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Convenient One-Pot Synthesis of Multisubstituted Tetrahydropyrimidines via Catalyst-Free Multicomponent Reactions

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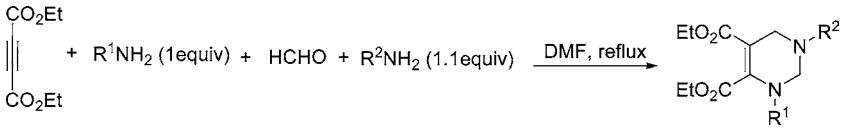
ABSTRACT



A novel and convenient one-pot synthesis of multisubstituted pyrimidine analogues via multicomponent reactions is disclosed. This catalyst-free domino reaction proceeded smoothly in good to excellent yields and offered several other advantages including short reaction time, a simple experimental workup procedure, and no toxic byproduct. In addition, the obtained products in our experiments are interesting nitrogen heterocyclic molecules containing α- and *β*-amino acid blocks.

Pyrimidines and their analogues represent an important class of nitrogen heterocycles, which is found in both various biologically active natural compounds and designed medicinal agents.[1] Specifically, tetrahydropyrimidines containing an amino acid unit have attracted much attention due to their interesting and unique properties such as muscarinic agonist activity,[2] protein−nucleic acids interaction,[3] antiviral activity,[4] and inflammatory activity.[5] Structure−activity relationship (SAR) studies of the tetrahydropyrimidine derivatives showed that the substituent groups on the rings are all critical for the activity.[6] However, to our knowledge, rare methods were developed to construct multiply substituted tetrahydropyrimidine rings.[7] Moreover, some of these protocols have not been entirely satisfactory because of such drawbacks as low yields, long reaction time, and cumbersome experimental processes. Recently, one-pot multicomponent reactions (MCRs) have emerged as a powerful tool in synthetic organic chemistry because of their significant advantages.[8−11] The convergent synthesis of these multisubstituted pyrimidine analogues from readily available starting materials along this line has also remained to be developed. In this context, we explore a novel multicomponent coupling strategy to synthesize multisubstituted tetrahydropyrimidines containing α- and *β*-amino acid units. Our approach could comprise the

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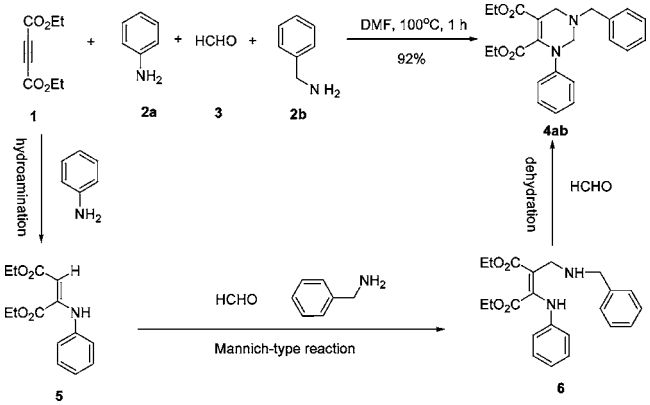
relay process of the following three domino sequences (Scheme 1): (1) two-component hydroamination; (2) three-component Mannich-type reaction; (3) two-component amine−aldehyde dehydration−cyclization process.

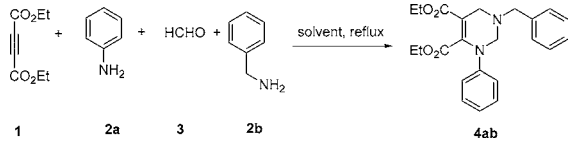
Scheme 1



But-2-ynedioic acid diethyl ester **1** reacts with aniline **2a**, formaldehyde **3**, and benzylamine **2b** to afford diethyl 1-benzyl-3-phenyl-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate **4ab**, one of the tetrasubstituted tetrahydropyrimidines with α- and β-amino acid building blocks, in excellent yield (Scheme 1, 92%).[12] The hydroamination of but-2-ynedioic acid diethyl ester **1** with aniline **2a** could rapidly form the active intermediate **5**,[13] which would then undergo a Mannich-type reaction with benzylamine **2b** and formaldehyde **3** to give intermediate **6**. The presence of formaldehyde promotes the amine−aldehyde dehydration−cyclization process to afford the target compound **4ab**. Significantly, these reactions occurred in a catalyst-free fashion with high selectivity and atom efficiency. To our knowledge, the use of three different catalyst-free reactions, namely, hydroamination, Mannich-type reaction, and sequent dehydration−cyclization, has not been reported previously.

Screening of the reaction conditions established the suitable solvents and the mole ratio of reactants for the desired MCRs (Table 1). It was exciting that the chosen solvents, such as dioxane, *N*,*N*-dimethylformamide (DMF), acetonitrile (MeCN), toluene, dimethyl sulfoxide (DMSO), and triethylamine (Et_3N), were suitable for the MCRs (Table 1, entries 1−6). DMF proved to be the best one among them (Table 1, entry 2). Under solvent-free conditions, a complex result was obtained (Table 1, entry 7). To modulate the ratio of reactants and improve the yield, we examined various ratios of but-2-ynedioic acid diethyl ester **1**, aniline **2a**, formaldehyde **3**, and benzylamine **2b** by using DMF as the solvent (Table 1, entries 8−12). The best result was obtained when but-2-ynedioic acid diethyl ester **1**/aniline **2a**/formaldehyde **3**/benzylamine **2b** = 1:1:4:1.1−1.2.

Table 1. Optimization of Reaction Conditions for the Multicomponent Reactions[a]



entry	solvent	1:2a:3:2b [mole ratio]	*t* (h)	yield (%)[b]
1	dioxane	1:1:6:2	5	72
2	DMF	1:1:6:2	1	92
3	MeCN	1:1:6:2	3	86
4	toluene	1:1:6:2	3	83
5	DMSO	1:1:6:2	3	85
6	Et_3N	1:1:6:2	3	63
7	none	1:1:6:2	3	complex
8	DMF	1:1:6:1.2	1	93
9	DMF	1:1:6:1	1	84
10	DMF	1:1:6:1.1	1	92
11	DMF	1:1:3:1.1	1	78
12	DMF	1:1:4:1.1	1	92

[a] All reactions were carried out in DMF (2 mL) at 100 °C using the substrates according to the indicated ratio in the mmol scale. [b] Isolated yields.

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(8) For recent examples on multicomponent reactions, see: (a) Ohno, H.; Ohta, Y.; Oishi, S.; Fujii, N. *Angew. Chem., Int. Ed.* **2007**, *46*, 2295. (b) Bonne, D.; Dekhane, M.; Zhu, J. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 2485. (c) Pinto, A.; Neuville, L.; Zhu, J. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 3291 and references therein. (d) Komagawa, S.; Saito, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 2446. (e) Yoshida, H.; Fukushima, H.; Ohshita, J.; Kunai, A. *J. Am. Chem. Soc.* **2006**, *128*, 11040. (f) Dondas, H. A.; Fishwick, C. W. G.; Gai, X.; Grigg, R.; Kilner, C.; Dumrongchai, N.; Kongkathip, B.; Kongkathip, N.; Polysuk, C.; Sridharan, V. *Angew. Chem., Int. Ed.* **2005**, *44*, 7570. (g) Pache, S.; Lautens, M. *Org. Lett.* **2003**, *5*, 4827.

(9) For recent examples on domino reactions, see: (a) Miyamoto, H.; Okawa, Y.; Nakazaki, A.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 2274. (b) Tietze, L. F.; Sommer, K. M.; Zinngrebe, J.; Stecker, F. *Angew. Chem., Int. Ed.* **2005**, *44*, 257. (c) Yamamoto, Y.; Hayashi, H.; Saigoku, T.; Nishiyama, H. *J. Am. Chem. Soc.* **2005**, *127*, 10804. (d) Tietze, L. F.; Ila, H.; Bell, H. P. *Chem. Rev.* **2004**, *104*, 3453.

(10) For a recent example on one-pot synthesis, see: Siamaki, A. R.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2006**, *128*, 6050.

(11) For recent books, see: (a) *Multicomponent Reactions*; Zhu, J., Bienaymé, H., Eds.; Wiley-VCH: Weinheim, 2005. (b) *Domino Reactions in Organic Synthesis*; Tietze, L.F., Brasche, G., Gericke, K., Eds.; Wiley-VCH: Weinheim, 2006.

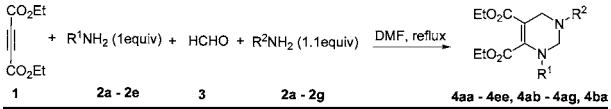
(12) For our early work on alkyne chemistry, see: (a) Huang, J.; Zhou, L.; Jiang, H. *Angew. Chem., Int. Ed.* **2006**, *45*, 1945. (b) Jiang, H.; Tang, J.; Wang, A.; Deng, G.; Yang, S. *Synthesis* **2006**, 1155. (c) Wang, Y.; Jiang, H.; Liu, H.; Liu, P. *Tetrahedron Lett.* **2005**, *46*, 3935. (d) Li, J.; Jiang, H.; Chen, M. *J. Org. Chem.* **2001**, *66*, 3627. (e) Li, J.; Jiang, H. *Chem. Commun.* **1999**, 2369. (f) Li, J.; Jiang, H.; Feng, A.; Jia, L. *J. Org. Chem.* **1999**, *64*, 5984.

(13) Intermediate **5** could be isolated as a pure compound and then react with benzylamine and formaldehyde to form the same product **4ab**. See Supporting Information for the detailed characterization data of **5**.

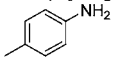
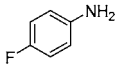
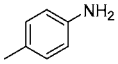
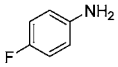
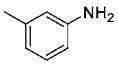
With the optimized conditions in hand, we examined the scope of the multicomponent reactions (Table 2). We were pleased to find that the reaction proceeded smoothly, and the desired products were afforded in excellent yields. Interestingly, although the reaction time of aliphatic primary amines (Table 2, entries 2 and 3) was shorter than that of aromatic primary amines (Table 2, entries 1, 4, and 5), aliphatic primary amines gave higher yields. The results indicated that the activity of aliphatic amines is higher. Notably, the electronic effects of the substituents on the aromatic ring, either the electron-donating methyl (Table 2, entry 4) or electron-withdrawing fluorine group (Table 2, entry 5), have no significant influence on the reaction.

Meaningfully, the substituted groups at the 1- or 3-position on the tetrahydropyrimidine ring could be selectively induced by changing the addition order of the two different amines under the same employed conditions. Aniline **2a** was dripped first resulting in product **4ab** in 93% yield (Table 2, entry 6). On the contrary, 1-phenyl-3-benzyl-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylic acid diethyl ester **4ba** was obtained in 86% yield when benzylamine **2b** was added first (Table 2, entry 7). The structures of **4ab** and **4ba** were distinguished via the HMBC spectra (Scheme 2). Obviously the correlation between the 1′-carbon in the benzene ring and hydrogen of CH_2 in the tetrahydropyrimidine ring is quite different in **4ab** and **4ba**. The HMBC spectrum of **4ab** showed the correlation from C-1′ to H-2, while the correlations from C-1′ to H-2 and H-6 are clearly observed in **4ba**.

Table 2. One-Pot Synthesis of Tetrasubstituted Tetrahydropyrimidines via the MCRs[a]

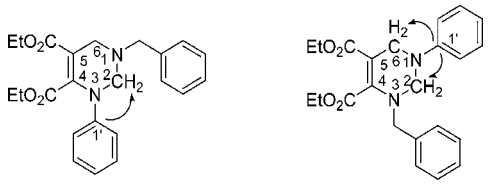


1 2a - 2e 3 2a - 2g 4aa - 4ee, 4ab - 4ag, 4ba

No.	R^1NH_2	R^2NH_2	t (h)	Product	Yield (%)[b]
1	$PhNH_2$ **2a**		3	**4aa**	89
2	$BnNH_2$ **2b**		1	**4bb**	92
3	*n*-$C_4H_9NH_2$ **2c**		1	**4cc**	96
4		 **2d**	3	**4dd**	86
5		 **2e**	3	**4ee**	88
6	$PhNH_2$ **2a**	$BnNH_2$ **2b**	1	**4ab**	93
7	$BnNH_2$ **2b**	$PhNH_2$ **2a**	1	**4ba**	86
8	$PhNH_2$ **2a**	*n*-$BuNH_2$ **2c**	1	**4ac**	90
9	$PhNH_2$ **2a**	 **2d**	3	**4ad**	83
10	$PhNH_2$ **2a**	 **2e**	3	**4ae**	80
11	$PhNH_2$ **2a**	 **2f**	6	**4af**	62
12	$PhNH_2$ **2a**	 **2g**	3	**4ag**	82

[a] All the reactions were carried out with **1** (1 mmol), amine **2** (2.1 mmol), formaldehyde (4 mmol), and DMF (2 mL) at 100 °C for the desired time. [b] Isolated yields.

Scheme 2



C-H correlations from HMBC of 4ab and 4ba

Similarly, other different amines were also successfully employed to produce the 1,3-position differently substituted cyclic products according to the addition order (Table 2, entries 8−12). All the substituted aryl, alkyl, and benzyl amines perform well, and the corresponding products were obtained in good to excellent yields, although the steric hindrance associated with the methyl group on the *ortho*-position of the benzene ring resulted in a lower yield (Table 2).

In conclusion, we have described a novel and convenient one-pot synthesis of multisubstituted pyrimidine analogues via multicomponent reactions. This catalyst-free domino reaction proceeded smoothly in good to excellent yields and offered several other advantages including short reaction time, simple experimental workup procedure, and no toxic byproduct. In addition, the obtained products in our experiments are interesting nitrogen heterocyclic molecules containing α- and *β*-amino acid blocks. Further studies and applications on this domino reaction are ongoing in our laboratory and will be published in due course.

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Supporting Information Available: Detailed experimental procedures and characterization data for the reaction products included in this paper. This material is available free of charge via the Internet at http://pubs.acs.org.

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