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Practical synthesis and mechanistic study of polysubstituted tetrahydropyrimidines with use of domino multicomponent reactions

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ABSTRACT

The practical synthesis of polysubstituted tetrahydropyrimidines **4** from but-2-ynedioates **1**, amines **2**, and formaldehyde **3** through a domino process of one-pot multicomponent reactions (MCRs) and the detailed mechanistic studies are described. The MCRs were performed under extremely mild reaction conditions and offered the desired products in excellent yields. The detailed studies on the mechanism of the MCRs proved that: (1) the proton-promoted domino sequence is composed of hydroamination, aza–ene-type reaction, nucleophilic addition, and dehydration–cyclization; (2) solvents could control the hydroamination stereoselectivity of **1** and **2**: *Z*-isomers in proton solvents with *Z*/*E* up to 95:5 and *E*-isomers in non-proton solvents with *E*/*Z* up to 98:2, and *Z*-isomers are more stable than *E*-isomers; (3) *Z*- and *E*-enamine intermediates led to the same desired products via aza–ene-type reaction model. Calculations verified the aza–ene-type process in the MCRs.

1. Introduction

For the recent two decades, tetrahydropyrimidines have received significant attention for their diverse biological activity,[1] and have served as M_1 muscarinic receptor agonists for treatment of Alzheimer's diseases,[2] human immunodeficiency virus (HIV) protease inhibitors,[3] and other inhibitors against mycobacterium tuberculosis,[4] etc. Structure–activity relationship studies of their polysubstituted derivatives showed that the substituent groups on tetrahydropyrimidine ring are all critical for the activity.[4,5] Besides their interesting bioactivities, these compounds are also versatile building blocks in synthetic organic chemistry.[6] However, very few examples have been presently reported on the synthetic methods for polysubstituted 1,2,3,4-tetrahydropyrimidines (Fig. 1),[2b,7–10] and in the cases, whatsoever, they have not been entirely satisfactory due to drawbacks such as poor yields, complex procedure, or the difficulties in obtaining starting materials. Thus, establishment of practical synthetic methods for the rapid construction of tetrahydropyrimidine rings from readily available starting materials remains to be one of the major challenges in modern organic synthesis.

One-pot multicomponent reactions (MCRs) have emerged as a powerful tool in synthetic organic chemistry because of their significant advantages.[11] Recently our research group has developed a new kind of MCRs leading to the formation of 1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylates **4**, a class of important heterocyclic rings with α- and β-amino acid blocks.[12a] Quite recently this protocol has been broadened to the MCRs of asymmetric electron-deficient alkyne, amines, and formaldehyde.[12b] The MCRs involve the following domino reactions: hydroamination, Mannich-type reaction, nucleophilic addition, and dehydration–cyclization process. This methodology has provided great advantages, such as atom economy, simplified procedure, excellent yields, and molecular diversity. In addition, the obtained products have been attractive targets in the primary evaluation against human hepatoma cell line HepG2 in vitro, thereby showing potential as clinical pharmaceuticals or synthetic intermediates.

In spite of the numerous advantages, the methodology of the MCRs is likely to be improved based on results obtained in mechanistic studies. A more practical and atom-economic multicomponent synthesis of **4** from readily obtained starting materials would be a more versatile and convenient route to the synthesis of high structural diversity of pharmaceutical compounds. Therefore, considerable effort has been dedicated to the development of the synthesis and mechanism of the MCRs. Herein, we describe a more efficient and practical synthesis method and a more reasonable reaction mechanism of the MCRs.

2. Results and discussion

2.1. Development and optimization of the protocol

Our approach to the development of a more practical, atom-economic protocol for the MCRs was targeted toward the reaction of ethyl

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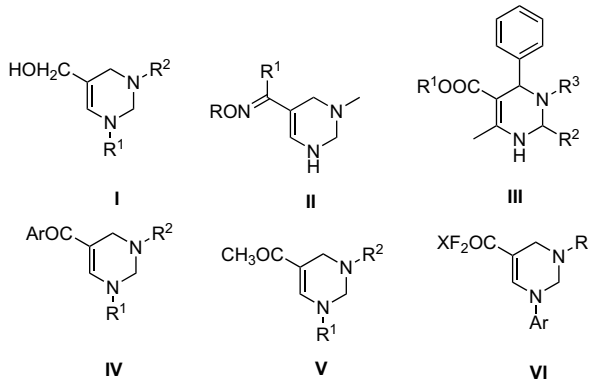


Figure 1. The reported 1,2,3,4-tetrahydropyrimidines.

but-2-ynedioate **1a**, aniline **2a**, and formaldehyde **3** in the presence of Brønsted acids. Brønsted acids have increasingly been used as catalysts in many types of reactions,[13] for example, Mannich reactions,[14] Michael-type additions,[15] because of their capability in accomplishing reactions under mild conditions. On the basis of this consideration, we assumed that the MCRs would proceed smoothly in the presence of a Brønsted acid as well. We first allowed **1a** to react with 2.0 equiv of aniline **2a**, 4.0 equiv of **3**, and 2.0 equiv of acetic acid (AcOH) in MeOH at room temperature. The MCR completed almost instantly (determined by TLC) and afforded diethyl 1,2,3,6-tetrahydro-1,3-diphenylpyrimidine-4,5-dicarboxylate **4aaa** with 98% isolated yield.

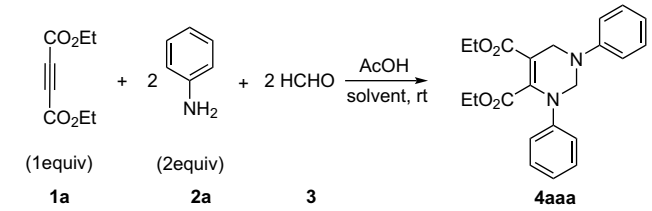
We then turned our attention to screening of the reaction conditions. During this process, MeOH was found to be more appropriate solvent (Table 1, entries 1 and 2), and the least amount of **3** for the MCR is 3.0 equiv (Table 1, entries 1, 6, and 7). By decreasing the amount of AcOH, a significant decrease in the reaction rate and product yield was observed for the MCR (Table 1, entries 1 and 3–5). Therefore, the optimal reaction conditions were determined as follows: mole ratio of **1**/**2a**/**3**/**2a**/AcOH=1:1:3:1:2 in MeOH at room temperature. Under optimal reaction conditions, product **4aaa** could be afforded as pure lemon crystal from reaction solution after one day, which was suitable for X-ray measurements (Fig. 2).

2.2. Synthesis of 4 under optimized reaction conditions

But-2-ynedioates **1**, formaldehyde **3**, and different kinds of amines **2** were subjected to the MCRs under the optimal reaction conditions, and the most representative results obtained are collected in Table 2. In an effort to obtain further evidence regarding the mechanism, we compared the results of proton-promoted MCRs with the heat-promoted MCRs reported in our previous work.[12a] We found that all of proton-promoted MCRs with different kinds of **2** worked well and gave the corresponding **4** in excellent yields. Although the activity of aromatic amines was obviously lower than that of aliphatic ones in the heat-promoted MCRs,[12a] interestingly the proton-promoted MCRs still proceeded smoothly (Table 2, entries 1, 12, 14, and 16). Structures of aromatic amines, with any one of them: electron-donating substituent (Table 2, entry 4), weak electron-withdrawing substituent (Table 2, entries 5, 13, and 19), or *o*-substituent (Table 2, entry 6) presented no significant influence on the product yields. With a strong electron-withdrawing substituent at the phenyl ring R^1, the MCRs also worked well to give the desired products with high yield (Table 2, entry 20), although complex products were afforded with such substituents at the phenyl ring R^2.

The replacement of substrate **1** exerted no significant influence on the one-pot synthesis (Table 2, entries 17–19). Compared with the previous work,[12a] the reaction temperature and time were much lower and shorter, respectively, but the yields of all products generally were higher especially for aromatic amines (Table 2, entries 4, 14, and 16). The results indicate that AcOH dramatically accelerates the MCRs rate.

Table 1
Optimization of reaction conditions for the MCR[a]



Entry	Solvent	CH_2O/AcOH (equiv)	*t* (h)	Yield[b] (%)
1	MeOH	4:2	0.5	98
2	DMF	4:2	24	71
3	MeOH	4:1	3	91
4	MeOH	4:0.2	6	89
5	MeOH	4:0	24	64
6	MeOH	3:2	0.5	98
7	MeOH	2:2	8	80

[a] Reaction was carried out with **1a** (1 mmol), **2a** (2 mmol), 38% **3** (2–4 mmol), and AcOH (0–2 mmol) in 6 mL solvents at room temperature for desired time.
[b] Isolated yields.

The reaction time and reactivity of the MCRs were mainly dependent on the structures of NH_2R^2: 15 min for aliphatic amines, 30 min for aromatic amines, 3 h for 2-aminoethanol, and almost no reaction for aromatic amines with strong electron-withdrawing substituents on the phenyl rings, which is in line with the nucleophilic activity of NH_2R^2. Besides, we also found that ethanol was the more suitable solvent for the MCRs when aromatic amines were replaced with aliphatic amines.

2.3. Influence of solvents on the hydroamination stereoselectivity

It was an interesting and useful finding that the hydroamination of **1a** and **2a** in MeOH and in DMF led to the formation of *Z*- and *E*-isomers with the reverse ratios of *Z*/*E* (Eq. 1). The two isomers were quite different in maximum absorption wave

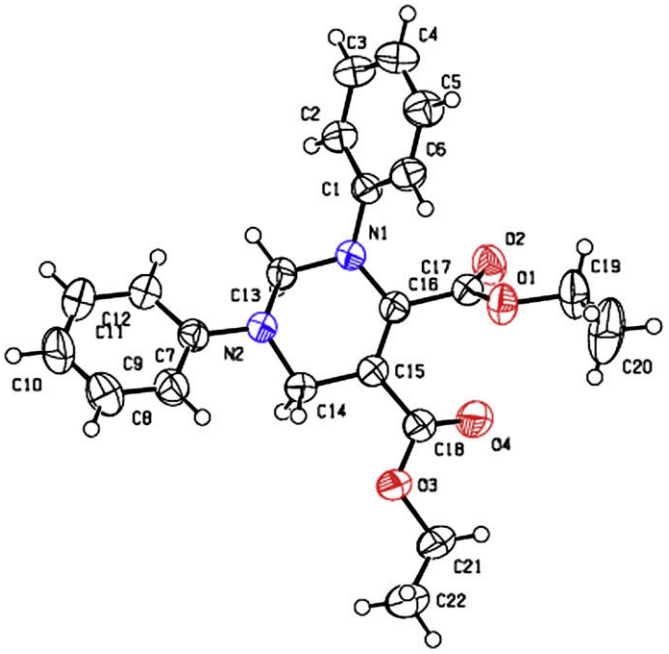


Figure 2. The single crystal X-ray structure of **4aaa**.[16]