Switchable Multicomponent Cyclization Reactions to Access Fluoroalkylated Dihydropyrimidines and Pyrimidines Under Sol-vent-Free Conditions

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Abstract

The development of switchable solvent-free multicomponent reactions to build high-value-added products is an important demand for organic synthesis. Herein, we detailed the successful implementation of a switchable strategy for the construction of diverse 4-fluoroalkyl-1,4-dihydropyrimidines and 4-fluoroalkyl-pyrimidines via a solvent/additive-free [3 + 2 + 1] annulation, starting from readily available enamines, trifluoroacetaldehyde hydrate or 1-ethoxy-2,2-difluoroethanol and amidines hydrochloride. This reaction conforms to the concept of green synthesis, and provides a new avenue to access valuable fluorinated heterocycles.

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Keywords

Switchable strategy | Multicomponent reactions | Solvent-free | Fluoroalkylated dihydropyrimidines | Fluoroalkylated pyrim

Comprehensive Summary

The development of switchable solvent-free multicomponent reactions to build high-value-added products is an important d

Background and Originality Content

Multicomponent reactions (MCRs) [1] have been extensively studied and are of enormous importance in synthetic organic and medicinal chemistry, due to its step economy and atom efficient nature. [2] This approach also has the potentiality in maximizing the efficiency of the preparation of the compound library with molecular diversity for the needs of drug screening. Notably, to meet the increasing demand for green chemistry, the development of harmless multicomponent reactions is urgent. Solvent-free systems have featured many advantages in reducing waste and pollution, even serious accidents, which might be a "green" answer in laboratory research or industrial production. [3] Therefore, the development of solvent-free multicomponent reactions has been a vibrant work, thereby opening green and efficient method for the diversity synthesis of valuable molecules. [4]

Pyrimidines and the corresponding dihydro-compounds found in many active molecules with a wide range of biological and pharmacological properties, [5] and therefore, attracting extensively attention from the synthetic community.[6] Meanwhile, to provide high-quality platform molecules for drug discovery, the direct introduction of fluoroalkyl group, especially difluoromethyl or trifluoromethyl, into heterocycles represents huge interest for chemical companies.[7,8] In 2017, Bi and Liang [9]reported a novel photoinduced multicomponent cyclization reaction to forge fluoroalkyl-functionalized pyrimidines from active methylenes, perfluoroalkyl iodides, and guanidines/amidines (Scheme 1a). Later on, Loh and Shen[10] reported the radical-polar crossover-enabled formal [3 + 2 + 1] heteroannulation to construct a variety of fluoroalkyl-pyrimidines from silylenol ether, amidines, and fluoroalkyl halide (Scheme 1b). The same group also realized the Cu-catalyzed cascade cyclization of styrenes, amidines, and fluoroalkyl halides to access diverse fluoroalkylated pyrimidines.[11] Despite these achievements, some disadvantages such as excess additives and harmful solvent limit the applications of these approaches. More importantly, although fluoroalkylated pyrimidines have been achieved, the corresponding fluoroalkylated dihydropyrimidines remain elusive. Thus, the discovery of novel strategies fulfilling modern reaction ideals of green chemistry for the switchable synthesis of both fluoroalkylated pyrimidines and dihydropyrimidines are challenging and urgent.

Herein, we wish to report the successful implementation of a switchable [3 + 2 + 1] annulation strategy for the direct construction of diverse fluoroalkylated dihydropyrimidines/pyrimidines under solvent-free conditions, using easily available enaminones, trifluoroacetaldehyde hydrate or 1-ethoxy-2,2-difluoroethanol and amidines hydrochloride as substrates (Scheme 1c). This reaction not only conforms to the concept of green synthesis, but also provides a new avenue to access diverse fluorinated heterocycles.

Scheme 1 Significance and synthetic design for fluoroalkylated dihydropyrimidines and pyrimidines.

Results and Discussion

We initiated our studies with readily available ethyl 3-(*N* ,*N* -dimethylamino)acrylate (**1a**), trifluoroacetaldehyde hydrate (**2a**) and benzamidine hydrochloride (**3a**) as model substrates. To our delight, a solvent-free and additive-free multicomponent cyclization reaction was conducted to give the desired product **4a** in 82% yield after heating at 130 °C for 1 h (Table 1, entry 1), while lower yields were obtained in DMSO, CH_3CN or THF as solvent (Table 1, entries 2-4). Decreasing or increasing the ratio of substrate **2a** both had negative impact on the yields of**4a** (Table 1, entries 5-7). Slightly reduced yields were achieved after altering the reaction temperature (Table 1, entries 8 and 9). When the reaction time was extended to 16 h, **4a** was obtained in 58% yield, along with the oxidative dehydrogenation product **6a** obtained in 8% yield. Fortunately, the yield of 4-CF_3-pyrimidines **6a**was increased up to 66% yield with CuCl (20 mol%) as catalyst under air atmosphere. Next, various copper salts were evaluated (Table 1, entries 12-15), but none of them were found to be superior to CuCl. Further decreasing the amount of CuCl to 5 mol% failed to give a higher yield of **6a** (Table 1, entry 16). However, O_2atmosphere did not improve the yield of **6a** (Table 1, entry 17). Meanwhile, **6a** was obtained in trace amount under N_2 atmosphere (Table 1, entry 18).

Table 1 Optimization of the reaction conditions[a]

Entry	Catalyst (mol %)	Reaction conditions	Yield of **4a** (%)[b]	Yield of **6a** (%)[b]
1	-	130 °C, 1 h, air	82	0
2	-	DMSO, 130 °C, 1 h, air	64	0
3	-	CH_3CN, 130 °C, 1 h, air	78	0
4	-	THF, 130 °C, 1 h, air	66	0
5[c]	-	130 °C, 1 h, air	51	0
6[d]	-	130 °C, 1 h, air	67	0
7[e]	-	130 °C, 1 h, air	76	0
8	-	120 °C, 1 h, air	70	0
9	-	140 °C, 1 h, air	74	0
10	-	130 °C, 16 h, air	58	8
11	CuCl (20)	130 °C, 16 h, air	Trace	66
12	CuBr (20)	130 °C, 16 h, air	Trace	39
13	CuI (20)	130 °C, 16 h, air	Trace	56
14	$CuCl_2$ (20)	130 °C, 16 h, air	Trace	53
15	CuO (20)	130 °C, 16 h, air	Trace	55
16	CuCl (5)	130 °C, 16 h, air	Trace	40
17	CuCl (20)	130 °C, 16 h, O_2	Trace	45
18	CuCl (20)	130 °C, 16 h, N_2	71	Trace

[a] Reaction conditions: **1a** (0.2 mmol),**2a** (0.6 mmol, 75% in water), **3a** (0.2 mmol), T °C, solvent (2.0 mL). [b] Isolated yield.[c] **1a** :**2a** :**3a** = 1:1.5:1.[d] **1a** :**2a** :**3a** = 1:2:1.[e] **1a** :**2a** :**3a** = 1:4:1.

Scheme 2 Substrate scope for fluoroalkylated dihydropyrimidines[a]

[a] 0.20 mmol scale under standard reaction conditions. [b] isolated yield of product**4** or **5** . [c] gram-scale reaction.

With the optimal reaction conditions in hand, we evaluated the generality of the solvent-free MCRs. As shown in Scheme 2, a variety of conjugated enamines successfully reacted with trifluoroacetaldehyde hydrate and benzamidine hydrochloride. As for enamine esters, including alkyl and benzyl derivatives, were smoothly converted to the desired products (**4a** -**h**) in moderate to good yields (68-88%). A gram-scale reaction was conducted to deliver 1.2 g of product**4a** in 80% yield. Complex molecules, such as enamine esters derived from (+)-menthol and (+)-fenchol also worked well to give the corresponding products in 89% and 72% yields, respectively. Alkyl enaminones with different chain lengths or cycloalkyl and phenyl enaminone were tolerated, but leading to the desired products (**4k** -**p**) in 41-60% yields, probably due to the interference of electrophilic carbonyl groups. Interestingly, the reaction was also applicable with alkenyl bridged enaminones, affording the respective product **4q** in 51% yield. Moreover, phenylsulfonyl enamine was also found to be compatible with the solvent-free MCR, and the corresponding product **4r** was obtained in 75% yield. Next, we examined the generality of aryl amidines hydrochloride. Generally, the *ortho* -, *meta* -, or*para* -substituted aryl amidines hydrochloride bearing electron-donating groups were found to be compatibility under the optimal reaction conditions, delivering the desired products (**5a** -**e**) in 64-79% yields. In addition, different kinds of halo-substituted aryl amidines hydrochloride exhibited good reactivity under standard conditions, and the corresponding products (**5f** -**j**) were obtained in satisfactory yields (65-78%). Substrates with strong electron-withdrawing groups at the*para*- position of phenyl rings (4-CF_3, 4-NO_2) were also investigated, affording **5k** and **5l** in 75% and 83% yields, respectively. Notably, the presence of sensitive group (OH) in aryl amidine hydrochloride did not affect this multicomponent cyclization reaction, affording **5m** in 73% yield. In addition, the reaction was also applicable to heteroaryl amidines hydrochloride under standard conditions to afford the desired products in good yields (**5n** , 82%; **5o** , 67%). We also investigated the

compatibility of 1-ethoxy-2,2-difluoroethanol, which reacted well with **1a** and**3a** , affording 4-CF_2H-1,4-dihydropyrimidines**5p** in 80% yield.

Scheme 3 Substrate scope for fluoroalkylated pyrimidines[a]

[a] 0.20 mmol scale under standard reaction conditions; [b] isolated yield of product**6** .

Next, the substrate scope for constructing 4-CF_3pyrimidines was investigated (Scheme 3). Esteryl enamines with diverse substituent groups reacted smoothly with trifluoroacetaldehyde hydrate and benzamidine hydrochloride, delivering the desired products (**6a -f**) in 49-71% yields. Alkyl or aryl enamine ketones were also tolerated to afford the desired products in slightly lower yields (**6g** , 38%; **6h** , 40%). Moreover, the reactions proceeded smoothly with a variety of aryl amidines hydrochloride under the optimal conditions, affording the corresponding products (**6i -u**) in moderate yields (40-62%). Finally, 4-CF_2H-pyrimidines **6v** could be obtained in 71% yield using 1-ethoxy-2,2-difluoroethanol as substrate.

After investigating the substrate scopes and the synthetic application of the solvent-free multicomponent cyclization, control experiments were carried out to investigate the reaction mechanism (Scheme 4a). In order to detect the possible intermediates, the reaction was lowered to 60 degC and reacted for 1 h. Fortunately, the possible intermediates **I**and **II** were confirmed by high-resolution mass spectrometry (HRMS), along with the target product **4a** obtained in 8% yield (Scheme 4a-1). However, other possible intermediate **III** or**IV** was not found (ESI for detail). This result implied that β-CF_3-vinylimine ion might be a key intermediate for this multicomponent cyclization. Moreover, 4-CF_3-1,4-dihydropyrimidine could be converted into 4-CF_3-pyrimidine in the presence of CuCl under air atmosphere (Scheme 4a-2).

On the basis of the experimental results and literature reports,[13,14] a postulated mechanism is illustrated, as shown in Scheme 5. This multicomponent cyclization starts from the addition of ethyl 3-(*N* ,*N* -dimethylamino)acrylate **1a** to trifluoroacetaldehyde **2a'** to generate intermediate **A** , which subsequently undergoes a sequential protonation and dehydration to afford β-CF_3-vinylimine ion intermediate **B** . Once formed, intermolecular [3 + 3] cyclization reaction with intermediate **B** and benzamidine **3a** will occur, leading to the formation of intermediate **C** . Subsequently, a deamination process of intermediate **C** provides the product **4a** , which could be oxidized to afford **6a** under copper-catalyzed aerobic condition. [15]

Scheme 4 Control experiments and proposed mechanism.

Conclusions

In summary, a switchable multicomponent cyclization of enaminones, trifluoroacetaldehyde hydrate or 1-ethoxy-2,2-difluoroethanol and amidines hydrochloride for accessing fluoroalkylated dihydropyrimidines and pyrimidines have been developed for the first time. The present multicomponent reaction tolerates a wide range of functional groups and can be performed without solvent. Notably, this strategy not only conforms to the concept of green synthesis, but also provides new opportunities for the sustainable formation of diverse fluorinated heterocyclics, thereby is expected to have widespread applications in pharmaceutical discovery. Further investigations on solvent-free multicomponent cyclization are ongoing in our laboratory.

Experimental

A 15 mL sealed tube with a magnetic stirrer bar was charged with enamine (**1** , 1.0 equiv, 0.20 mmol), trifluoroacetaldehyde hydrate or 1-ethoxy-2,2-difluoroethanol (**2** , 3.0 equiv, 0.60 mmol), amidines (**3** , 1.0 equiv, 0.20 mmol). The reaction vessel was stirred at 130 °C in heating mantle for 1 h. After completion of the reaction, the resulting mixture was extracted with ethyl acetate, and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified with silica gel chromatography (petroleum ether/ethyl acetate = 1:1 7:1, V/V) to afford the corresponding product **4** or **5** .

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for 16 h. After completion of the reaction, the resulting mixture was extracted with ethyl acetate, and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified with silica gel chromatography (petroleum ether/ethyl acetate = 2:1 100:1, V/V) to afford the corresponding product **6** .

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2023xxxxx.

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Entry for the Table of Contents

Switchable Multicomponent Cyclization Reactions to Access 4-Fluoroalkyl-1,4-Dihydropyrimidines and 4-Fl
Herein, we detailed the successful implementation of a switchable strategy for the construction of diverse 4-fluoroalkyl-1,4-d