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Ambient-Light-Promoted Three-Component Annulation: Synthesis of Perfluoroalkylated Pyrimidines

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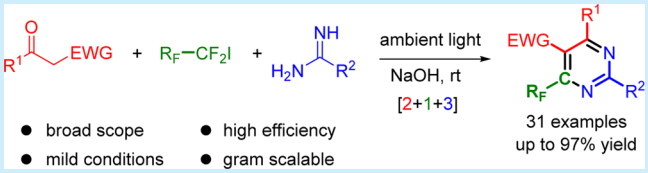
Supporting Information

ABSTRACT: An ambient-light-promoted and metal-free three-component reaction of active methylene compounds, perfluoroalkyl iodides, and guanidines/amidines is reported. This constitutes a powerful method to prepare perfluoroalkylated pyrimidines with mild reaction conditions, broad substrate scope, excellent functional group tolerance, and simple operation. A radical/polar mechanism involving the formation of a halogen-bond adduct and radical cross-coupling is proposed.



Pyrimidine and its derivatives are ubiquitous in natural products, synthetic drugs, and functional materials.[1] Traditionally, pyrimidines could be synthesized by the condensation of amidines or amidinium salts with 1,3-dicarbonyl compounds,[2] cyclization of amides, nitriles mediated by trifluoromethanesulfonic anhydride and 2-chloropyridine reagent combination,[3] inverse-electron-demand Diels–Alder reactions of 1,2,3-triazines with amidine dienophiles,[4] and transition-metal-catalyzed modification by cross-coupling of halogen precursors.[5] In past years, transition-metal-catalyzed multicomponent assembly of pyrimidines has emerged as a powerful and useful alternative strategy. Representative work includes the palladium-catalyzed alkynone intermediate-based three- or four-component pyrimidine synthesis reported by the Müller group[6] (Figure 1a); titanium-catalyzed one-pot and two-step cycloaddition of alkynes, nitriles, amines, and almidines developed by Odom and co-workers;[7] (Figure 1b) and Kempe's iridium- or manganese-catalyzed multicomponent synthesis of pyrimidines from amidines and alcohols[8] (Figure 1c). In addition, Wu and Jiang reported an elegant palladium-catalyzed oxidative three-starting-material, four-component reaction strategy for the synthesis of pyrimidine carboxamides (Figure 1d).[9] While remarkable progress has been made, the method for assembling fluorine-functionalized pyrimidines by a multicomponent reaction has been less developed so far.[10] Electron-donor–acceptor (EDA) complexes have recently found exciting applications in organic synthesis.[11] The halogen-bond adduct, which is formed on the basis of intermolecular noncovalent weak interaction,[12] is undoubtedly classified as an EDA complex. As part of our continued interest in halogen-bond chemistry,[13] we here report a metal-free and visible-light-promoted three-component reaction[14] to assemble the pyrimidine scaffold via formal [2 + 1 + 3] cyclization of active methylenes, perfluoroalkyl iodides, and guanidines/amidines (Figure 1e).[15] This research represents the first photopromoted halogen-bond adduct enabled three-component cascade strategy leading to perfluoroalkylated pyrimidines. The introduction of fluorine(s) into pyrimidine ring is of great value because the perfluoroalkyl group would strongly modify their lipophilicity, bioactivity, and metabolic stability.[16]

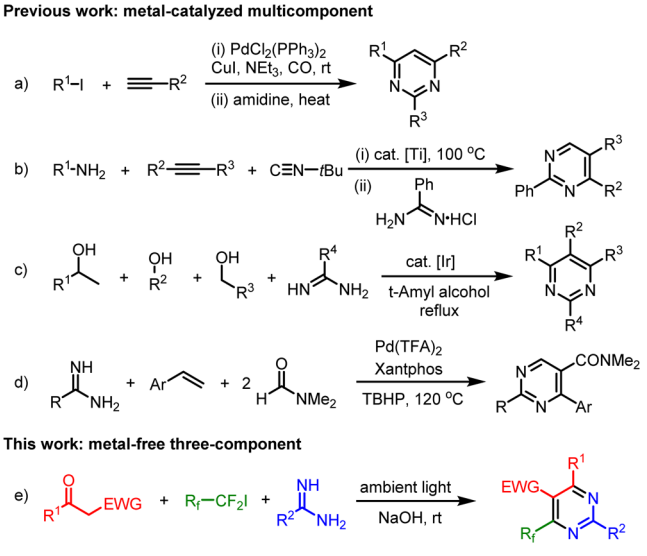


Figure 1. Multicomponent assembly of functionalized pyrimidines.

Our initial investigation focused on the condition optimization with the model reaction of ethyl acetoacetate **1a**, perfluorobutyl iodide **2a** (1.1 equiv), and guanidine hydro-

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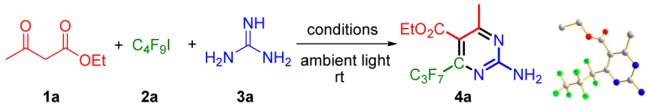
chloride **3a** (1.1 equiv) in the presence of a base (4.1 equiv) (Table 1). Note that 1 equiv of the base is used to neutralize

Table 1. Optimization of the Reaction Conditions[a]



1a 2a 3a 4a

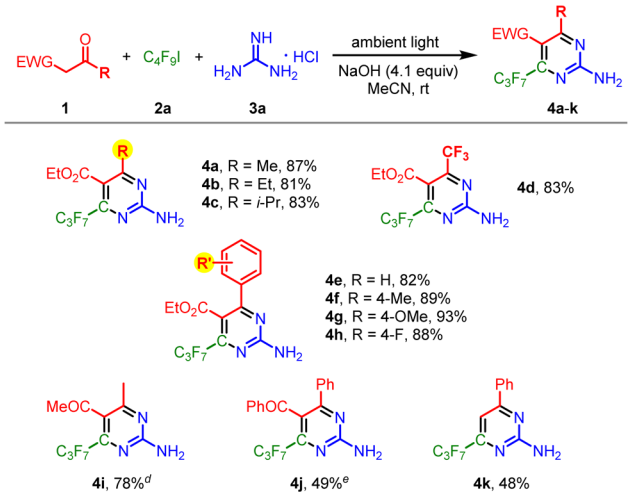
entry	base[b]	solvent	time (h)	yield[c] (%)
1	K_2CO_3	MeCN	24	nr
2	Cs_2CO_3	MeCN	10	39
3	KOH	MeCN	7	70
4	NaOH	MeCN	6	87
5	NaOEt	Me_3CN	11	24
6	NaO*t*Bu	MeCN	15	nr
7	Et_3N	MeCN	12	nr
8	DABCO	MeCN	9	nr
9	NaOH	DMF	6	80
10	NaOH	DMSO	6	83
11	NaOH	DCM	12	nr
12	NaOH	toluene	14	nr
13[d]	NaOH	MeCN	6	38
14[e]	NaOH	MeCN	6	86

[a]Reaction conditions: **1a** (0.1 mmol), base (4.1 equiv), **2a** (1.1 equiv), and **3a** (1.1 equiv) in solvent (0.5 mL). [b]1 equiv of the base is used to neutralize HCl from **3a**. [c]Isolated yield. [d]In the dark. [e]Reaction under N_2 atomosphere. nr = no reaction.

HCl from **3a**. No reaction occurred with K_2CO_3 (4.1 equiv) as the base in MeCN (0.5 mL) (entry 1). Delightfully, in the case of using Cs_2CO_3 as the base, fully substituted pyrimidine **4a** was obtained in 39% yield (entry 2). An improved yield of 70% was achieved with KOH (entry 3), and NaOH proved to be more effective, giving **4a** in 87% yield (entry 4). The structure of **4a** was unequivocally resolved by single-crystal X-ray analysis (CCDC 1485697). Other bases like NaOEt led to significantly decreased yield (24%), and NaO*t*Bu was completely inactive (entries 5 and 6). Organic bases such as triethylamine and 1,4-diazabicyclo[2.2.2]octane (DABCO) proved to be ineffective (entries 7 and 8). We supposed that organobases mentioned above may function as electron donors to interact with **2a**, an electron acceptor, thus inhibiting the formation of EDA complex between the enolates of **1a** and **2a**. The choice of the solvent is also crucial for the reaction (entries 9–12). In comparison with MeCN, DMSO and DMF were less efficient (entries 9 and 10), whereas dichloromethane (DCM) and toluene were totally inert (entries 11 and 12). Notably, all of the reactions were carried out at room temperature under ambient light conditions. However, reactions conducted in the dark led to remarkably decreased yield (entry 13), illustrating that visible light is helpful in promoting the reaction. In addition, reaction under N_2 atomosphere proceeded as well (entry 14), thus indicating oxygen has no effect on the transformation.

With the optimized conditions in hand (Table 1, entry 4), we set out to study the reaction scope. Initially, a range of active methylene compounds were subjected to the reaction sequence at room temperature in the open air conditions (Scheme 1). The reactions of *β*-keto esters containing alkyl substituents (R = Me, Et, *i*-Pr, CF_3) with perfluorobutyl iodide **2a** (1.1 equiv) and guanidine hydrochloride **3a** (1.1 equiv) in the presence of NaOH (4.1 equiv) in MeCN (0.5 mL) proceeded smoothly,

Scheme 1. Scope of Active Methylenes[a–c]

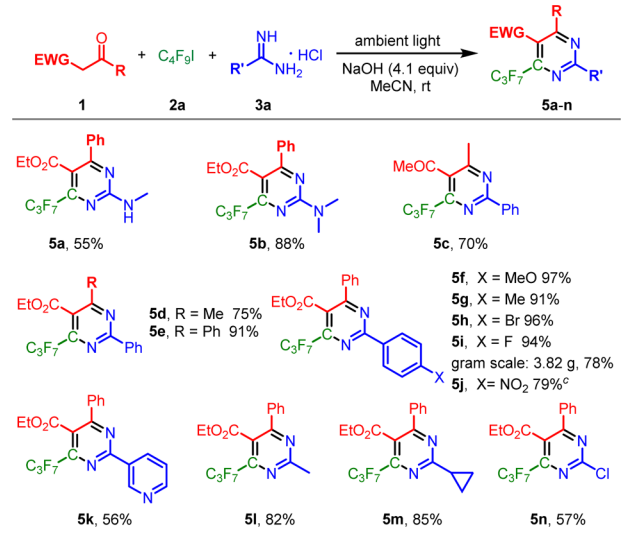


[a]Reaction conditions: **1** (0.1 mmol), NaOH (4.1 equiv), **2a** (1.1 equiv), and **3a** (1.1 equiv) in MeCN (0.5 mL). [b]1 equiv of the base was used to neutralize HCl from **3a**. [c]Isolated yields. [d]In DMSO (0.5 mL). [e]In DMF (0.5 mL).

giving the corresponding 4-perfluoropropyl pyrimidines **4a–d** in 81–87% yields. *α*-Aroyl esters (R = H, 4-Me, 4-MeO, 4-F) afforded 6-arylpyrimidines **4e–h** in good to excellent yields. However, ethyl 4-nitrobenzoylacetate was inactive, while *β*-diketones proved to be suitable substrates. For example, pentane-2,4-dione and dibenzoylmethane furnished 5-acyl-substituted pyrimidines **4i** and **4j** in 78% and 49% yields, respectively. However, deacetylation was observed for benzoylacetone, giving trisubstituted pyrimidine **4k** in 48% yield.

To further examine the scope and utility of this reaction, the scope of guanidine and amidine derivatives was examined by reaction with *β*-keto esters and **2a** under otherwise identical conditions (Scheme 2). To our delight, *N*-methyl- and *N*,*N*-dimethylguanidines gave fully substituted pyrimidines **5a** and

Scheme 2. Scope of Guanidines and Amidines[a,b]



[a]Reaction conditions: 1 (0.1 mmol), base (4.1 equiv), **2a** (1.1 equiv) and **3** (1.1 equiv) in MeCN (0.5 mL). [b]Isolated yield. [c]In DMF (0.5 mL).

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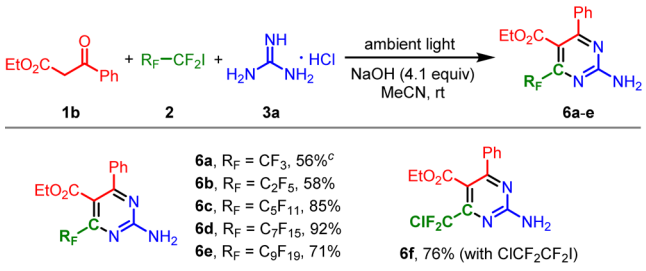
5b in 55% and 88% yields, respectively. A number of amidines with different steric and electronic properties were appropriate partners. The reactions proceeded efficiently for both alkyl- and arylamidines, affording highly functionalized pyrimidines **5c–n** in moderate to excellent yields as well as good functional group tolerance. Note that pyrimidine-cored *m*-teraryls **5e–k** were successfully prepared by the reaction of α-benzoyl ester, **2a**, and arylamidines, which are generally obtained via a transition-metal-catalyzed aryl–heteroaryl coupling protocol.[17] To demonstrate the scalability of this protocol, we conducted a reaction on large scale and observed that the gram-scale synthesis of **5i** (3.82 g) proceeded well under the standard conditions with a yield of 78% (see Scheme S1 for details).

Next, we turn our attention to the scope of perfluoroalkyl halides.[18] As shown in Scheme 3, a variety of perfluoroalkyl

Scheme 3. Scope of Fluoroalkyl Halides[a,b]

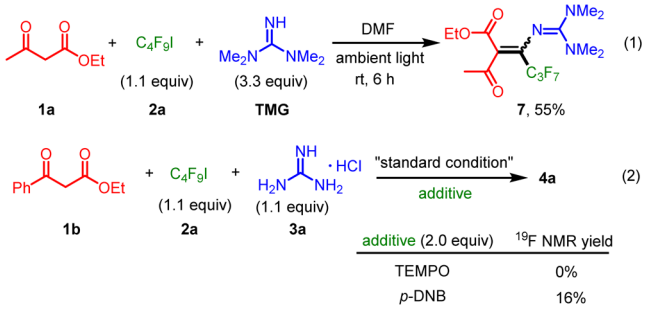


[a]Reaction conditions: **1b** (1.0 mmol), **2** (1.1 equiv), and **3a** (1.1 equiv), NaOH (4.1 equiv), MeCN (0.5 mL). [b]Isolated yields. [c]In DMF (0.5 mL).

iodides with different chain lengths were suitable substrates in this multicomponent reaction. Both shorter and longer perfluorinated chains could be installed in pyrimidines, giving the corresponding perfluoroalkylated **6a–f** in good to excellent yields (56–92%). In particular, gaseous CF_3CF_2I was a good partner for this reaction, affording 4-trifluoromethyl-containing pyrimidine **6a** in 56% yield. Interestingly, a chlorodifluoromethyl functionality could be introduced onto the 4-position of pyrimidines when using 1-chloro-1,1,2,2-tetrafluoro-2-iodoethane (**6f**, 76% yield). The results listed in Schemes 1–3 demonstrate the broad substrate scope, excellent functional group tolerance, and high efficiency of this three-component reaction, thus providing a new and practical method for the synthesis of pharmacologically relevant perfluoroalkylated pyrimidines.

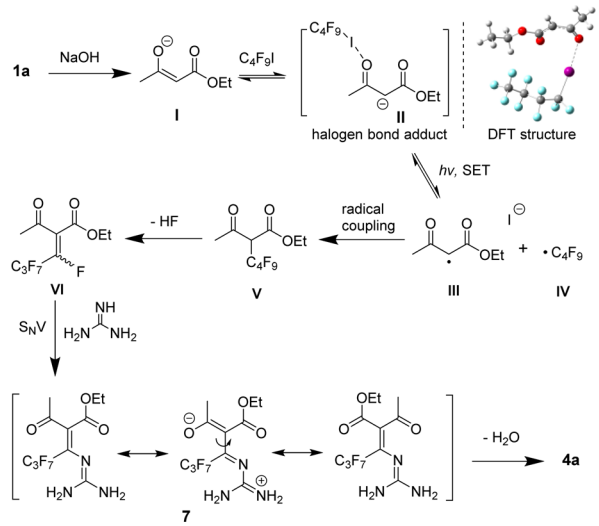
To gain insight into the reaction mechanism, we conducted a mechanistic study (Scheme 4). In the reaction of ethyl 3-oxobutanoate, perfluorobutyl iodide (1.1 equiv), and tetramethyl guanidine (3.3 equiv), tetrasubstituted alkene **7** was isolated in 55% yield (eq 1), thus suggesting a S_NV reaction might take place. To probe whether radical intermediates are involved in this three-component reaction, 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO), an efficient free radical scavenger, was introduced as an additive under the standard conditions (eq 2). The reaction to form **4a** was completely inhibited, suggesting that TEMPO has significant effect on the reaction. Furthermore, we examined the reaction in the presence of a single electron transfer (SET) inhibitor, *p*-dinitrobenzene (*p*-DNB), which led to a significant decrease in the product yield (16%). Notably, the homodimer of **1b** was isolated as a byproduct during the reaction (Scheme S2). Taken together, these observations indicate that a mechanism involving radical and SET pathways is most likely.

Scheme 4. Mechanistic Investigation



On the basis of the above results, a tandem radical/polar mechanism[19] for the three-component reaction is proposed (Scheme 5). (i) A halogen-bond adduct **II** ($r_{I\cdots O}$ = 2.61 Å) is

Scheme 5. Proposed Mechanism



formed in situ by the interaction of transiently generated enolate **I** (halogen-bond acceptor) and perfluorobutyl iodide (halogen-bond donor).[20,21] (ii) Collapse of complex **II** via SET leads to the generation of carbon radical **III** and C_4F_9I radical anion, which releases an iodide anion to give C_4F_9 radical **IV**. (iii) Radical cross-coupling between **III** and **IV** delivers α-perfluoroalkylated intermediate **V**. (iv) Alkene **VI** is formed via elimination of HF. (v) An S_NV type reaction of electron-poor alkene **VI** by guanidine nucleophile gives alkene **7**, in which resonance structures can be formulated via the push–pull electronic effect. (vi) Intramolecular condensation leads to the final product **4a**.[22] In the ambient-light-promoted halogen-bond adduct enabled three-component process, fully functionalized pyrimidines are assembled in a formal [2 + 1 + 3] annulation in which one C–C bond and two C–N bonds are built up.

In conclusion, we have developed the first photopromoted three-component reaction enabled by a halogen-bond adduct. The result of the research allows for highly efficient assembly of perfluoroalkylated pyrimidines via formal [2 + 1 + 3] annulation of the readily available active methylene compounds, perfluoroalkyl iodides, and guanidines/amidines. This work has provided an elegant example of the utilization of noncovalent

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weak interaction like halogen bonding in multicomponent reaction, thus illustrating the power and potential of EDA complex in photocatalyzed synthetic chemistry. In addition, these easily available and highly functionalized perfluoroalkylated pyrimidines would be of great interest in medicinal research and further synthetic derivatization.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00894.

Experimental procedure and characterization data for all compounds (PDF)

X-ray crystallographic data for **4a** (CIF)

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Notes

The authors declare no competing financial interest.

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(20) A distinct coloration can be observed (Figure S1), indicating the formation of halogen bond adduct. For the DFT calculation, see Figure S2.

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(22) The formation of intermediates **V** via nucleophilic substitution of perfluoroalkyl iodide by enolate was tentatively ruled out (Scheme 4 and Scheme S2).

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