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ARTICLE TYPE

First synthesis of unexpected functionalized trifluoromethylated 8-oxa-2,4-diazaspiro[5.5]undecanes via one-pot MCRs

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Ethyl-7,11-diaryl-9-hydroxy-1,3,5-trioxo-9-(trifluoromethyl)-8-oxa-2,4-diazaspiro[5.5]undecane-10-carboxylate derivatives 4 were synthesized from barbituric acid, aromatic aldehydes and ethyl 4,4,4-trifluoro-3-oxobutanoate via one-pot, multi-component reaction catalyzed by Et_3N. The effect of catalyst and temperatures on the reaction efficiency and yield was investigated. In addition, treatment of 4 with $SOCl_2$/pyridine in the solvent of CH_3CN afforded the corresponding dehydrated products 5. A plausible reaction mechanism for the formation of compounds 4 was presented.

Introduction

Incorporation of the trifluoromethyl group into organic molecules has attracted great attention[1] because of the triflurormethyl group's different physical, chemical and biological properties. As a consequence, trifluoromethyl-substituted compounds are becoming increasingly important for the development of new agrochemicals and medicines[2]. The CF_3 group has unique size and specical electronic properities, it often impart increased metabolic stability, elevated lipophilicity and enhanced binding selectivity of the biocative molecules[3]. In recent years, The synthesis of trifluoromethyl heterocycles have been investigated extensively[4].

Multicomponent reactions (MCRs) are generally defined as one of the most important and useful methods in conventional chemical reactions, because they reduce operative steps and enhance synthetic efficiency[5]. MCRs, such as the Biginelli[6], Passerini[7], Ugi[8], and Hantzsch[9], provide a wide variety of important heterocycles. Therefore, combined with the wide use of MCRs[10], it is fascinating to apply MCRs in the synthesis of trifluoromethylated heterocycles.

Pyrimidine-2,4,6(1*H*, 3*H*, 5*H*)-trione (barbituric acid) core is an important structural unit present in a variety of products with wide-ranging biological activities and pharmacological properties[11], especially spiro-compounds with barbituric acid frameworks. As a result, many pyrimidine-2,4,6(1*H*, 3*H*, 5*H*)-trione spiro-derivatives are treated as potent drugs against to different kinds of tumour and bacteria, such as SKLB016[12], PUN-286607[13], 5-[(2*E*)-1-(1*H*-benzimidazol-2-yl)-3-substituted phenylprop-2-en-1-ylidene] pyrimidine-2,4,6(1*H*,3*H*,5*H*)-triones[14] and pyrano[2,3-*d*]pyrimidine[15]. In addition, the methylene group of barbituric acid is considerably active in the organic synthesis, and according to the product structures, it can be divided into three parts: monocyclic pyrimidinones[16], polycyclic benzofuropyrimidinones[17] and dispiropyrimidinones[18]. In order to proceed our ongoing exploration to the synthesis of fluorine-containing heterocycles via MCRs based on the trifluoromethyl-1,3-dicarbonyl compounds, a versatile fluorine-containing building-blocks[19], herein, we wish to report the first example for synthesis of ethyl-9-hydroxy-1,3,5-trioxo-7,11-diaryl-9-(trifluoromethyl)-8-oxa-2,4-diazaspiro[5.5]undecane-10-carboxylate derivatives and their further dehydration reaction.

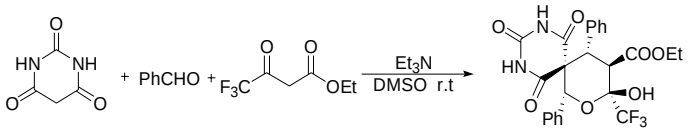
Results and Discussion

Initially, we carried out the reaction of pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione **1** and benzaldehyde **2g** with ethyl-4,4,4-trifluoro-3-oxobutanoate **3** in the molar ratio of 1:1:1 in the presence of a catalytic amount of Et_3N in DMSO at room temperature, TLC analysis showed that the reaction proceeded, but ethyl-4,4,4-trifluoro-3-oxobutanoate **3** and barbituric acid **1** did not be consumed completely. After the completion of the reaction, general workup afforded a new product **4g** in the yield about 30%. Surprisingly, according to the ^{1}H NMR spectrum of newly formed product **4g**, it was clear that two molecules of benzaldehyde **2g** condensate with one molecule of barbituric acid **1** and one molecule of ethyl-4,4,4-trifluoro-3-oxo-butanoate **2** in the new compound. Thus, the molar ratio of ethyl-4,4,4-trifluoro-3-oxobutanoate **3** with pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione **1** and benzaldehyde **2g** was modified to 1:1:2, and the reaction was carried out under the same reaction conditions. After stirring 12 hours at room temperature, TLC analysis showed that the reaction proceeded smoothly and general workup afforded the product **4g** in the yield of 60% as a white solid. The structure of resultant oxospiro product was quite different from the literature reported [2,3-*d*]pyrimidine derivatives, obtained from the reaction of two similar components with the non-fluorinated beta-keto esters or analogs[20]. This difference was attributed to the unique reactivity of fluorinated substrate. Note that the reactions in commonly used solvents were not effective due to the poor solubility of barbituric acid.

Based on the results above, the reaction conditions were optimized to improve the yield by changing catalysts and temperatures. The effects of a variety of organic bases and the

amount on the reaction efficiency and yield were firstly screened (Table 1). As shown in table 1, only a trace amount of product was formed under the condition of reflux. Furthermore, in the absence of base, no corresponding product formed (entry 1, Table 1), the Et_3N catalyst was superior to the most other commonly used bases (entry 2-11, Table 1). Obviously, 0.5 equiv of Et_3N was identified as the optimal catalyst loading with product **4a** being isolated in 72% yield (entry 12, Table 1). In addition, it was also found that the prolonged reaction time did not improve the product yield (entry 15, table 1).

Table 1 Optimization of this one-pot reaction[a]



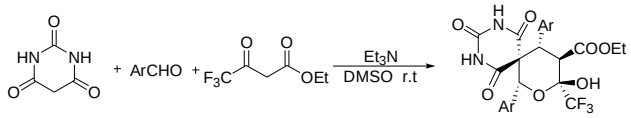
1 2 3 4g

Entry	Base/equiv.	Time/T	Yield of **4g**[b] (%)
1	--[c]	24/reflux	0
2	Et_3N/0.25	12/r.t	60
3	Et_3N/0.25	12/reflux	trace
4	Pyridine /0.25	12/r.t.	30
5	Pyridine /0.25	12/reflux	0
6	Piperidine/0.25	12/r.t.	trace
7	Piperidine/0.25	12/reflux	trace
8	NH_4OAc/0.5	12/r.t.	0
9	NH_4OAc/0.5	12/reflux	0
10	L-proline/0.25	12/r.t.	0
11	L-proline/0.25	12/reflux	0
12	Et_3N/0.5	12/r.t.	72
13	Et_3N/1	12/r.t	72
14	Et_3N/10	12/r.t.	72
15	Et_3N/0.5	24/r.t.	72

[a] Reaction conditions: **1** (1.0 mmol), **2g** (2.0 mmol), **3** (1.0 mmol), solvent: DMSO, 6 mL. [b] Isolated yield. [c] In the absence of base.

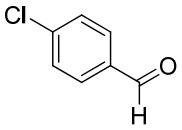
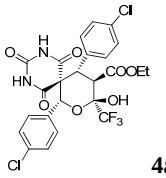
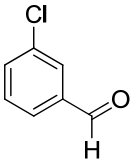
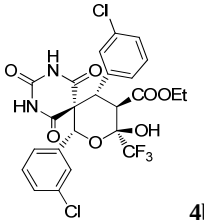
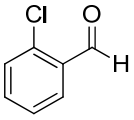
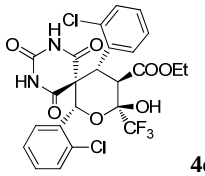
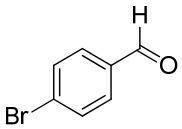
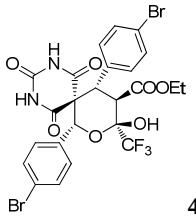
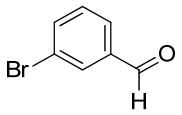
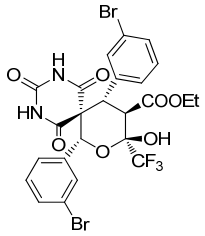
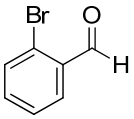
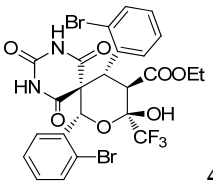
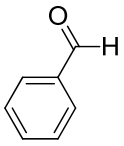
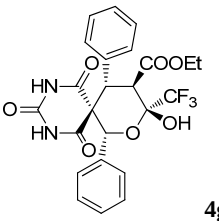
Having identified the optimal reaction conditions (entry 12, Table 1), we investigated the scope and limitation of this one-pot, three-component, atom-economical reaction. Various aromatic aldehydes with subsuituents of different electronic property reacted smoothly and efficiently under the optimal conditions to give the corresponding product **4** in moderate to good yields. The reaction results are summarized in Table 2. In general, it was found that aromatic aldehydes with withdrawing groups gave slightly higher yields than did those with weak electron-donating groups (entries 1, 8). However, the aromatic aldehydes with strong electron-donating group, such as 4-methoxybenzaldehyde and 4-hydroxy-3-methoxybenzaldehyde, failed to participate in the reaction, and TLC analysis showed that the starting materials remained (entry 13). On the other hand, in the case of 4-nitrobenzaldehyde as a reaction substrate, this compound did not give expected product, but diethyl 2,6-dihydroxy-4-nitro-phenyl-2,6-bis-trifluoromethyl-tetrahydro-pyran-3,5-dicarboxylate **6** was obtained under the present reaction conditions (entry 12)[21]. Furthermore, the aromatic aldehyde with ortho substituted groups gave the lower yields than did those with para or meta substituents due to the effect of steric hindrance (entries 1-6). Note that the reaction of aliphatic aldehyde, such as 2-methyl-propanal, also failed (entry 14).

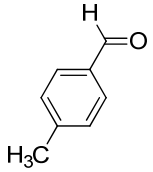
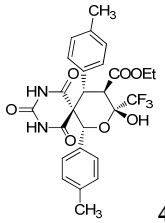
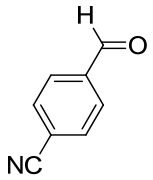
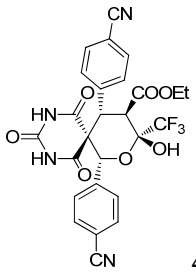
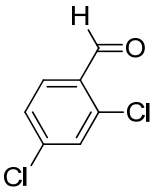
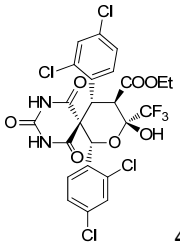
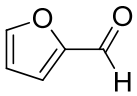
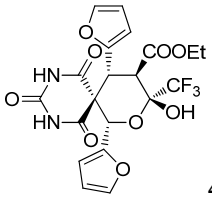
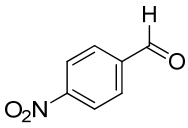
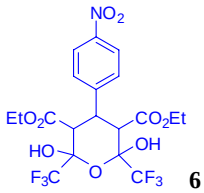
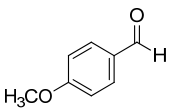
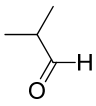
Table 2 Results of the one-pot, three component reaction[a]



1 2 3 4

Entry	Ar	Time/h	Products	Yield (%)[b]

1		24	 **4a**	78
2		24	 **4b**	73
3		12	 **4c**	63
4		12	 **4d**	82
5		8		72
6		12	 **4f**	65
7		24	 **4g**	72

8		12	 **4h**	71
9		12	 **4i**	76
10		12	 **4j**	74
11		24	 **4k**	76
12		12	 **6**	68[c]
13		12	–	–
14		24	–	–

[a] Reaction conditions: **1** (1.0 mmol), **2** (2.0mmol), **3** (1.0 mmol), Et_3N (0.5 eq.), DMSO (6.0 mL), Room temperature. [b] Isolated yield. [c] Yield is calculated based on ethyl -4,4,4-trifluoro-3-oxobuanoate.

The structures of compounds **4(a–k)** were fully confirmed by ^{1}H, ^{19}F, and ^{13}C NMR spectroscopy, mass spectrometry, High-resolution mass spectrometry and IR spectroscopy. For instance, among the characteristic features of the ^{1}H NMR spectrum of **4g** in $CDCl_3$, showed the doulblets at δ = 4.40 and 4.56 ppm with a coupling constant $J_{H\text{-}H}$ = 13.0 Hz for *H*-10 and *H*-11 protons, respectively, indicating that a *trans* configuration of the vicinal pair of hydrogen atoms. The stereochemistry of **4** was attributed to that the intra-molecular cyclization would be an energetically favorable process, affording more stable '*trans*' configuration of **4**. For the same reason, the stereochemistry of carbons *C*-7 and *C*-11 were the R* and S*, respectively. In the ^{19}F NMR spectrum, The trifluoromethyl group appeared as a singlet peak at δ = -85.14 ppm (s, 3F), which indicated that this group was bonded to a quaternary carbonatom. The structure of compound **4d** was further confirmed by single crystal X-ray analysis, this supported our speculations regarding the structures of the products (Figure 1)[22].

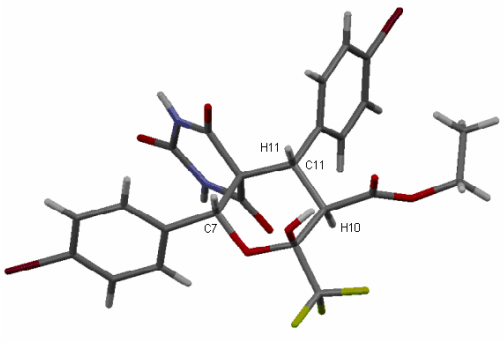
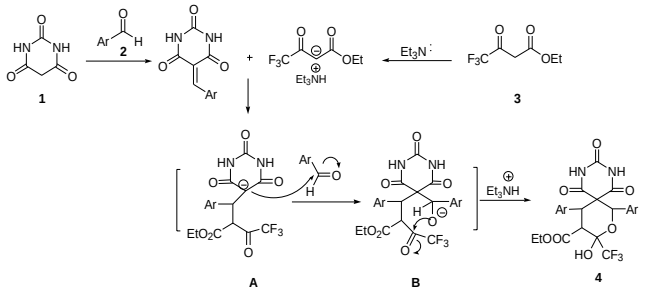


Figure 1. X-Ray crystal structure of compound **4d**

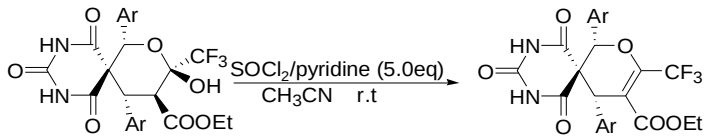
On the basis of our results, we propose a plausible mechanism for the formation of compounds **4** (Scheme 1). First, one molecule of barbituric acid condensated with one molecule of aromatic aldehyde via initial Knoevenagel condensation reaction, then followed by Michael addition reaction catalyzed by Et_3N, thus, the intermediate **A** was formed. Intermediate **A** reacted with the second molecule of aromatic aldehyde to afford the intermediate **B**, which underwent the intramolecular cyclization reaction to afford the products **4** eventually.



Scheme 1. Plausible mechanism for formation of **4**

Furthermore, we studied the dehydration of compounds **4**. It should be indicated that the hemi-ketal moiety in compounds **4** is stable and resists dehydration under the conditions for formation of **4** because of the strong electron-withdrawing effect of trifluoromethyl group on the six-membered ring[23]. Thus, the effect of different dehydrated reagents were briefly screened, and reaction results showed that the excess of 4-toluensulfonic acid or phosphorus pentoxide were not effective even though the reaction was performed under reflux in toluene. It was found that treatment of **4** with an excess of $SOCl_2$/pyridine in CH_3CN at room temperature caused the smooth elimination of water form **4** to afford the corresponding dehydrated derivatives **5**. The reaction results were listed in Table 3. The structure identity of compounds **5** was fully supported by appropriate methods.

Table 3 Reaction results of dehydration of **4** to **5**[a]



4 **5**

Entry	Ar	Time/h	Products (Yield/%)[b]
1	*p*-ClC_6H_4	2	**5a** (59)
2	*m*-BrC_6H_4	2	**5b** (50)
3	*o*-ClC_6H_4	2	**5c** (63)
4	C_6H_5	2	**5d** (51)
5	2,4-$(Cl)_2C_6H_3$	2	**5e** (50)
6	*p*-$CH_3C_6H_4$	2	**5f** (52)
7	Furyl-2-	2	**5g** (58)

[a] Reactions were performed with **4** (1.0 mmol), $SOCl_2$ (5.0mmol) and pyridine (5.0 mmol) in CH_3CN (10mL)..

From the step-economical reaction point of view, we finally developed the step-wise cycloaddition-dehydration reaction into one-pot strategy. The reaction mixture **4g** was allowed to react with an excess of thionyl-chloride (5.0eq) and pyridine (5.0eq) after the cycloaddition was finished. By combination of cycloaddition and dehydration sequences, this one-pot reaction gave the final product **5d** in comparable yields (55%, compared to 72%X51% under the separated step reaction). During this process, the structure of **5a** was also confirmed by spectral data.

Conclusions

In conclusion, we have demonstrated a simple and convenient multi-component protocol for the synthesis of a library of ethyl 7,11-diaryl-9-hydroxy-1,3,5-trioxo-9-(trifluoromethyl)-8-oxa-2,4-diazaspiro[5.5]undecane-10-carboxylate derivatives from readily available simple starting materials. Dehydration of the himiketal moiety to form the corresponding ethyl-7,11-diaryl-1,3,5-trioxo-9-(trifluoromethyl)-8-oxa-2,4-diazaspiro[5.5]undec-9-ene-10-carboxylate derivatives was also achieved. Furthermore, the step-wise cycloaddition and dehydration reactions can be further developed into one-pot strategy with enhanced yields. These novel compounds can be considered as useful trifluoromethyl-containing substrates for the synthesis of a variety of heterocyclic compounds with potential biological activities in the biomedical field.

Acknowledgments

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Notes and references

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Electronic Supplementary Information (ESI) available: [Typical experimental procedure and characterization for all products].

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22 CCDC-981363 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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