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ORIGINAL ARTICLE

An efficient diastereoselective synthesis of novel fused 5*H*-furo[2,3-*d*]thiazolo[3,2-*a*]pyrimidin-5-ones via one-pot three-component reaction

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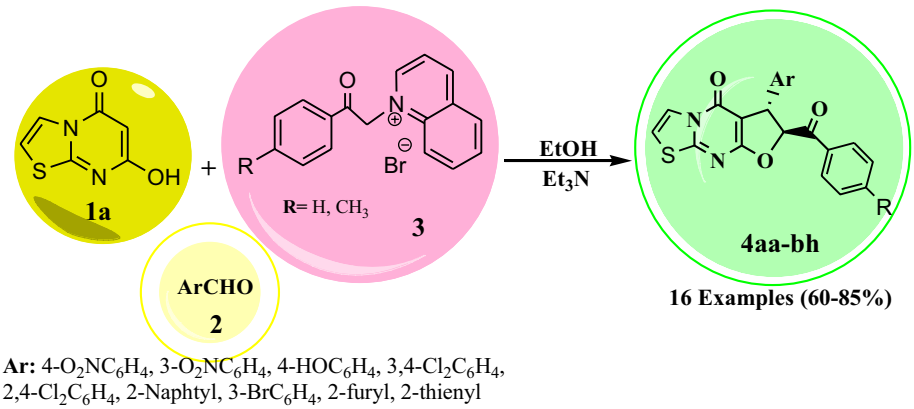
Abstract

Herein, a convenient and efficient synthesis of 7-benzoyl-6-(aryl)-6,7-dihydro-5*H*-furo[2,3-*d*]thiazolo[3,2-*a*]pyrimidin-5-one derivatives was achieved from the reaction of isoquinolinium *N*-ylides, aromatic aldehydes, and heterocyclic 1,3-dicarbonyl compounds via one-pot three-component diastereoselective domino reaction in good-to-excellent yields. The advantages of this protocol are easily available starting materials, operational simplicity, and avoidance of hazardous organic solvents and catalyst. The synthesized products were characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectra. Additionally, the conclusive structure of target compounds was confirmed by X-Ray diffraction analysis.

Graphic abstract



Keywords 7-benzoyl-6-(aryl)-6,7-dihydro-5*H*-furo[2,3-*d*]thiazolo[3,2-*a*]pyrimidin-5-one · Phenacyl bromide · Isoquinoline · Thiazolo[3,2-*a*]pyrimidin · Three-component reaction

Introduction

Heterocyclic compounds are significant for medicinal chemists due to their importance in the synthesis of pharmacologically active compounds [1–3]. The furopyrimidine is an important five-membered heterocycle containing a furan ring fused with a pyrimidine ring that dominates an important area in medicinal chemistry. Among its isomer, the furo[2,3-*d*]pyrimidine shows various biological activity including the inhibition of dihydrofolate reductase

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(DHFR) as the primary target [4]. Furo[2,3-*d*]pyrimidine has been synthesized as potential inhibitors of folic acid cycle enzymes [5], multireceptor tyrosine kinase inhibitors [6], and glycogen synthase kinase-3 inhibitors [7]. Also, this compound has been exhibited as antifungal [8], antitumor [9, 10], antifolate [11], antibacterial [12], antiviral [13, 14], and anti-HCMV (human cytomegalovirus) [15] activities.

Furthermore, furopyrimidine **A** was the most active Akt1 kinase inhibitor, with an IC50 value of 24 Mm (Fig. 1, **A**) [16]. The furopyrimidine derivatives **B** and **C** exhibited more potent nanomolar GSK-3 inhibition with IC50 of 32 and 5 nM, respectively (Fig. 1, **B** and **C**) [17].

In addition to that, thiazolopyrimidines belong to a main family of compounds with significant biological activity. For example, thiazolopyrimidine carboxylates **D** is used as potential antibacterial and antidiabetic agents [18], pyrimidobenzothiazole derivatives **E** exhibited as a new class of H1-antihistaminic agent [19], and Ritanserin F is one of the thiazolo[3,2-*a*]pyrimidine derivatives that is antagonist of 5HT2 serotonin receptors (Fig. 1, **A**) [20].

The isoquinolinium ylides as a cyclic nitrogen *N*-ylides which can be generated from the deprotonation of isoquinolinium salts are one of the practical potential synthons in synthetic reactions [21–32]. These ylides can undergo Michael additions, with various electron-deficient acetylene and alkenes to produce the corresponding 2,3-dihydrofurans [33–39].

Due to biological importance of furo[2,3-*d*]pyrimidines, and in continuation of related studies and our growing interest in developing reactions of 1,3-heterocyclic diones [40–43], we decided to synthesize 7-benzoyl-6-(aryl)-6,7-dihydro-5*H*-furo[2,3-*d*]thiazolo[3,2-*a*]pyrimidin-5-one derivatives. To the best of our knowledge, this is the first report of three-component, of *N*-phenacyl isoquinolinium bromide, and aromatic aldehydes with 5*H*-thiazolo[3,2-*a*]pyrimidine-5,7(6*H*)-dione leading to novel functionalized fused 5*H*-Furo[2,3-*d*]thiazolo[3,2-*a*]pyrimidin-5-ones (Scheme 1).

Result and discussion

Initially, *N*-phenacylisoquinolinium bromide generated in situ from isoquinoline and phenacyl bromide was used to react with 5*H*-thiazolo[3,2-*a*]pyrimidine-5,7(6*H*)-dione (**1a**) and *p*-nitrobenzaldehyde (**2a**) which was selected as a model. In that, the effect of different catalysts, solvents, temperatures (Table 1), and different *N*-heterocycles was investigated (Table 2). Firstly, the model reaction was carried out in the absence of a catalyst in refluxing ethanol. However, it was unsuccessful to produce the preferred product and the starting materials remained completely unconsumed even after 24 h (Table 1, entry 1). We checked the progress of reaction in the presence of diisopropylethylamine (DIPEA), which afforded the desired product **4aa** in 70% yield (Table 1, entry 2). Nevertheless, the above reaction was investigated farther, using different bases including DABCO, DBU, Et_3N, K_2CO_3, DMAP in stoichiometric amounts (1 mmol), in refluxing ethanol. The experimental data showed that the reaction was carried out with higher yield (80%, Table 1, entry 7) when Et_3N was used as a base.

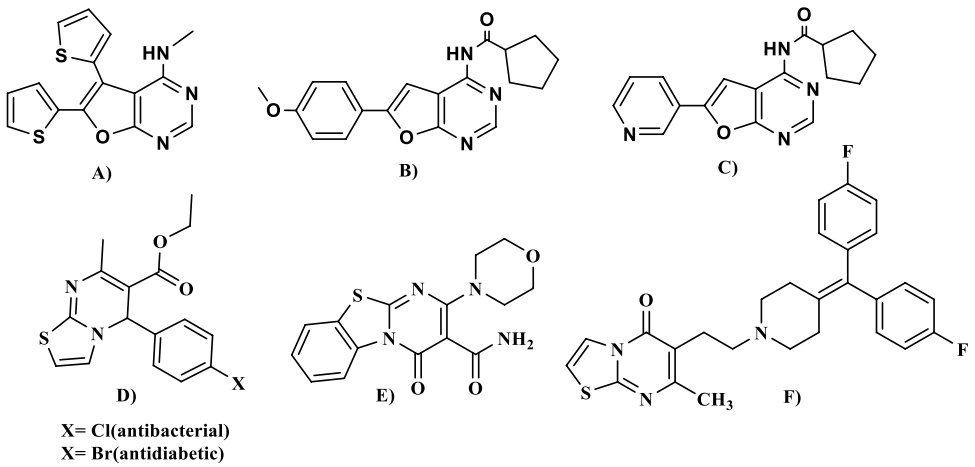
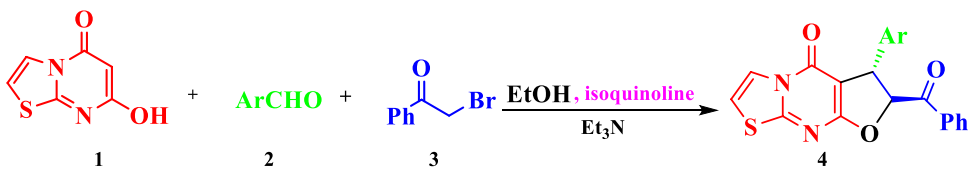


Fig. 1 Selected bioactive molecules containing furopyrimidine (A, B, C) and thiazolopyridimine (D, E, F) moiety



Scheme 1 Synthesis of furo[2,3-d]thiazolo[3,2-a] pyrimidin-5-ones **4**

Table 1 Solvent and base screening for synthesis of compound (**4aa**)

Entry	Solvent	Base	Yield (%)	Time (h)
1	EtOH/reflux	–	**10**	**24**
2	EtOH/reflux	DIPEA	70	4
3	EtOH/reflux	DBU	50	4
4	EtOH/reflux	DABCO	20	24
5	EtOH/reflux	K_2CO_3	25	24
6	EtOH/reflux	DMAP	60	4
7	**EtOH/reflux**	**Et_3N[a]**	**80**	**4**
8	EtOH/reflux	Et_3N[b]	40	4
9	EtOH/reflux	Et_3N[c]	80	4
10	EtOH/60 °C	Et_3N[a]	40	24
11	H_2O/reflux	Et_3N	10	24
12	CH_3CN/reflux	Et_3N	80	4
13	MeOH/reflux	Et_3N	70	24
14	THF/reflux	Et_3N	10	8
15	DMF/100 °C	Et_3N	10	6
16	CH_2Cl_2/r.t	Et_3N	20	11
17	–	Et_3N	36	24

Reaction condition: 5*H*-thiazolo[3,2-*a*]pyrimidine-5,7(6*H*)-dione (1 mmol), *p*-nitrobenzaldehyd (1 mmol), phenacyl bromide (1 mmol), isoquinolin (1 mmol)

[a]1 mmol

[b]0.5 mmol

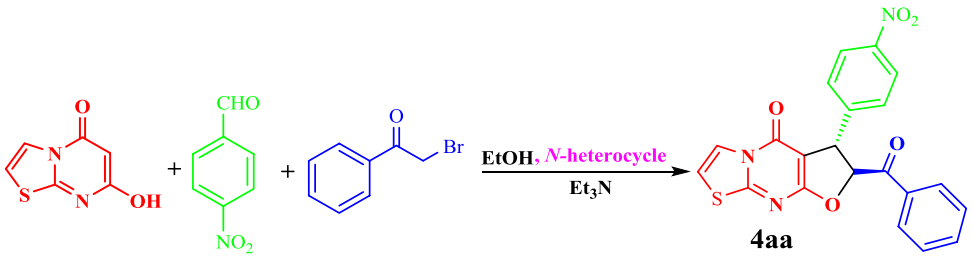
[c]1.5 mmol

Further experiments showed that the yield was decreased by taking the amount of 0.5 mmol of Et_3N. No significant improvement in the yield was observed when the amount was more than 1 mmol of Et_3N (Table 1, entries 7, 8 and 9). With regard to the effect of solvent, we performed the model reaction in EtOH, CH_3CN, DMF, H_2O, CH_2Cl_2, MeOH, THF and solvent-free condition (Table 1, entry 7 and 11–17). The results indicated that the most effective reaction occurred using EtOH, CH_3CN leading to a higher yield (Table 1, entry 7, 12).

Considering the view of green chemistry, we selected ethanol as a green solvent for this three-component reaction. Experiment was performed in the presence of 1 mmol Et_3N in ethanol at different temperatures (60 °C and refluxing condition) to observe the possible formation of product **4aa**. It was shown that the desired product **4aa** was provided with 40% and 80% yields, respectively (Table 1, entry 7, 10). The screening reveals that the reaction in ethanol as a green solvent with Et_3N as the base at reflux temperature gave the best result (Table 1, entry 7).

In the final step, we also examined a broad range of structurally diverse *N*-heterocycles like pyridine, quinoline, *N*-methyl imidazole, phenanthroline, Caffeine, and 4-methyl pyridine instead of isoquinoline to afford the corresponding products. The experimental data showed that using isoquinoline led to a higher yield and shorter reaction time in comparison with other *N*-heterocycle compounds (Table 2).

Table 2 Optimization of the reaction conditions using *N*-heterocyclic compound

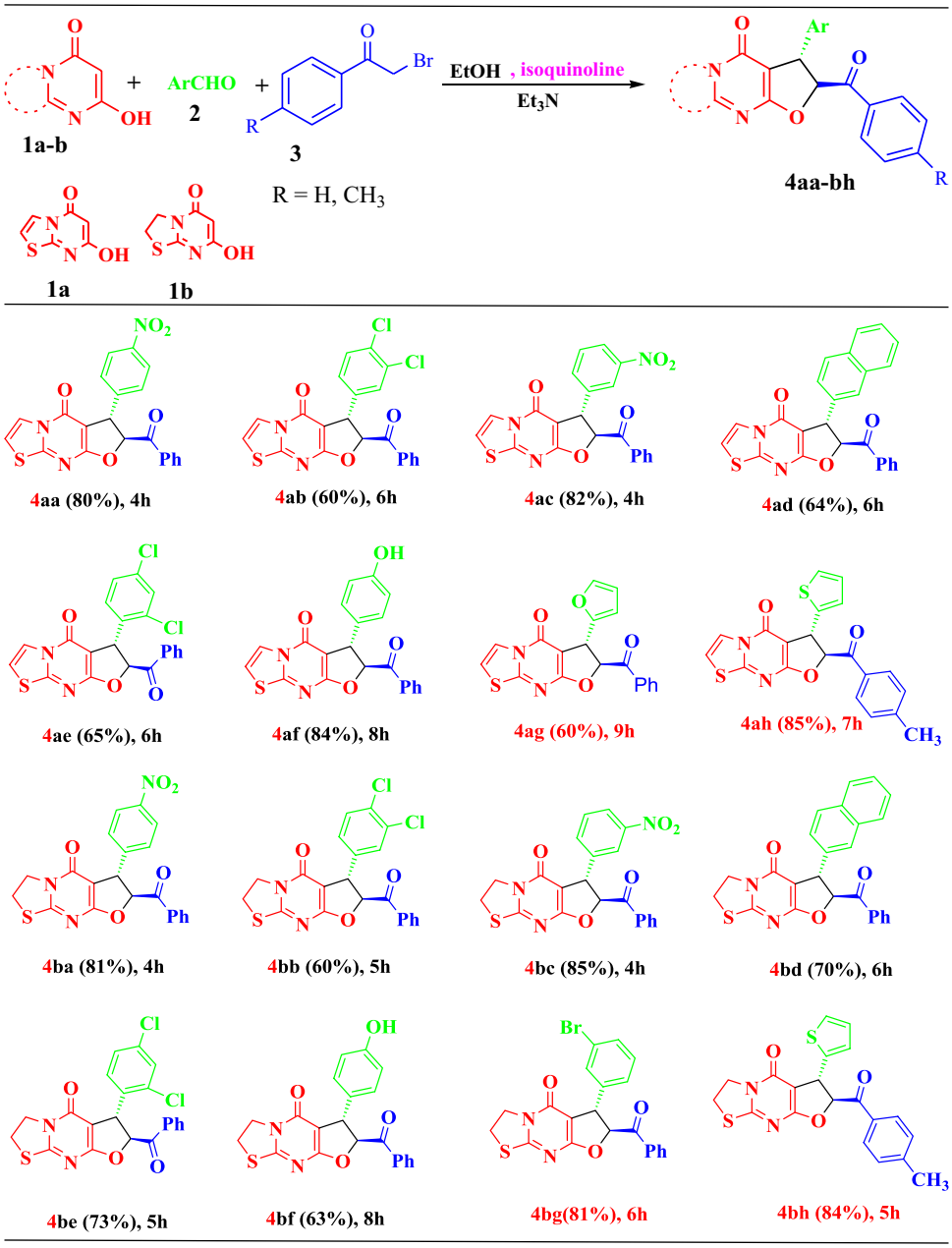


Entry	*N*-heterocycle	Base	Reaction condition	Time	Yield (%)[a]
1	Pyridine	DABCO	EtOH	24 h	Trace
2	Pyridine	Et_3N	EtOH	6 h	70
3	Pyridine	DIPEA	EtOH	6 h	70
4	Quinoline	DABCO	EtOH	24 h	Trace
5	N-methyl imidazol	Et_3N	EtOH	20 h	30
6	phenanthridine	Et_3N	EtOH	20 h	N.R
7	Caffeine	Et_3N	EtOH	20 h	Trace
8	**Isoquinoline**	**Et_3N**	EtOH	**4 h**	**80**
9	p-Me-pyridine	Et_3N	EtOH	20 h	Trace

Reaction condition: 5*H*-thiazolo[3,2-*a*]pyrimidine-5,7(6*H*)-dione (1 mmol), *p*-nitrobenzaldehyd (1 mmol), phenacyl bromide (1 mmol), *N*-heterocyclic (1 mmol) and base (1 mmol)

[a]Isolated yields

Table 3 Synthesis of fused 5*H*-furo[2,3-*d*]thiazolo[3,2-*a*]pyrimidin-5-ones



Reaction condition: heterocyclic-1,3-dione (1 mmol), aromatic aldehyde (1 mmol), isoquinoline (1 mmol), phenacyl bromide (1 mmol), triethylamine (1 mmol) and ethanol (10 ml)

[a]Isolated yield

Consequently, the result demonstrates that isoquinoline (1 mmol,) phenacyl bromide (1 mmol) *p*-nitrobenzaldehyd (1 mmol) and 5*H*-thiazolo[3,2-*a*]pyrimidine-5,7(6*H*)-dione (1 mmol) using 1 mmol Et_3N in ethanol under reflux conditions is the optimum reaction conditions in order to attain the efficient synthesis.

Under the optimized reaction conditions given in Table 1, entry 7 and Table 2, entry 8, the scope and limitations of this process were investigated. A variety of substrates, including two heterocyclic 1,3-dicarbonyls **1** (**a**–**b**), different aromatic aldehydes **2** (**a**–**h**), phenacyl bromide and paramethyl phenacyl bromide **3** and isoquinoline, were tested in this new multicomponent reaction. The results presented in Table 3

show that all the reactions proceeded smoothly to afford the corresponding products.

This result demonstrated that aromatic aldehydes carrying electron-withdrawing groups, *p*-nitro-benzaldehyde, *m*-nitro-benzaldehyde, 2,4-dichloro-benzaldehyde and 3,4-dichloro-benzaldehyde, *m*-bromo-benzaldehyde, heterocyclic aldehydes such as furan-2-carbaldehyde and thiophene-2-carbaldehyde reacted efficiently to generate the final products in good to excellent yields. The model reaction using 2-naphthaldehyde and *p*-HO-benzaldehyde was also performed efficiently, leading to corresponding products with good to high yields (Table 3). Our experiment has limitations to some extent. Benzaldehyde, 1-naphthaldehyde, *p*-methyl-benzaldehyde, p-methoxy-benzaldehyde, *p*-(*N*,*N*-dimethyl amino)-benzaldehyde and aliphatic aldehyde such as acetaldehyde were also examined, but all attempts to purify the product failed, and the use of column chromatography and screen chromatography for purification led to the decomposition of the product. Furthermore, the desired products were produced in traces when 4-Nitro-phenacyl bromide, 2-naphthacyl bromide and ethyl bromoacetate were employed instead of phenacyl bromide under the optimum reaction. Given all that, using ethanol as the medium of reaction prevented the usage of ecologically hazardous organic solvents.

The structure of products was clarified with IR, ^{1}H NMR, ^{13}C NMR spectroscopy, mass spectrometry, and elemental analysis. The mass spectra of these compounds exhibited molecular ion peaks at the appropriate *m/z* values (See Supplementary Material).

For example, the ^{1}H NMR spectrum of **4aa** contained two methine protons at 2,3-position dihydrofuran ring shows two doublets at 4.79 and 6.42 ppm ($J = 4.2$ Hz), the J values indicating that two methine proton are trans to each other. The signals due to vinyl protons were visible as two doublets at 7.42 and 7.85 with $J = 5.0$ Hz. Aromatic protons were demonstrated as multiplet in the aromatic region (7.46–7.66). Four aromatic protons in the benzene ring of the benzaldehyde moiety displayed two doublet signals at 7.83 ($J = 8.2$ Hz) and 8.1 ppm ($J = 8.2$ Hz). The assignment

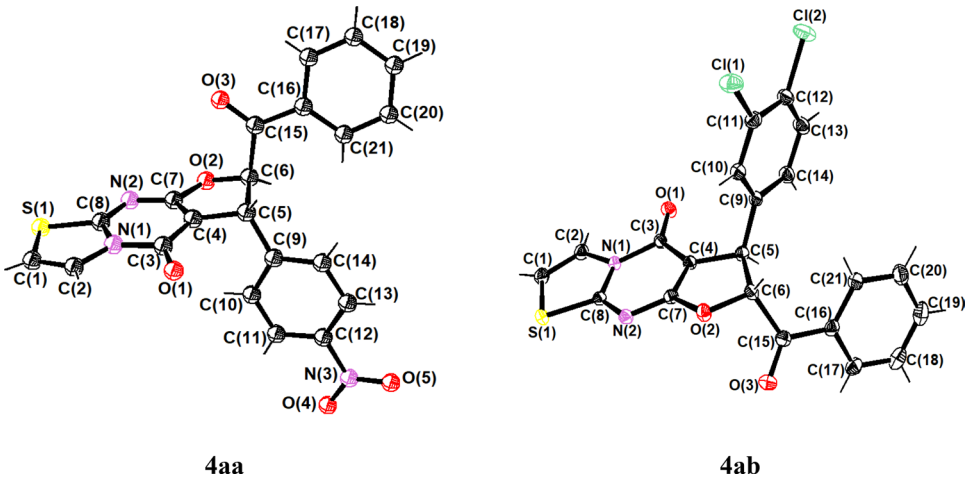
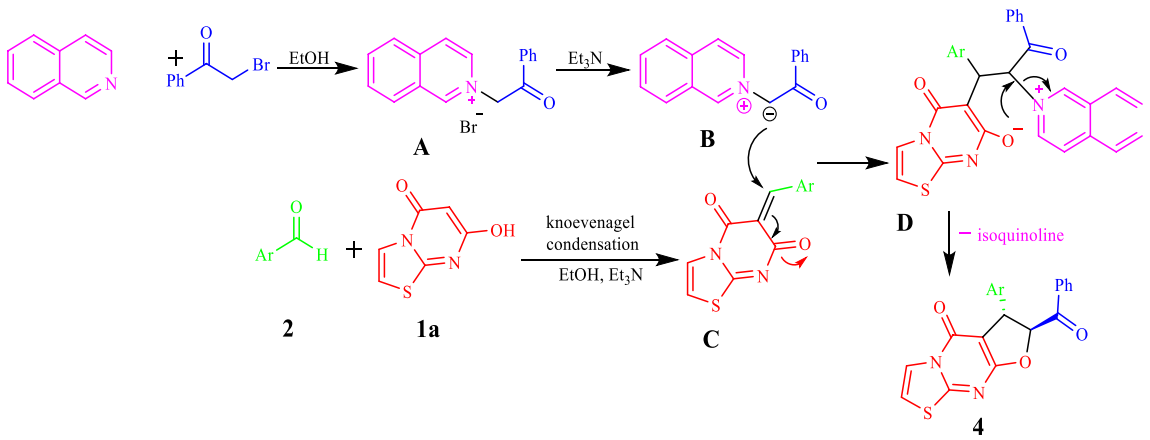


Fig. 2 ORTEP diagram for crystal structure of **4aa** and **4ab**



Scheme 2 Proposed mechanism for the one-pot formation of **4**

is supported by IR absorptions at 1696 and 1595 cm^{-1} (2 C=O). The proton-decoupled ^{13}C NMR spectrum of **4aa** showed 17 distinct resonances. One characteristic ^{13}C NMR signal due to the C=N carbons was observed at δ=165.9 ppm, and the carbonyl carbons appeared at δ=171.5, 193.8 ppm. Moreover, the structure of the fused trans-2,3-dihydrofuran derivatives **4aa**, **4ab** were further confirmed by means of single-crystal x-ray diffractometry (see Supplementary Material).

It appears that two protons in the 2,3-dihydrofuran ring are in trans-orientation (Fig. 2), (see Supplementary Material). The same structures were assumed for the other derivatives on the basis of their NMR spectroscopic similarities.

A proposed mechanism for this one-pot three-component reaction is shown in Scheme 2. The formation of the product can be explained as follows. The phenacyl bromide reacts with isoquinoline to form the corresponding isoquinolinium bromide **A**, which undergoes deprotonation in the presence of triethylamine to give the reactive isoquinolinium ylide **B** at room temperature. The aromatic aldehyde **2** reacts with 5*H*-thiazolo[3,2-*a*]pyrimidine-5,7(6*H*)-dione **1a** in the presence of Et_3N to give the Knoevenagel product **C**. The intermediate **C** reacts instantly with the isoquinolinium ylide **B** to form the zwitterionic intermediate **D**. The intermediate **D** undergoes cyclization with the elimination of isoquinoline to give the desired product **4** in a diastereoselective manner. In this proceeding, the cascade approach and the reaction sequence of Knoevenagel condensation/Michael-addition/intramolecular cyclization were completed in a single step in a one-pot system in EtOH.

Conclusion

In summary, we have successfully demonstrated an efficient three-component domino reaction for the synthesis of novel biologically interest three cyclic nitrogen-containing heterocycles via available starting materials. This synthetic strategy is high diastereoselective, eco-friendly, easy purification without chromatographic separation and a green route to generate the products in good-to-excellent yield, using cheap and commercially available reagents.

Experimental

Melting points were recorded on an Electrothermal type 9100 melting point apparatus and were uncorrected. The IR spectra were obtained on an Avatar 370 FTIR Thermo-Nicolet spectrometer. ^1H and ^{13}C NMR spectra were measured with a Bruker DRX-300 Avance spectrometer at 300.13 and 75.47 MHz, respectively. The mass spectra were scanned on a Varian Mat CH-7 at 70 eV. Elemental analysis was performed using a Thermo Finnigan Flash EA microanalyzer. Aldehydes, isoquinoline and other chemicals were purchased from Merck or Sigma–Aldrich and used without prior purification. 5*H*-thiazolo[3,2-*a*]pyrimidine-5,7(6*H*)-dione and 2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidine-5,7(6*H*)-dione were produced according to the previously reported procedures [44], and their spectroscopic data were described. Phenacyl bromide derivatives prepared by known method [45].

General procedure for the synthesis of 7-benzoyl-6-(phenyl)-6,7-dihydro-5*H*-furo[2,3-*d*]thiazolo[3,2-*a*]pyrimidin-5-one (4)

At first, phenacyl bromide **3** (1 mmol) and isoquinoline (1 mmol) were added to a 25-mL round-bottomed flask containing EtOH (5 mL) as solvent. The flask was fitted with a condenser, and the resulting mixture was stirred at room temperature. After the required time (10 min) for the formation of corresponding salt, 5*H*-thiazolo[3,2-*a*]pyrimidine-5,7(6*H*)-dione **1a** (1 mmol), aromatic aldehyde **2** (1 mmol), and Et_3N (1 mmol) as base were added into the reaction mixture and were heated under reflux conditions for appropriate times (Table 3). Upon the accomplishment of the reaction, monitored by TLC, the reaction mixture was cooled to room temperature, and the solid product was filtered and washed twice with ethanol (2 × 5 mL). The product **4aa**, **4ab** was more purified by crystallization (Ethanol/DMF) to prepare the desired crystals for single-crystal x-ray diffractometry (see Supplementary Material).

Supplementary material

Experimental procedures, characterization of synthesized products and X-ray diffraction data are accessible in supplementary information. [Copies of the NMR, IR and mass spectra are available].

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