cyclopropane-1-carboximidamide hydrochloride; **F**: cyclohexanecarboximidamide hydrochloride; **G**: 4-morpholinecarboximidamide monohydroiodide; **H**: pyridine-2-carboximidamide hydrochloride; **I**: 6-methylpyridine-2-carboximidamide hydrochloride; **J**: pyrimidine-2-carboximidamide hydrochloride; **K**: pyrazole-1-carboximidamide hydrochloride; **L**: *tert*-butyl *N*-(diaminomethylidene)carbamate; **L'**: guanidine hydrochloride; **M**: *O*-methylisourea hydrochloride; **N**: 2-methyl-2-thiopseudourea sulphate; **O**: urea; **P**: thiourea; **Q**: 2-chloroethanimidamide hydrochloride; **R**: trifluoroethanimidamide. [a] ¹⁹F NMR yield using PhF as internal standard. [b] 60wt.% purity. [c] 100 °C. [d] HCOOH, 50 °C, 18 h. [e] Cat. TFA, DCM, 25 °C, 18 h. [f] Saponification led to degradation of pyrazole core instead of ester hydrolysis. [g] Saponification under basic conditions afforded highly hygroscopic product rapidly turning into a gum.

Other functional groups were targeted in position 2 of pyrimidines, such as amino, hydroxy, thiohydroxy, methoxy, thiomethoxy and others. In the case of the amino group, the use of guanidine hydrochloride did not allow the formation of the desired 2-aminopyrimidine carboxylate **4t**. Alternatively, the preparation of the Boc-protected analogue **4s** was efficient using *tert*-butyl *N*-(diaminomethylidene)carbamate **L**, and **4s** could be converted into aminopyrimidine **4t** under acidic conditions with quantitative yield. The pyrimidine carboxylic acid **5s** could not be isolated, as the saponification was only partial, and the resulting solid transformed rapidly into a gum over a few days (Table 3, entries 19-21). The formation of 2-methoxy- and 2-thiomethoxy-substituted pyrimidines was achieved (Table 3, entries 22 and 23) with respectively 77% and 32% yields for **4u** and **4v**. The substitution of the thiomethoxy group by dimethylamine, released during ring formation, was also observed to afford the substituted pyrimidine **4w** with maximum 20% yield.

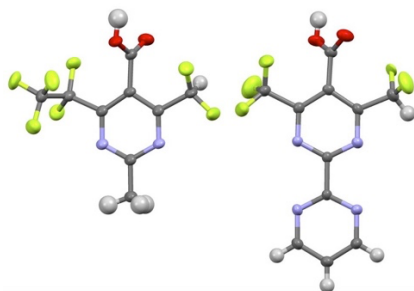
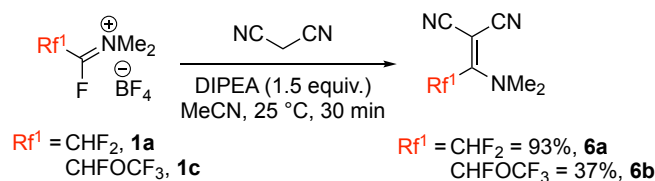


Figure 2. Crystallographic structures of **5c** (left) and **5q** (right).^[13]

As a further development of these results, we investigated on the access to compounds based on the 4-amino-6-(fluoroalkyl)-pyrimidine-5-carbonitrile scaffold. First, α -aminoalkylidene- β -malononitriles **6a-b** were prepared by addition of malononitrile on activated FARs **1a** and **1c** followed by the addition of Hünig's base.^[11e] The two fluorinated enamines were isolated after filtration through neutral alumina (ether/cyclohexane 1:3) with a 93% yield from **1a** but only 37% for the OCF₃-analogue **1c** (Scheme 2). The purity of **6a-b** could range from 80 to 95%.



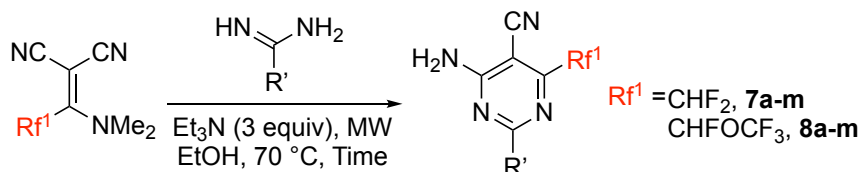
Scheme 2. Synthesis of α -aminoalkylidene- β -malononitriles **6a** and **6b**.

Then, the cyclization of **6a-b** with various amidine-type 1,3-nucleophiles was assessed. First of all, convenient thermic conditions, namely reflux in EtOH for 12 h, were applied to **6a** to afford the desired compound **7a** with 80% yield. In order to decrease the long reaction time, we employed microwave irradiation, which proved efficient with the parent vinamides **3** (*vide supra*), to prepare a large variety of 4-amino-6-(fluoroalkyl)-pyrimidine-5-carbonitriles **7** and **8** (Table 4). The general conditions consisted in the heating of a mixture of α -aminoalkylidene- β -malononitriles **6a-b** (1 equiv.), 1,3-dinucleophile reagent (2 equiv.) and Et₃N (3 equiv.) in EtOH at 70 °C under microwave irradiation for 30 min. Full conversion of starting materials **6a-b** was observed for the most of the used cyclisation partners under these conditions to afford the desired products **7** and **8** in usually good isolated yields. With acetamide and (hetero)aromatic amidine hydrochlorides **A**, **C**, **H-J**, the desired fluorinated pyrimidines were collected with 67-92% yields (Table 4, entries 1,3, 6-8 and 14, 16, 19-21). Starting from *O*-methylisourea hydrochloride, the syntheses of methoxy-derivatives were also satisfying (71% for **7i** and 77% for **8i**, entries 12 and 25). However, like in the series of pyrimidine-5-carboxylates, 2-H analogues **7b** and **8b** (Table 4, entries 2 and 15) were difficultly prepared due to the highly hygroscopic starting formamide. In the case of slower reactions, most of the time, additional 15 to 60 min were sufficient to observe a complete conversion. It was particularly true for cyclopropane derivatives **7d** and **8d** (Table 4, entries 4 and 17) or pyrazole ones **7i** and **8i** (Table 4, entries 9 and 22). The *N*-Boc protected analogues **7j** and **8j** (Table 4, entries 10 and 23) were also prepared with a short additional time (15-30 min) and converted easily to free 2,4-diaminopyrimidines under acidic conditions to afford **7k** and **8k** (Table 4, entries 11 and 24). Finally, the obtention of pyrimidines

substituted in position 2 by thiomethoxy and *N*-morpholyl groups was achieved with more difficulty. First, isolated yields of thiomethoxypyrimidines **7m** and **8m** (Table 4, entries 13 and 26) were moderate to good (88 and 54%) but a prolonged reaction time was necessary to observe a complete conversion of starting materials (additional 75 min for **6a** and 4 hours for **6b**). Moreover, the synthesis of **8m** required the further addition of 2 and 3

equivalents of *S*-methylisourea hemisulfate and Et₃N respectively after 2 hours. Regarding *N*-morpholypyrimidines, a long reaction time was needed to afford the desired aromatic compounds **7e** and **8e** with good yields (Table 4, entries 5 and 18). These results match with those observed in the carboxylate series (Table 3, entries 14 and 23) where the same 1,3-dinucleophiles were used under hemisulfate and hydroiodide forms.

Table 4. Preparation of diversely substituted pyrimidine-5-carbonitriles **7** and **8**.



Entry	Substrate	Amidine (2 equiv.)	Rf ¹	Time	R'	Cmpd.	Yield
1	6a	A	CHF ₂	30 min	Me	7a	79%
2	6a	B	CHF ₂	30 min	H	7b	33%
3	6a	C	CHF ₂	30 min	Ph	7c	92%
4	6a	E	CHF ₂	60 min	<i>c</i> -Pr	7d	75%
5	6a	G	CHF ₂	105 min	<i>N</i> -morpholinyl	7e	77%
6	6a	H	CHF ₂	30 min	2-pyridinyl	7f	62%
7	6a	I	CHF ₂	30 min	2-(6-Me)pyridinyl	7g	92%
8	6a	J	CHF ₂	30 min	2-pyrimidinyl	7h	75%
9	6a	K	CHF ₂	75 min	1- <i>N</i> -pyrazolyl	7i	56%
10	6a	L	CHF ₂	45 min	NH(Boc)	7j	73%
11	From 7j		CHF ₂		NH ₂	7k	79% ^[a]
12	6a	M	CHF ₂	30 min	OMe	7l	78%
13	6a	N	CHF ₂	105 min	SMe	7m	88% ^[b]
14	6b	A	CHFOCF ₃	30 min	Me	8a	67%
15	6b	B	CHFOCF ₃	30 min	H	8b	27%
16	6b	C	CHFOCF ₃	30 min	Ph	8c	91%
17	6b	E	CHFOCF ₃	60 min	<i>c</i> -Pr	8d	83%
18	6b	G	CHFOCF ₃	210 min	<i>N</i> -morpholinyl	8e	58%
19	6b	H	CHFOCF ₃	30 min	2-pyridinyl	8f	84%
20	6b	I	CHFOCF ₃	30 min	2-(6-Me)pyridinyl	8g	74%
21	6b	J	CHFOCF ₃	30 min	2-pyrimidinyl	8h	74%

22	6b	K	CHFOCF ₃	90 min	1- <i>N</i> -pyrazolyl	8i	65%
23	6b	L	CHFOCF ₃	60 min	NH(Boc)	8j	80%
24	From 8j		CHFOCF ₃		NH ₂	8k	91% ^[a]
25	6b	M	CHFOCF ₃	30 min	OMe	8l	71%
26	6b	N	CHFOCF ₃	270 min	SMe	8m	54% ^[a]

A: acetamidine hydrochloride; **B:** formamidine hydrochloride; **C:** benzamidine; **E:** cyclopropane-1-carboximidamide hydrochloride; **G:** 4-morpholinecarboximidamide 4-morpholinecarboximidamide monohydroiodide; **H:** pyridine-2-carboximidamide hydrochloride; **I:** 6-methylpyridine-2-carboximidamide hydrochloride; **J:** pyrimidine-2-carboximidamide hydrochloride; **K:** pyrazole-1-carboximidamide hydrochloride; **L:** *tert*-butyl *N*-(diaminomethylidene)carbamate; **M:** *O*-methylisourea hydrochloride; **N:** 2-methyl-2-thiopseudourea sulphate. [a] Cat. TFA, DCM, 25 °C, 48 h. [b] 45 min at 70 °C and 60 min at 80 °C. [c] 2 eq. of **N** and 3 equiv. of Et₃N were added in the mixture after 2 hours.

Conclusions

We have developed a rapid access to three new valuable series of pyrimidines bearing a single or two fluoroalkyl substituents. Indeed, 4,6-bis(fluoroalkyl)-pyrimidine-5-carboxylates and their carboxylic acid analogues were prepared efficiently starting from α -aminoalkylidene- β -ketoesters. The latter could be isolated when avoiding aqueous treatment, and an optimization step was carried out to determine the most efficient conditions for the pyrimidine formation step. A majority of the pyrimidine-carboxylic esters thus prepared in good yields were converted to the corresponding carboxylic acids with high efficiency. Then, a third series of pyrimidines was accessed, namely numerous 4-amino-6-(fluoroalkyl)-pyrimidine-5-carbonitriles, from α -aminoalkylidene- β -malononitriles in good yields as well. We demonstrated a broad scope of application by obtaining the 3 series of compounds decorated with several different fluoroalkyl groups in position 6 (or 4 and 6) of the pyrimidines, and a large variety of alkyl, aryl, heteroaryl or other, heteroatom-based functional groups in position 2. The many pyrimidine derivatives synthesized hereby are novel innovative building blocks, which could find interesting applications in medicinal and agrochemical research.

Experimental Section

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/MS-number>. It collects experimental protocols and characterization data for new compounds and copies of ¹H, ¹³C, ¹⁹F NMR spectra.

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