# New One-Pot Four-Component Synthesis of Disubstituted Pyrido[2,3-*d*]pyrimidine-6-carboxamide Derivatives

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In this work, 1,2,3,4,5,8-hexahydro-1,3,7-trimethyl-2,4-dioxopyrido[2,3-*d*]pyrimidine-6-carboxamide derivatives were synthesized in a simple and efficient method from the four-component condensation reaction of diketene, an aliphatic or aromatic amine, an aromatic aldehyde, and 6-amino-1,3-dimethyluracil in the presence of a catalytic amount of *p*-toluenesulfonic acid under mild conditions at ambient temperature in high yields.



## Introduction

Multicomponent[1] and domino[2] reactions allow the creation of several bonds in a single operation and are attracting increasing attention as one of the most powerful emerging synthetic tools for the creation of molecular diversity and complexity.[3] They also have considerable advantages in terms of user and environmental friendliness because of the step reduction and atom economy associated to their use.

Several fused pyrimidines and pyrido[2,3-*d*]pyrimidines were synthesized and evaluated for antibacterial activities.[4−6] Pyrido[2,3-*d*]pyrimidine ring system is present in a number of biologically active compounds which includes antitumor,[7] antipyretic,[8] analgesic,[9] antihistaminic,[10] PDE4 inhibitor,[11] adenosine kinase inhibitor,[12] tyrosine kinase inhibitor,[13] and diuretic[14,15] activities. As an example, 5-deaza isostere 4,7-diamino-*N*-(2-morpholinoethyl)-2-phenylpyrido[2,3-*d*]pyrimidine-6-carboxamides have been reported as potential diuretic agents.[16]

Within the framework of developing libraries of the aforementioned bioactive compounds and in continuing of our interest in multicomponent reactions (MCRs),[17] we are currently investigating the synthesis of various 1,2,3,4,5,8-hexahydro-1,3,7-trimethyl-2,4-dioxopyrido[2,3-*d*]pyrimidine-6-carboxamide derivatives **5** via a one-pot four-component condensation of amines **1**, diketene **2**, aldehydes **3**, and 6-amino-1,3-dimethyluracil **4** in the presence of *p*-toluenesulfonic acid (*p*-TsOH·$H_2O$) as a catalyst in high yields in $CH_2Cl_2$ at ambient temperature (Scheme 1).

## Results and Discussion

In a pilot experiment, the reaction of *N*-alkyl-3-oxobutanamide **6**, which was derived from the addition of a benzyl amine **1** to diketene with 4-chlorobenzaldehyde and 6-amino-1,3-dimethyluracil in the presence of *p*-TsOH·$H_2O$ as a catalyst proceeds in dichloromethane at ambient temperature. The progress of the reaction was monitored by TLC. After completion of the reaction after 8 h, the product *N*-benzyl-5-(4-chlorophenyl)-1,2,3,4,5,8-hexahydro-1,3,7-trimethyl-2,4-dioxopyrido[2,3-*d*]pyrimidine-6-carboxamide **5a** was obtained in 83% yield.

We have shown that the use of a wide diversity of substituents in amines **1** and aromatic aldehydes **3** in this four-component reaction makes possible the synthesis of libraries under similar circumstances. The results are shown in Table 1. As anticipated from our original results, these reactions proceeded very cleanly under mild conditions at room temperature, and no undesirable side reactions were

**Scheme 1.** Synthesis of 1,2,3,4,5,8-Hexahydro-1,3,7-trimethyl-2,4-dioxopyrido[2,3-*d*]pyrimidine-6-carboxamides **5a**−**s**

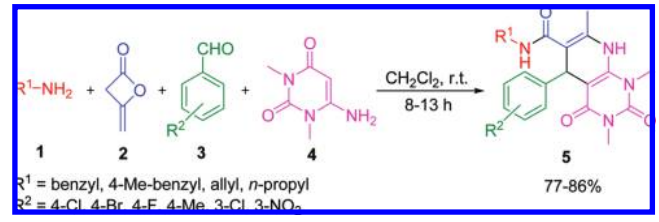


**Table 1.** 1,2,3,4,5,8-Hexahydro-1,3,7-trimethyl-2,4-dioxopyrido-[2,3-*d*]pyrimidine-6-carboxamide Derivatives **5a**−**s**

| entry | amine | aldehyde | product | time (h) | yield[a] (%) |
|---|---|---|---|---|---|
| 1 | benzyl | 4-chlorobenzaldehyde | **5a** | 8 | 83 |
| 2 | benzyl | 3-nitrobenzaldehyde | **5b** | 9.5 | 81 |
| 3 | benzyl | 3-chlorobenzaldehyde | **5c** | 8 | 85 |
| 4 | benzyl | 4-fluorobenzaldehyde | **5d** | 10 | 83 |
| 5 | benzyl | 4-methylbenzaldehyde | **5e** | 13 | 79 |
| 6 | benzyl | 4-bromobenzaldehyde | **5f** | 9 | 86 |
| 7 | 4-methylbenzyl | 4-chlorobenzaldehyde | **5g** | 9 | 82 |
| 8 | 4-methylbenzyl | 3-nitrobenzaldehyde | **5h** | 11 | 78 |
| 9 | 4-methylbenzyl | 3-chlorobenzaldehyde | **5i** | 9.5 | 79 |
| 10 | 4-methylbenzyl | 4-methylbenzaldehyde | **5j** | 14 | 78 |
| 11 | allyl | 4-chlorobenzaldehyde | **5k** | 10.5 | 80 |
| 12 | allyl | 3-chlorobenzaldehyde | **5l** | 10 | 81 |
| 13 | allyl | 4-fluorobenzaldehyde | **5m** | 9.5 | 77 |
| 14 | allyl | 4-methylbenzaldehyde | **5n** | 12.5 | 78 |
| 15 | allyl | 4-bromobenzaldehyde | **5o** | 11 | 83 |
| 16 | *n*-propyl | 4-chlorobenzaldehyde | **5p** | 9.5 | 84 |
| 17 | *n*-propyl | 3-nitrobenzaldehyde | **5q** | 10.5 | 79 |
| 18 | *n*-propyl | 3-chlorobenzaldehyde | **5r** | 11 | 80 |
| 19 | *n*-propyl | 4-methylbenzaldehyde | **5s** | 13 | 77 |

[a] Isolated yield.

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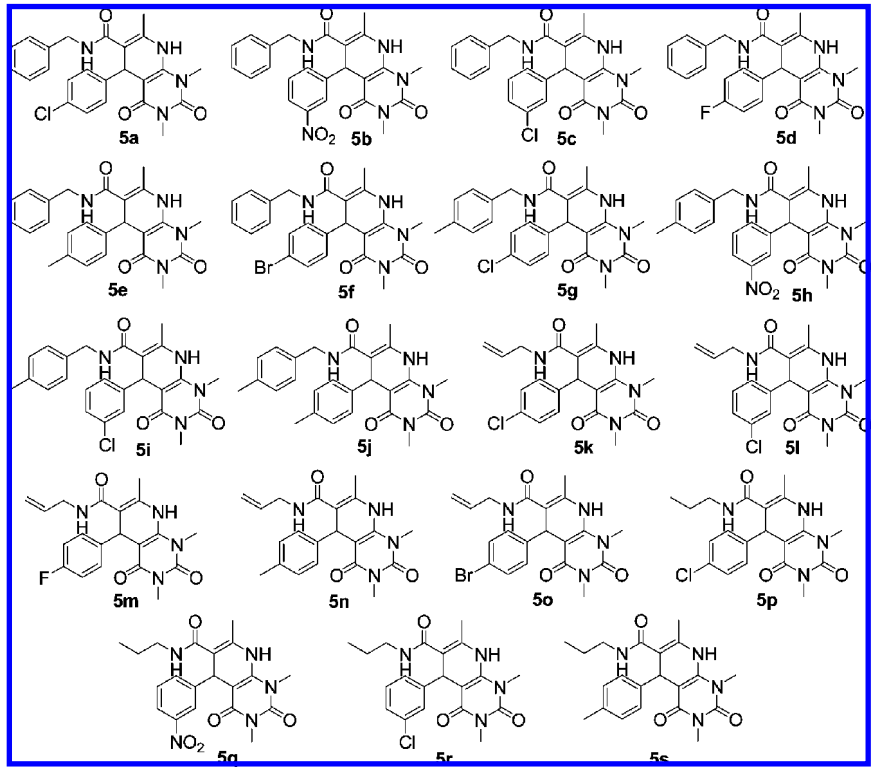
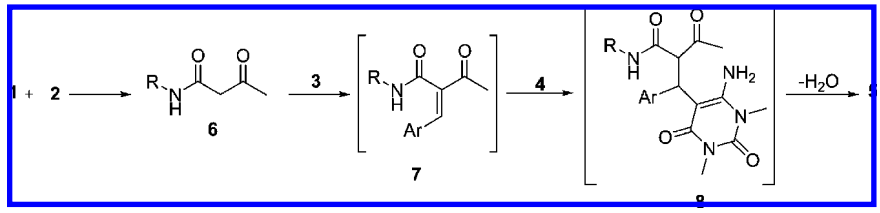



**Figure 1.** Structure of products **5a**−**s**.

**Scheme 2.** Possible Mechanism for the Formation of Products **5a**−**s**




observed. All compounds described in the paper were synthesized for the first time.

The aromatic aldehydes carrying both electron-withdrawing and electron-releasing substituents were also converted to their corresponding 1,2,3,4,5,8-hexahydro-1,3,7-trimethyl-2,4-dioxopyrido[2,3-*d*]pyrimidine-6-carboxamide derivatives in good yields. It is noteworthy that the reactions of halosubstitueted benzaldehydes proceeded with the expected mechanism and exhibit excellent yields. We have also examined the aliphatic amines to survey the scope and generality of this reaction; thus allylamine and propylamine were successfully reacted under the same reaction conditions (entries 11−19).

The reaction proceeds under mild conditions and is compatible with a wide range of functional groups. Two substituents in the products can be varied independently of each other. Representative examples of this reaction are shown in Figure 1.

Compounds **5a**−**s** are stable solids whose structures were established by IR, $^1$H, and $^{13}$C NMR spectroscopy, mass spectrometry, and elemental analysis. The mass spectra of products **5a**−**s** displayed molecular ion peaks at appropriate values, which were consistent with the proposed 1:1:1:1 adduct of amine **1**, diketene, aldehyde **2**, and 6-amino-1,3-dimethyluracil.

The possible mechanism for the formation of products **5a**−**s** is shown in Scheme 2. It is reasonable to assume that **7** results from initial addition of an aldehyde **3** to *N*-alkyl-3-oxobutanamide **6**, which derived from the addition of an amine **1** to diketene **2**. Then, the subsequent Michael-type addition of the 6-amino-1,3-dimethyluracil **4** to **7**, followed by an intramolecular condensation reaction of intermediate **8** to afford the corresponding product **5** (Scheme 2).

## Conclusions

In summary, we demonstrated an effective one-pot four-component approach for the synthesis of 1,2,3,4,5,8-hexahydro-1,3,7-trimethyl-2,4-dioxopyrido[2,3-*d*]pyrimidine-6-carboxamide derivatives via cyclocondensation reaction of primary aliphatic or aromatic amines, diketene, 6-amino-1,3-dimethyluracil, and aromatic aldehydes in $CH_2Cl_2$ by using *p*-TsOH·$H_2O$ at ambient temperature. All of the products were prepared with high purity and in good yields using very simple and accessible starting materials. The two variable groups derived from easily available aliphatic or aromatic amines and electron-withdrawing or electron-releasing sub-

stituted benzaldehydes. We hope that these new classes of compounds could be provided for biological screening.

## Experimental Section

**Typical Procedure for the Synthesis of *N*-Benzyl-5-(4-chlorophenyl)-1,2,3,4,5,8-hexahydro-1,3,7-trimethyl-2,4-dioxopyrido[2,3-*d*]pyrimidine-6-carboxamide (5a).** To a magnetically stirred solution of benzylamine (0.107 g, 1.0 mmol) and diketene (0.084 g, 1.0 mmol) in 5 mL dry $CH_2Cl_2$ for 2 h were added 4-chlorobenzaldehyde (0.140 g, 1.0 mmol), 6-amino-1,3-dimethyuracil (0.155 g, 1.0 mmol), and *p*-TsOH·$H_2O$ (0.019 g, 0.1 mmol), simultaneously. The reaction mixture was allowed to stir for 6 h until the precipitate was appeared. After completion of the reaction, as indicated by TLC (EtOAc/*n*-hexane, 1:2), the reaction mixture was filtered off and the residue was washed with water and then with ethanol to give **5a** as white powders (0.37 g, 83%): mp 286−288 °C; IR (KBr) $cm^{-1}$ 3427, 3284, 3080, 2928, 1691, 1614, 1514, 1443, 1398; $^1$H NMR (300.13 MHz, DMSO-$d_6$) $\delta$ 2.10 (3H, s, $CH_3$), 3.06 (3H, s, $NCH_3$), 3.40 (3H, s, $NCH_3$), 4.10−4.30 (2H, m, $CH_2$), 4.94 (1H, s, CH), 6.90−6.93 (2H, m, H−Ar), 7.16−7.30 (7H, m, H−Ar), 8.20−8.30 (2H, m, NH and NHCO); $^{13}$C NMR (75.47 MHz, DMSO-$d_6$) $\delta$ 17.8, 27.9, 30.3 ($CH_3$), 42.4 ($CH_2$), 87.3 (CH), 111.1, 126.9, 127.3, 128.2, 128.4, 130.2, 131.1, 133.9, 140.0, 145.1, 145.3 (C−Ar and C═C), 151.1, 161.1, 168.0 (CO); MS *m*/*z* 453 ($M^+$ + 1, $^{37}$Cl, 3), 452 ($M^+$, $^{37}$Cl, 9), 451 ($M^+$ + 1, $^{35}$Cl, 10), 450 ($M^+$, $^{35}$Cl, 23), 435 (25), 339 (100), 316 (85), 232 (27), 106 (25), 91 (78), 65 (15), 42 (13). Anal. Calcd for $C_{24}H_{23}ClN_4O_3$: C, 63.93; H, 5.14; N, 12.43; found C, 63.97; H, 5.20; N, 12.36.

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**Supporting Information Available.** Experimental procedures and mass, IR, $^1$H NMR, and $^{13}$C NMR spectra for compounds **5a**−**s**. This material is available free of charge via the Internet at http://pubs.acs.org.

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