



## One-pot, four-component sequential synthesis of novel 4-arylamino-5-carboxyl pyrimidine derivatives

Chengyuan Liang<sup>a,\*</sup>, Chunyang Shi<sup>a,c</sup>, Huihui Song<sup>a</sup>, Hailong Jiang<sup>b</sup> and Qizheng Yao<sup>b,\*</sup>

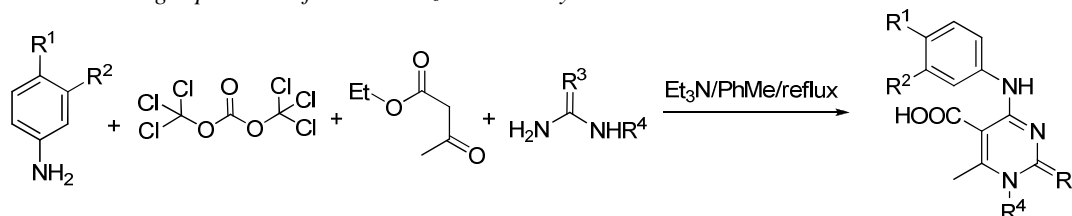
<sup>a</sup>Department of Pharmacy, Shaanxi University of Science & Technology, Xi'an, P. R. China

<sup>b</sup>School of Pharmacy, China Pharmaceutical University, Nanjing, P. R. China

<sup>c</sup>Shaanxi Institute of Agricultural Products Processing Technology, China

### ABSTRACT

An operationally simple, one-pot, three-step tandem method has been developed to afford 4-arylamino-5-carboxyl pyrimidine derivatives, which engages four reactive substrates (triphosgene, arylamine, ethyl acetoacetate, substituted ureas) employing triethylamine as catalyst. The key advantages of this unique, atom-economical reaction are short reaction time, high yields, simple workup, purification of products by non-chromatographic methods and avoiding separation of volatile hazardous isocyanate intermediates.

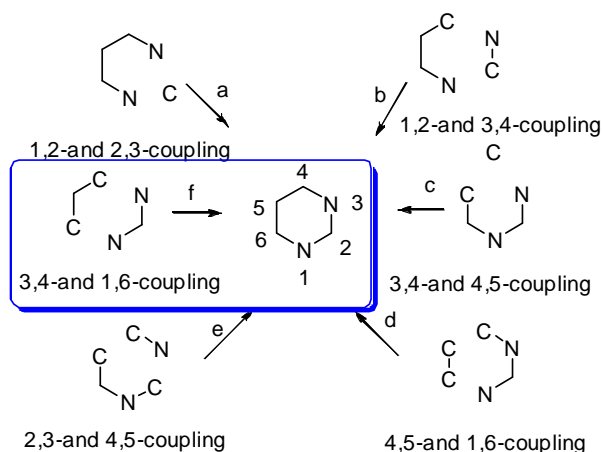


**Keywords:** Multi-component reactions (MCRs); Sequential synthesis; Isocyanate; Pyrimidine; One-pot

### INTRODUCTION

Among six-membered aromatic heterocycles, pyrimidines play central and peculiar roles as three nucleobases found in nucleic acids, cytosine (C), thymine (T), and uracil (U). In nature, pyrimidine is an important subunit in numerous natural products[1]. Both natural and synthetic pyrimidines demonstrate various biological and pharmacological activities such as anticonvulsant [2-4], cardiotoxic [5,6], vasorelaxant [7,8] and antitumor[ 9-11] properties.

Well established synthetic strategies of pyrimidine scaffolds include: 1,2- and 2,3-bond coupling reactions (path a); 1,2- and 3,4-bond coupling reactions (path b); 3,4- and 4,5-coupling reactions (path c); 4,5- and 1,6-bond coupling reactions (path d); 2,3- and 4,5-bond coupling reactions (path e); Pinner pyrimidine synthesis and Biginelli condensation(3,4- and 1,6-bond forming reactions, path f) [12-14]. Despite many methods being available for the synthesis of pyrimidine derivatives, their broad utility has accentuated the need to develop new synthetic routes for novel pyrimidine compounds.



Scheme 1: Strategies of pyrimidine synthesis

On the other hand, efficient high-throughput synthesis of organic compounds via multi-component reactions (MCRs) plays an important role in combinatorial chemistry and modern drug discovery[15] because of its capability to synthesize target compounds with greater efficiency and atom economy by generating structural complexity in a small cascade from three or more substrates[16]. Moreover, MCRs offer the advantage of synthetic simplicity and facility over conventional chemical reactions[17]. Up till now, much emphasis has been put on the implementation of numerous MCRs based on active carbonyl compounds (various aldehydes and ketones) [18,19]. In contrast, isocyanates have been intentionally or inadvertently ignored, partly due to its volatility, fugitiveness, acute lethality, sensory and pulmonary irritation[20]. As a greener tandem reaction including consecutive preparation and avoiding isolation of isocyanate is in urgent need, we turned our attention first to isocyanates, which are comparable to aldehydes and ketones in the Biginelli dihydropyrimidone synthesis.

## EXPERIMENTAL SECTION

All the substrates and solvents were commercially available and purified before use. Reactions were carried out under  $N_2$  using standard Schlenk technique. Mass spectra were recorded on a using electron impact ionization (EI) techniques. Compounds were visualized under UV lamp (254 nm).  $^1H$  NMR and  $^{13}C$  NMR spectra were obtained on a Bruker AV-300 NMR spectrometer. Analytical TLC was carried out with plates pre-coated with silicagel 60 F<sub>254</sub> (0.25 mm thick).

### 2.1. General experimental procedure for synthesis of 4-arylamino-5-carboxyl pyrimidines:

The order of addition of reagents was important in our tandem MCR reaction, A typical reaction was carried out in the following way under an optimized reaction condition. To a solution of  $Et_3N$  (30mmol) in toluene (150mL) was added triphosgene (6mmol) and phenylamine (11 mmol) at room temperature. The resulting mixture was stirred for 3h at 90 °C. After cooling to room temperature, ethyl acetoacetate (11 mmol) was added, which was stirred for 6 h. Whereafter the resulting mixture was added substituted urea (10 mmol) and refluxed for 4 h. On completion of the reaction indicated by TLC (n-hexane/ethylacetate: 40:60), the reaction mixture was cooled to room temperature. The miscible liquids (or suspension) was concentrated under reduced pressure, which was poured into cold water (50mL). The crude product was isolated by filtration that further purified by recrystallization (EtOH/ $H_2O$ : 80:20) to obtain an analytical sample.

### 2.2. Spectral data for new derivatives of trifurcate 4-arylamino-5-carboxyl pyrimidines 7a-m

#### 1,2-dihydro-1-phenyl-6-methyl -2-oxo-4-(m-tolylamino)-5-pyrimidinecarboxylic acid (7a)

White solid; Mp 219-221°C;  $^1H$ -NMR(300 MHz, DMSO)  $\delta$ : 11.78(1H, s), 10.42(1H, s), 7.6-6.8(9H, m), 2.29(3H, s), 1.93(3H, s);  $^{13}C$ -NMR(75 MHz, DMSO)  $\delta$ : 162.1, 161.5, 154.0, 150.2, 138.8, 137.9, 136.5, 129.5, 129.1, 128.9, 128.6, 124.2, 119.7, 116.4, 110.6, 21.1, 18.7; HRMS (EI) for  $(M+Na)^+$ : calcd 358.1168, found 358.1179

*1,2-dihydro-1-ethyl-6-methyl-2-oxo-4-(m-tolylamino)-5-pyrimidinecarboxylic acid (7b)*

White solid; Mp 207-210°C; <sup>1</sup>H-NMR(300 MHz, DMSO) δ: 11.59(1H, s), 10.50(1H, s), 7.5-6.8(4H, m), 3.81(2H, q, *J*=7.13), 2.37(3H, s), 2.28(3H, s), 1.16(3H, t, *J*=7.13); <sup>13</sup>C-NMR(75 MHz, DMSO) δ: 162.5, 160.9, 150.2, 149.5, 138.7, 138.0, 128.5, 124.1, 119.7, 116.4, 105.5, 35.1, 21.1, 18.1, 16.6; HRMS (EI) for (M+Na)<sup>+</sup>: calcd 310.1168, found 310.1173

*1,2-dihydro-1,6-dimethyl-2-oxo-4-(m-tolylamino)-5-pyrimidinecarboxylic acid (7c)*

White solid; Mp 203-205°C; <sup>1</sup>H-NMR(300 MHz, DMSO) δ: 11.59(1H, s), 10.31(1H, s), 7.5-6.8(4H, m), 3.34(3H, s), 2.38(3H, s), 2.29(3H, s); <sup>13</sup>C-NMR(75 MHz, DMSO) δ: 162.4, 161.1, 155.1, 150.6, 138.9, 137.9, 128.5, 124.2, 119.7, 116.4, 110.6, 30.6, 21.1, 17.5; HRMS (EI) for (M+Na)<sup>+</sup>: calcd 296.1011, found 296.1018

*1,2-dihydro-6-methyl-2-oxo-4-(m-tolylamino)-5-pyrimidinecarboxylic acid (7d)*

White solid; Mp 190-192°C; <sup>1</sup>H-NMR (300 MHz, DMSO) δ: 11.56(1H, s), 11.43(1H, s), 10.89(1H, s), 7.5-6.8(4H, m), 2.42(3H, s), 2.28(3H, s); <sup>13</sup>C-NMR(75 MHz, DMSO) δ: 164.0, 161.9, 158.6, 149.5, 138.7, 138.0, 128.6, 124.0, 119.9, 116.5, 104.7, 21.1, 18.6; HRMS (EI) for (M+Na)<sup>+</sup>: calcd 282.0855, found 282.0861

*1,2-dihydro-6-methyl-2-thioxo-4-(m-tolylamino)-5-pyrimidinecarboxylic acid (7e)*

White solid; Mp 164-166°C; <sup>1</sup>H-NMR(300 MHz, DMSO) δ: 11.58(1H, s), 11.47(1H, s), 10.89(1H, s), 7.5-6.8(4H, m), 2.41(3H, s), 2.28(3H, s); <sup>13</sup>C-NMR(75 MHz, DMSO) δ: 164.0, 161.9, 158.6, 149.5, 138.7, 138.0, 128.6, 124.0, 119.9, 116.6, 107.5, 21.1, 15.9; HRMS (EI) for (M+Na)<sup>+</sup>: calcd 275.3262, found 275.3278

*1,2-dihydro-6-methyl-2-imino-4-(m-tolylamino)-5-pyrimidinecarboxylic acid (7f)* Brown solid ;Mp 178-181°C; <sup>1</sup>H-NMR(300 MHz, DMSO) δ: 11.47(2H, s), 10.91(1H, s), 9.97(1H, s), 7.5-6.8(4H, m), 2.28(3H, s), 2.07(3H, s); <sup>13</sup>C-NMR(75 MHz, DMSO) δ: 165.8, 162.7, 159.4, 149.3, 136.3, 135.0, 128.0, 118.1, 117.6, 115.0, 110.4, 26.7, 20.8; HRMS (EI) for (M+Na)<sup>+</sup>: calcd 281.1014, found 281.1021

*1,2-dihydro-1-phenyl-6-methyl-2-oxo-4-((4-chlorophenyl)amino)-5-pyrimidinecarboxylic acid (7g)*. White solid; Mp 209-211°C; <sup>1</sup>H-NMR(300 MHz, DMSO) δ: 11.82(1H, s), 10.63(1H, s), 7.8-7.3(9H, m), 1.93(3H, s); <sup>13</sup>C-NMR(75 MHz, DMSO) δ: 162.3, 161.4, 154.2, 150.2, 137.8, 136.4, 129.5, 129.1, 128.9, 128.6, 127.1, 120.8, 110.4, 18.7; HRMS (EI) for (M+Na)<sup>+</sup>: calcd 378.0621, found 378.0639

*1,2-dihydro-1-ethyl-6-methyl-2-oxo-4-((4-chlorophenyl)amino)-5-pyrimidinecarboxylic acid (7h)*

White solid; Mp 221-223°C; <sup>1</sup>H-NMR(300 MHz, DMSO) δ: 11.13(1H, s), 10.34(1H, s), 7.7-7.3(4H, m), 3.87(2H, q, *J*=6.9Hz), 2.43(3H, s), 1.22(3H, t, *J*=6.9Hz); <sup>13</sup>C-NMR(75 MHz, DMSO) δ: 166.7, 162.7, 158.5, 143.7, 137.8, 137.7, 129.0, 128.9, 118.9, 115.2, 106.7, 30.2, 24.4, 21.8; HRMS (EI) for (M+Na)<sup>+</sup>: calcd 330.0621, found 330.0627

*1,2-dihydro-1,6-dimethyl-2-oxo-4-((4-chlorophenyl)amino)-5-pyrimidinecarboxylic acid (7i)*

White solid; Mp 206-209°C; <sup>1</sup>H-NMR(300 MHz, DMSO) δ: 11.09(1H, s), 9.63(1H, s), 7.5-7.3(4H, m), 3.09(3H, s), 2.37(3H, s); <sup>13</sup>C-NMR(75 MHz, DMSO) δ: 167.6, 164.5, 154.0, 148.3, 137.1, 136.8, 130.1, 123.0, 116.0, 110.3, 29.5, 16.3. HRMS (EI) for (M+Na)<sup>+</sup>: calcd 316.0465, found 316.0469

*1,2-dihydro-6-methyl-2-oxo-4-((4-chlorophenyl)amino)-5-pyrimidinecarboxylic acid (7j)*

White solid; Mp 195-197°C; <sup>1</sup>H-NMR(300 MHz, DMSO) δ: 11.55(2H, s), 11.02(1H, s), 7.7-7.3(4H, m), 2.40(3H, s); <sup>13</sup>C-NMR(75 MHz, DMSO) δ: 162.4, 161.1, 155.0, 150.6, 138.9, 137.9, 128.5, 124.2, 119.7, 110.6, 17.5; HRMS (EI) for (M+Na)<sup>+</sup>: calcd 302.0308, found 302.0314

*1,2-dihydro-6-methyl-2-thioxo-4-((4-chlorophenyl)amino)-5-pyrimidinecarboxylic acid (7k)*

White solid; Mp 166-168°C; <sup>1</sup>H-NMR (300 MHz, DMSO) δ: 12.90(1H, s), 12.65(1H, s), 10.79(1H, s), 7.7-7.3(4H, m), 2.37(3H, s); <sup>13</sup>C-NMR(75 MHz, DMSO) δ: 166.5, 159.3, 154.2, 150.7, 142.9, 138.3, 129.3, 123.1, 121.1, 117.7, 106.7, 24.5; HRMS (EI) for (M+Na)<sup>+</sup>: calcd 318.0080, found 318.0086

*1,2-dihydro-6-methyl-2-imino-4-((4-chlorophenyl)amino)-5-pyrimidinecarboxylic acid (7l)*

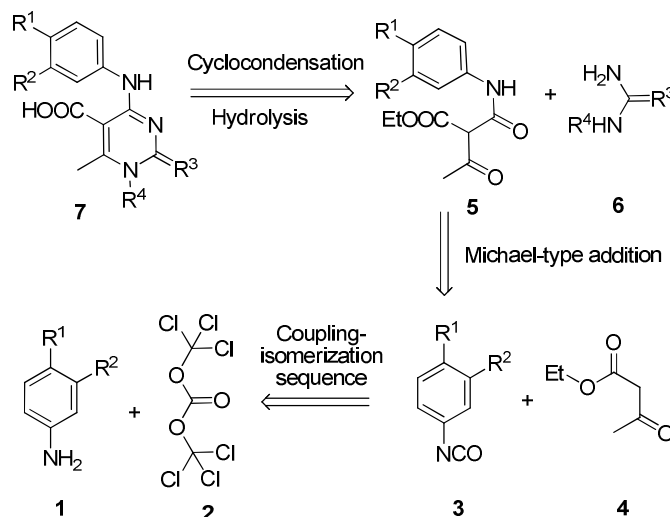
Brown solid ;Mp 171-173°C; <sup>1</sup>H-NMR (300 MHz, DMSO) δ: 11.51(2H, m), 10.91(1H, s), 9.49(1H, m), 7.5-7.1(4H, m), 2.33(3H, s); <sup>13</sup>C-NMR(75 MHz, DMSO) δ: 166.7, 162.7, 153.5, 143.7, 137.9, 137.8,129.0, 118.8, 115.2, 106.7, 21.8; HRMS (EI) for (M+Na)<sup>+</sup>: calcd 301.0468 ,found 301.0476

*1,2-dihydro-6-methyl-2-oxo-4-(phenylamino)-5-pyrimidinecarboxylic acid (7m)*

White solid; Mp 206-208°C; <sup>1</sup>H-NMR (300 MHz, DMSO) δ: 11.15(1H, s), 9.9(2H, s), 8.1-7.0(5H, m), 2.21(3H, s); <sup>13</sup>C-NMR(75 MHz, DMSO) δ: 166.7, 158.5, 155.1, 154.6, 137.8, 137.7, 129.0, 128.9, 122.5, 118.8, 106.7, 24.4; HRMS (EI) for (M+Na)<sup>+</sup>: calcd 268.0698, found 268.0706

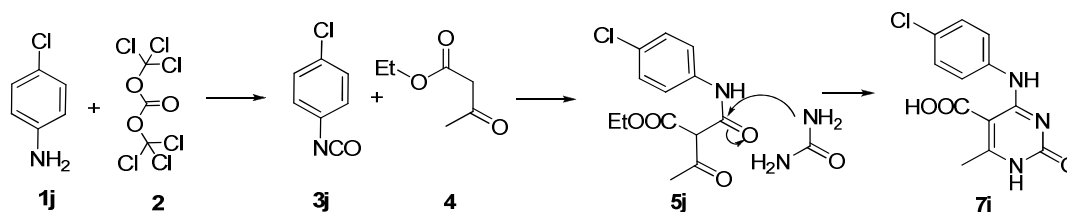
## RESULTS AND DISCUSSION

Many former studies have established the procedure that isocyanate rendered by primary amine and phosgene[21]. Based on this approach, we have suggested for the synthesis of aromatic isocyanate via condensation of arylamine with triphosgene as a safer substitute for phosgene utilizing triethylamine as catalyst[22]. Moreover, in order to synthesize cytosine derivatives **7**, our retro-synthetic analysis indicates the relay moiety **5** can be formed from isocyanate group in situ by Michael-type addition with ethyl acetoacetate. Subsequent nucleophilic cyclization of urea **3** followed by hydrolysis of the ester group affords the corresponding terminal product **7**.



Scheme 2: Retro-synthetic concept for the four component cytosine analogs synthesis

As mentioned above, we found a strategy to synthesize cytosine derivatives **7a-m** via a one-pot consecutive three-step process. In an initial endeavor, to search for the appropriate reaction medium, the template reaction (Scheme. 3) between 4-chloroaniline **1j** (1mmol), triphosgene **2** (0.6mmol), ethyl acetoacetate **4** (1.1 mmol) and urea (1.1 mmol) was examined in several reaction catalysts and solvents (Table 1). In case of triethylamine was selected as the activator in refluxing toluene, to our delight, we observed the precipitation of desired product **7j** after the volume has been reduced by evaporation followed by the addition of cold water. As depicted in Table 1, although the multi-component reaction could be efficiently carried out in most of the aprotic alkaline solvent system, the use of three-fold equivalent stoichiometric Et<sub>3</sub>N combining with non-polar aprotic solvents resulted in consistently slightly higher yields and shorter reaction time (entries 1 and 9) compared with other bases in polar aprotic solvents (entries 11 and 13 ). These findings could be accounted for the non-polar aprotic “solvent effect” in this multi-component reaction. The best results were obtained in the presence of toluene, of which attributed to its fabulous dissolving capacity of all components and intermediates. Therefore, toluene and triethylamine were selected as the reaction medium for all further chemical reactions.



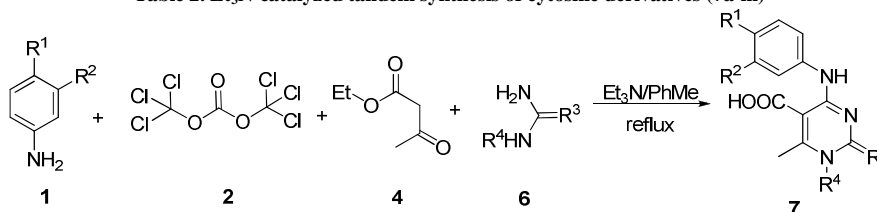
Scheme 3: Representative synthetic route for 7j

Table 1. Optimization of reaction conditions for the formation of 7j

Entry	Catalyst(eq.) <sup>a</sup>	Solvent	Total time(h)	Yield(%) <sup>b</sup>
1	Et <sub>3</sub> N(3)	Toluene	4	55
2	Pyridine(3)	Toluene	6	42
3	DABCO(1)	Toluene	4	Trace
4	DMAP(1)	Toluene	4	14
5	DBU(1)	Toluene	4	26
6	Imidazole(3)	Toluene	4	Trace
7	Morpholine(3)	Toluene	8	Trace
8	None	Toluene	4	None
9	Et <sub>3</sub> N(3)	ClCH <sub>2</sub> CH <sub>2</sub> Cl	4	51
10	Et <sub>3</sub> N(3)	THF	4	43
11	Et <sub>3</sub> N(3)	DMF	5	27
12	Et <sub>3</sub> N(3)	EtOH	5	None
13	Et <sub>3</sub> N(3)	Acetonitrile	5	28

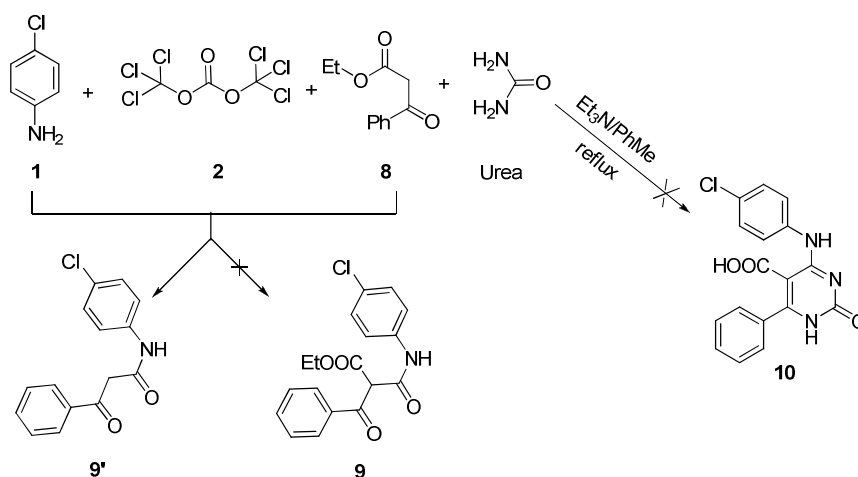
<sup>a</sup> eq.=equivalent; <sup>b</sup> Isolated yields.

Structurally diverse arylamines (bearing electron withdrawing or electron releasing groups) were submitted to this reaction successfully, and corresponding products were obtained in good to excellent yields. As shown in Table 2, the electronic nature of substituent on the aromatic ring of primary amines did not show any remarkable effect in terms of yields, under the same reaction conditions. Nevertheless, substituted ureas bearing electron-donating groups (such as ethyl group) persistently and significantly increased the yields. This phenomenon is consistent with the electron-donating capabilities of substituted ureas (Et->Me->H-). Although phenyl ring is an electron-withdrawing fragment of sp<sup>2</sup>-hybridized system (phenyl ring is in a conjugation with amino-group), phenylurea provided the highest yields (entry a and entry g). It is noteworthy to mention that easy hydrolysis of ester groups on the final stage under action of water produced in situ of cycloaddition rendered 5-carboxy group, which remain intact after the reaction and can obviously serve in further functionalizations to produce molecular diversity. The structures of isolated new products **7a-m** were determined by physical and spectroscopic data such as: <sup>1</sup>H-NMR, <sup>13</sup>C-NMR, NOESY and ESI-HRMS spectra.

Table 2. Et<sub>3</sub>N-catalyzed tandem synthesis of cytosine derivatives (7a-m)

Entry	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	Product	Isolated Yield(%)
a	H	Me	O	Ph	<b>7a</b>	87
b	H	Me	O	Et	<b>7b</b>	81
c	H	Me	O	Me	<b>7c</b>	63
d	H	Me	O	H	<b>7d</b>	51
e	H	Me	S	H	<b>7e</b>	59
f	H	Me	N	H	<b>7f</b>	26
g	Cl	H	O	Ph	<b>7g</b>	89
h	Cl	H	O	Et	<b>7h</b>	73
i	Cl	H	O	Me	<b>7i</b>	57
j	Cl	H	O	H	<b>7j</b>	55
k	Cl	H	S	H	<b>7k</b>	46
l	Cl	H	N	H	<b>7l</b>	32
m	H	H	O	H	<b>7m</b>	81

Encouraged by these results, we investigated an expeditionary reaction utilizing ethyl benzoylacetate **8** instead of ethyl acetoacetate **4** (Scheme 4) to further explore the realm and illustrate the utility of our depicted domino MCR. Disappointingly, the corresponding reaction solution turned out to be mixture under the same condition without rendering expectative molecular **10** according to mass spectrometric analysis, instead the unexpected *N*-(4-chlorophenyl)-3-oxo-3-phenylpropanamide **9'** was obtained as byproduct in one pot without adding any additional reagents. We envisioned that the intermediate **9** was thermally unstable, which readily converted into **9'** by eliminating ethoxycarbonyl group.



Scheme 4: An expeditionary synthesis of **12** ignited by ethyl benzoylacetate

## CONCLUSION

In summary, our work is devoted to an efficient and straightforward synthesis of 1,2-dihydro-6-methyl-4-aryl-amino-5-pyrimidinecarboxylic acids, which are promising biologically active compounds. The method proceeds via sequential aromatic isocyanate forming reaction and in situ Michael-type addition with ethyl acetoacetate affording a tri-carbonyl intermediate followed by an intermolecular cycloaddition with ureas. This approach has several inimitable advantages such as milder conditions, higher yields, shorter reaction time, and greener work-up, which would widen significantly the versatility and scope of the carbonyl-based MCRs. Additionally, substrate scope, multicomponent examples, and mechanistic insights also have been discussed.

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