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Acid-promoted one-pot synthesis of substituted furan and 6-methylpyrazin-2(1*H*)-one derivatives *via* allene intermediate formed in situ

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KEYWORDS Allene; Multicomponent reaction (MCR); Ugi reaction; 6-methylpyrazin-2(1*H*)-one; Substituted furans

ABSTRACT Under the acidic conditions, substituted furans were constructed from γ-alkynyl ketones through corresponding allene intermediates in one-pot. The methodolgy was also tailored to a series of the Ugi reaction products for the synthesis of 6-methylpyrazin-2(1*H*)-one

derivatives. The current method offered significant advantages for the combinatorial applications of these chemcial scaffolds.

INTRODUCTION

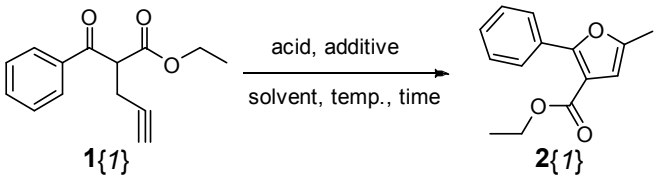
Allenes are versatile structural motifs in organic transformations,[1] which possess inherent advantages for the construction of hetereocycles and have received considerable attentions for the synthesis of biologically active compounds.[2,3] In view of the high convertability of alkyne to allene, the construction of alkyne derivatives has recently become a key focus to build the complex heterocycles.[4]

Furan and piperazinone play a significant role in medicinal chemistry. Numerous biologically active molecules, pharmaceuticals, and natural products bear the core structures of these two heterocycles.[5] During the past decades, the carbene-transfer reaction with conjugated enynones as the carbine precursors have been extensively reported by using medal catalysts such as Rh[6], Zn[7], Cu[8], Pd[9] or Lewis acid $Bi(OTf)_3$[10-11] Notebally, the γ-alkynyl ketones could be converted to the furan-carbine precursors *in situ* and had been widely used in the carbene-transfer reactions.[6-11] Similary, the alkyne can be also efficiently converted to the corresponding allene intermediate under a medal catalyst, or even under a basic condition, which led the syntheis of various hetercycles including dihydropyrazinones.[10-14] However, all cases reported, a two or more step optional process or hazardous solvent $MeNO_2$ were required. The synthesis of substituted furans or piperazinones via the allene intermediate in one pot with an easy work-up would be significantly combinatorial application-friendly and cost-effcient.

RESULTS AND DISCUSSION

As part of our continued efforts to develop cascade reactions based on MCRs for the combinatorial applications, we hypothesized that an acid catalyst could potenttially transfer γ-alkynyl ketones to the furan-carbine precursors and the acid catalyst could also promote a sequential cyclization in one-pot. To test the hypothesis, compound 1{*1*} was selected as a model substrate to evaluate the feasibility for the synthesis of substituted furans. To our delight, two sequential reactions occurred in one-pot at the first attempt with *p*-TsOH (*p*-toluenesulfonic acid) at 70 °C for 5 h in toluene, although the isolated yield was low at 45% (entry 1). We then investigated a variety of different Brønsted acids, catalyst loadings, temperature, reaction times and solvents to optimize yields (Table 1). Higher reaction temperatures afforded higher yields (78-87%, entries 2-3). Unfortunately, decreasing the loading of *p*-TsOH from 20% to 10% resulted in a sharp reduction of the yield from 87% to 53% (entry 4). Interestingly, when *p*-TsOH was combined with a Lewis acid catalyst, the starting material was transformed to the corresponding product just in 1 h (entry 5 and 6). To confirm the superiority of *p*-TsOH in this reaction, more acids were tested. However, none of other acids (entries 7-9) were better. When solvents such as DMSO, CH_3CN, CH_3OH and DMF were explored, lower yields were obtained (Table 1, entries 10-13). Most importantly, with DCE (1,2-dichloroethane) as the solvent and 20 mol% *p*-TsOH as the catalyst the reaction yielded the desired product in an excellent yield (92%, entry 14). As expected, DCM (dichloromethane) and $CHCl_3$ (chloroform), the twins of DCE, gave the desired product in good yields (80% and 81%, resepctively entries 15 and 16). In a sharp contrast, the reaction without *p*-TsOH did not yield the product (entry 17). Hence, the optimized reaction condition is summaried here: the reaction was stirred with the acid catalyst *p*-TsOH (20 mol%) in the solvent of DCE (2.0 mL) at 110 ^{o}C for 3 h (entry 14).

Table 1. Optimization for synthesizing compound fruan 2{*1*}.[a]



1{*1*} **2**{*1*}

Entry	Acid	Additive	Solvent	Temp. (°C)	Time (h)	Yield (%)[b]
1	*p*-TsOH	-	toluene	70	3	45
2	*p*-TsOH	-	toluene	90	3	78
3	*p*-TsOH	-	toluene	110	3	87
4[c]	*p*-TsOH	-	toluene	110	3	53
5[d]	*p*-TsOH	$ZnCl_2$	toluene	110	1	89
6[d]	*p*-TsOH	$ZnBr_2$	toluene	110	1	88
7	TFA	-	toluene	110	3	NR
8	AcOH	-	toluene	110	3	NR
9	PPOA	-	toluene	110	3	15
10	*p*-TsOH	-	DMSO	110	3	NR
11	*p*-TsOH	-	CH_3CN	110	3	35
12	*p*-TsOH	-	CH_3OH	110	3	27
13	*p*-TsOH	-	DMF	110	3	NR
14	***p*-TsOH**	**-**	**DCE**	**110**	**3**	**92**
15	*p*-TsOH	-	DCM	110	3	80
16	*p*-TsOH	-	$CHCl_3$	110	3	81
17[e]	-	-	DCE	110	3	NR

[a] Reaction conditions: compound **1**{*1*} (1.0 mmol), acid (20 mol%), solvent (2.0 mL).

[b] Yield (%) based on the integral of the LC/MS peaks detected at 254nm.

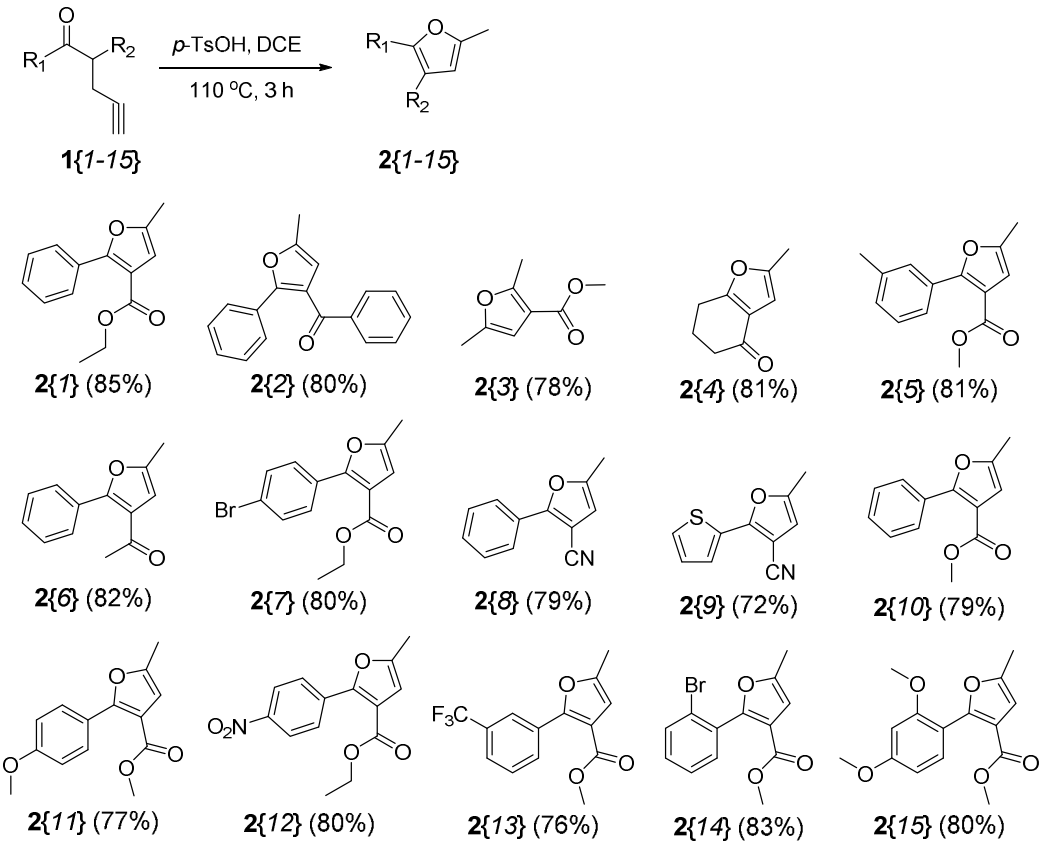
[c] The acid loading was increased to 10 mol%.

[d] Lewis acid (20 mol%).

[e]The reaction was carried out in the absence of acid.

With the optimized reaction conditions, the scope of this transformation was subsequently explored. As shown in Scheme 1, various starting materials were successfully transformed into corresponding products in moderate to good yields. Morover, the thiophen substrate **2**{*9*} could be well tolerated with the yield of 72%.

Scheme 1. Synthesis of furan 2{*1-15*}.

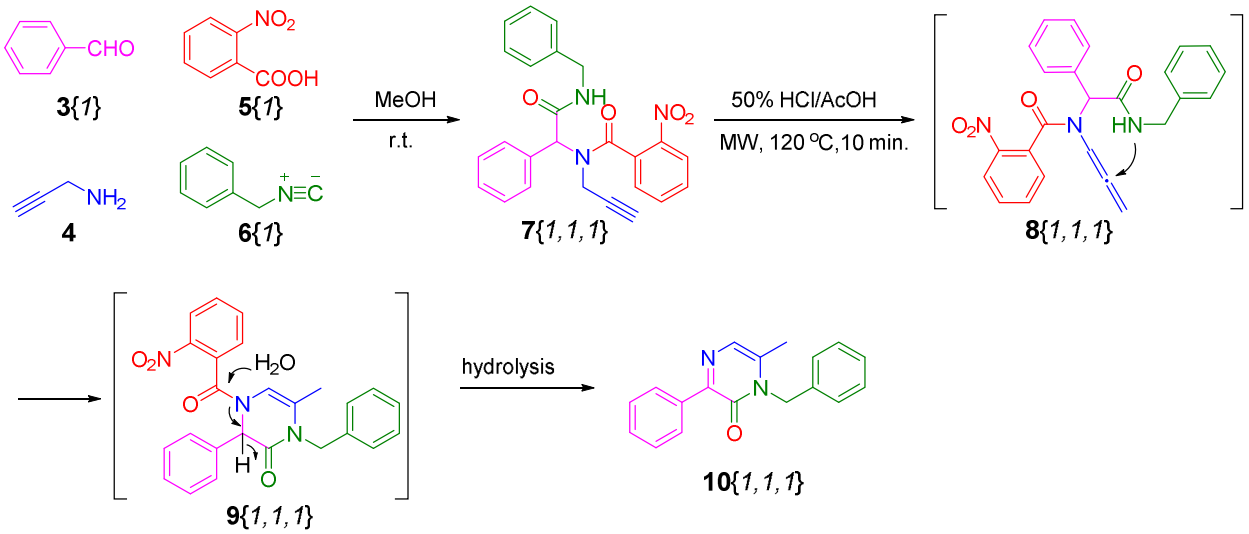


Isolated yield (%) in parentheses.

Based on our aforementioned acid-catalyzed two sequnetial transformation for the synthesis of furan analogues in one-pot, we envisoned that an acid catalyst could be also useful for converting the Ugi 4-CR/propargyl products to the 6-methyl-3,4-dihydropyrazinone derivatives (Scheme 2). We first selected the Ugi-product **7**{*1,1,1*} as the model substrate which was obtained by mixing benzaldehyde **3**{*1*}, 2-propynylamine **4**, 2-nitrobenzoic acid **5**{*1*}, and benzyl isocyanide **6**{*1*} with a standard Ugi reaction condition. The Ugi adduct **7**{*1,1,1*} was then treated with the aforementioned acidic condition. Unfortunately, the desired prodcut **9**{*1,1,1*} was not detected in the reaction mixture by the LC/MS determination and also not found after work-up and column purification. Instead, compound **10**{*1,1,1*} was isolated as the

only reaction product. It was found that the dehydrogenation and hydrolysis reactions were took place for intermediate **9**{*1,1,1*} to afford 10{*1,1,1*}. The chemcial structure of compound **10**{*1,1,1*} was determined by the combination of ^{1}H NMR, ^{13}C NMR, LC/MS, and HRMS. It was further confirmed by the X-ray crystal structure analysis (Figure 2).[15]

Scheme 2. Synthetic route of 6-methylpyrazin-2(1*H*)-one 10{*1,1,1*}.



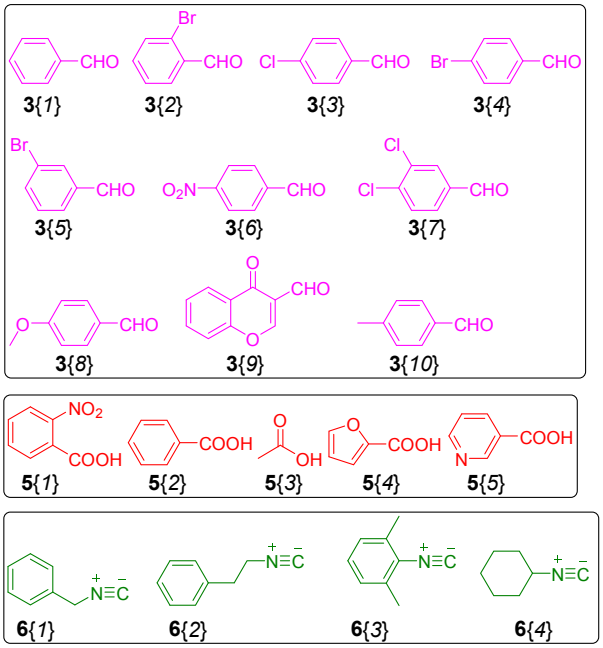


Figure 1. Building blocks for Ugi reaction.

Table 2. Optimization of cyclization step for compound 10{*1,1,1*}.

Entry	Cat.	Solvent	Condition	Yield (%)[a]
1	*p*-TsOH	DCE	110 °C, 3 h	10
2	*p*-TsOH	DCE	110 °C, 12 h	21
3	10% TFA/DCE		MW 110 °C, 10 min.	trace
4	10% TFA/DCE		MW 120 °C, 10 min.	trace
5	10% HCl/AcOH		MW 110 °C, 10 min.	trace
6	50% HCl/AcOH		MW 110 °C, 10 min.	52
7	**50% HCl/AcOH**		**MW 120 °C, 10 min.**	**75**
8	50% HCl/AcOH		MW 130 °C, 10 min.	59
9[b]	50% HCl/AcOH		MW 120 °C, 10 min.	72
10[c]	50% HCl/AcOH		MW 120 °C, 10 min.	71
11[d]	50% HCl/AcOH		MW 120 °C, 10 min.	75
12[e]	50% HCl/AcOH		MW 120 °C, 10 min.	70

[a] Isolated yield (%) after column chromatography. MW = microwave.

[b] 2-Nitrobenzoic acid **5**{*1*} was replaced by benzoic acid **5**{*2*} as acid sources in Ugi reaction.

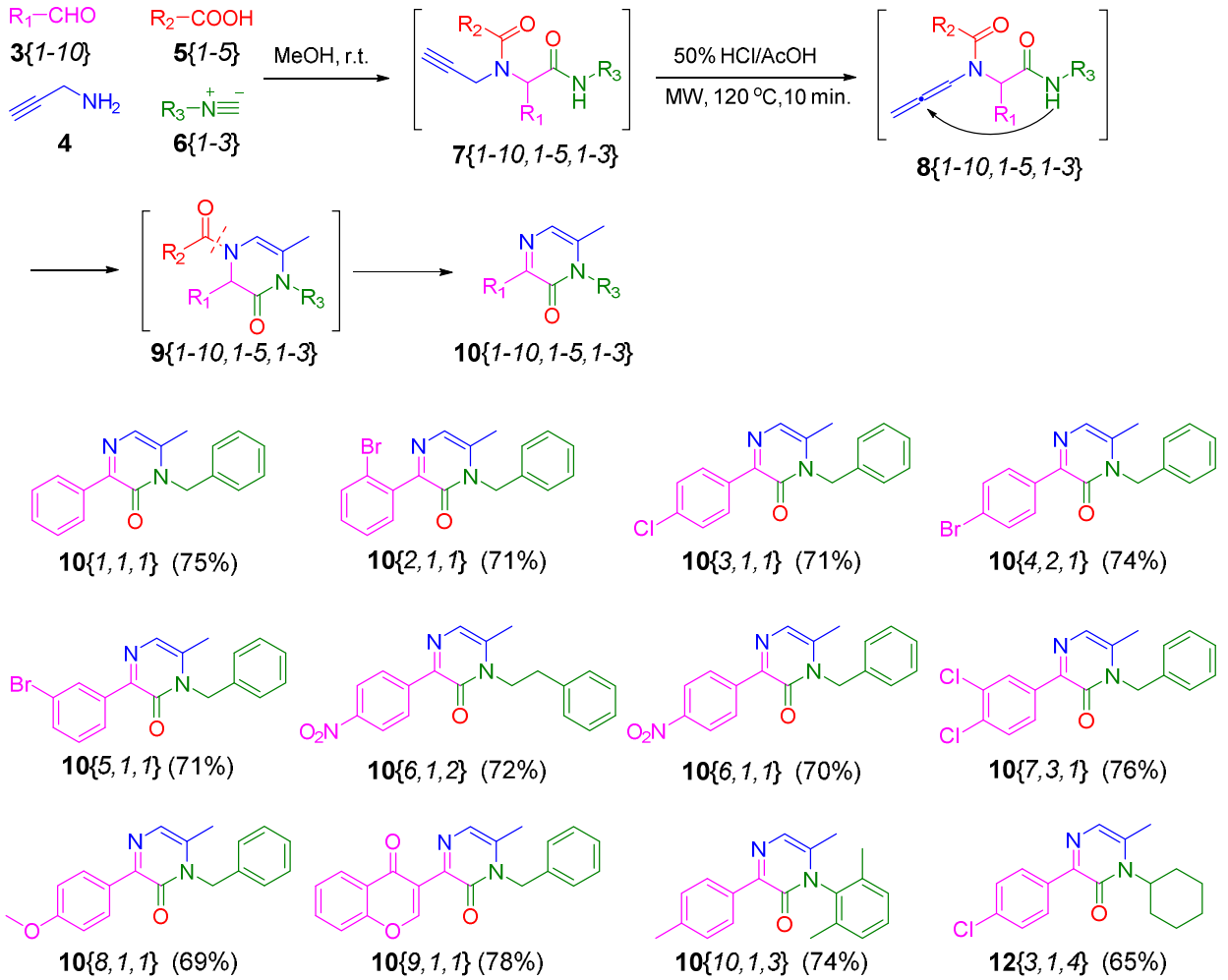
[c] 2-Nitrobenzoic acid **5**{*1*} was replaced by acetic acid as acid **5**{*3*} sources in Ugi reaction.

[d] 2-Nitrobenzoic acid **5**{*1*} was replaced by 2-furoic acid **5**{*4*} as acid sources in Ugi reaction.

[e] 2-Nitrobenzoic acid **5**{*1*} was replaced by nicotinic acid **5**{*5*} as acid sources in Ugi reaction.

To understand the mechanism of action for producing compound **10**{*1,1,1*}, rather than **9**{*1,1,1*} with the Ugi product **7**{*1,1,1*} which was derived from 2-nitrobenzoic acid **5**{*1*}, we replaced 2-nitrobenzoic acid **5**{*1*} with much less eletron withdrawing benzoic acid **5**{*2*}, acetic acid **5**{*3*}, 2-furoic acid **5**{*4*}, and nicotinic acid **5**{*5*} as shown in Figure 1. The reaction yields (Table 2, entries 9-12) were compriable for all different Ugi products, indicating that the nitro-functionality doesn't plays a role in the reaction. Obviously, the dehydrogenation of the dihydropyrazinone ring occurred first and then the hydrolysis was followed as shown in Scheme 2.

Scheme 3. Synthetic route and structures of 6-methylpyrazin-2(1*H*)-ones 10{*1-10,1-5,1-3*}.



Isolated yield (%) in parentheses

The literatures search revealed that the previous synthesis of 6-methylpyrazin-2(1*H*)-ones was complex and required 5 step protocols.[16] One-pot synthesis would offer a quick entry of 6-methylpyrazin-2(1*H*)-one analogues for the combinatiorail applications. We therefore conducted the optimization of the reaction conditions in Table 2. Among the acids tested, 50% HCl/AcOH at 120 ^{o}C for 10 min gave the best yield (75%) (entry 7). The increase of the temperature to 130 ^{o}C lowed the yield to 59% (entry 8).

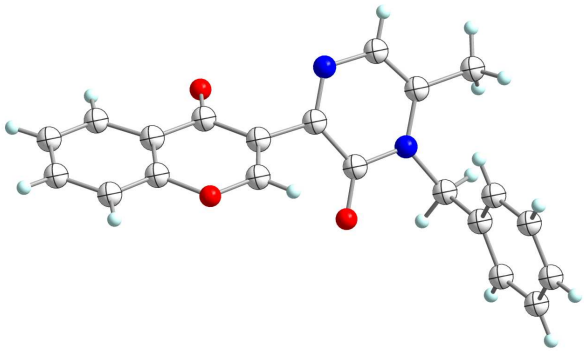


Figure 2. X-ray analysis of compound 10{*9,1,1*}**.**

With the optimized reaction conditions, the scope of this reaction were explored and representative final products were presented in scheme 2. For this reaction, aldehydes with electro-drawing, electron-donating, and heterocyclic substituents all afforded good yields. A diverse collection of isocyanides including benzyl isocyanide **6**{*1*}, 2-phenylethan-1-isocyanide **6**{*2*}, 2,6-dimethylphenyl isocyanide **6**{*3*} and cyclohexyl isocyanide **6**{*4*} were converted to the corresponding products in moderate (65%) to good yields (78%). In contrast, the previous methdology (citation) was restricted to the 2,6-dimethylphenyl isocyanide and required multiple work-up procedrues. It is worth to mention that, in addition to classical carboxylic acids, carbolic acid, a phenol analogue {*1-5*} also demonstrated a robust reactivity in the reaction to afford compound **10**{*1-10,1-5,1-3*} in a good yield (see SI for detailed information).

CONCLUSION

We have developed an efficient protocol for the acid-catalyzed (*p*-TsOH) synthesis of allene intermediates from alkynes *in situ*. The allene intermediates were sequntially transferred to polysubstituted furans in one-pot. The combination of HCl and ACOH in a ratio of 1/1 was tailored to the Ugi 4-CR/propargyl products for the construction of 6-methylpyrazin-2(1*H*)-one

derivatives. With the concise synthesis of diverse furan and pyrazinone derivatives combinatorially, this one-pot protocol of the acid-catalyzed conversion of alkynes to allene intermediates could provide a new tool for the diversification of complex heterocycles in an expeditious manner. The biological tests are undergoing for these furans and pyrazinone derivatives. The results will be reported in due course.

EXPERIMENTAL SECTION

a) General procedures for γ-alkynyl ketones 2{*1-15*}.[10]

To a solution of ketone starting material (1.0 mmol) in DCE (10 mL), *p*-TsOH (0.20 mmol) was added and the mixture was heated to 110 ^{o}C for 3 h. The reaction mixture was monitored by TLC. When no starting material was left, the reaction mixture was diluted with EtOAc (15.0 mL), washed with sat. Na_2CO_3 and brine. The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by silica gel column chromatography using a gradient of ethyl acetate/hexane (10-60%) to afford the relative targeted products **2**{*1-15*}.

b) General procedures for compounds 10{*1-10,1-5,1-3*}.

A solution of propargylamine (1.0 mmol), benzyl isonitriles (1.0 mmol), 2-nitrobenzoic acid (1.0 mmol) and benzaldehyde (1.0 mmol) in MeOH (2.0 mL) was stirred overnight at room temperature. The reaction mixture was monitored by TLC. When no isonitrile was left, the solvent was removed under nitrogen blowing and the crude residue was dissolved in 50% HCl/AcOH solution in microwave at 120 ^{o}C for 10 min. After the microwave vial was cooled to room temperature, the reaction mixture was diluted with EtOAc (15.0 mL), washed with sat. Na_2CO_3 and brine. The organic layer was dried over $MgSO_4$ and concentrated. The residue was

purified by silica gel column chromatography using a gradient of ethyl acetate/hexane (10-100%) to afford the relative targeted product **10**{*1-10,1-5,1-3*}.

ASSOCIATED CONTENT

Supporting Information

The supporting information is available free of charge on the ACS Publications website at DOI:XXX

Full analytical data of compounds for intermediates and final products, along with the copies of ^{1}H NMR, ^{13}C NMR and X-ray of compound **10**{*9,1,1*} spectra of all the synthesized compounds, and complete description of the studies for the reactions (PDF).

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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Notes

The authors declare no competing financial interest.

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(15) CCDC 1813706 (**10**{*9,1,1*}) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center.

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Graphical abstract

Acid-promoted one-pot synthesis of substituted furan and 6-methylpyrazin-2(1*H*)-one derivatives *via* allene intermediate formed in situ

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The construction of substituted furans from allene intermediates was successfully applied to Ugi products for the synthesis of 6-methylpyrazin-2(1*H*)-one derivatives.