Tetrahedron 65 (2009) 4604–4613

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

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

Qiuhua Zhu, Huanfeng Jiang *, Jinghao Li, Min Zhang, Xiujun Wang, Chaorong Qi

School of Chemistry and Chemical Engineering, South China University of Technology, 381 Wushan Road, Guangzhou 510640, China

ARTICLE INFO

Article history:
Received 8 February 2009
Received in revised form 20 March 2009
Accepted 24 March 2009
Available online 1 April 2009

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

* Corresponding author. Tel.: +86 20 22236518; fax: +86 20 87112906.
E-mail address: jianghf@scut.edu.cn (H. Jiang).

0040-4020/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2009.03.071

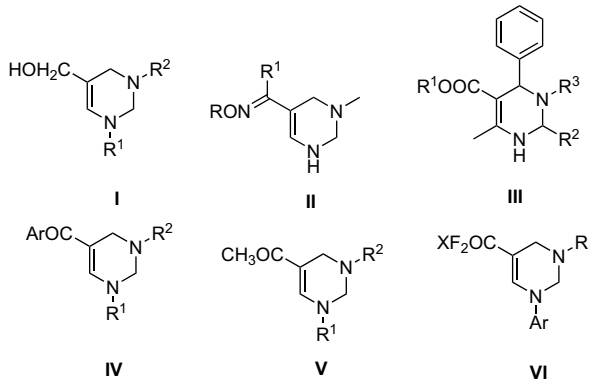


Figure 1. The reported 1,2,3,4-tetrahydropyrimidines.

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.

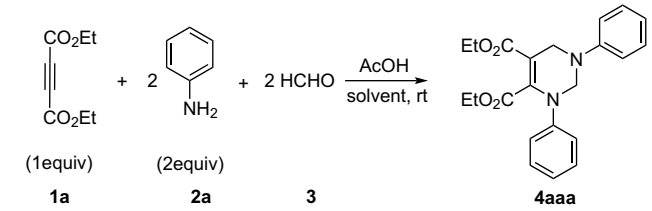
We then turned our attention to screening of the reaction conditions. During this process, MeOH was found to be more appropriate solvent (Table 1, entries 1 and 2), and the least amount of **3** for the MCR is 3.0 equiv (Table 1, entries 1, 6, and 7). By decreasing the amount of AcOH, a significant decrease 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

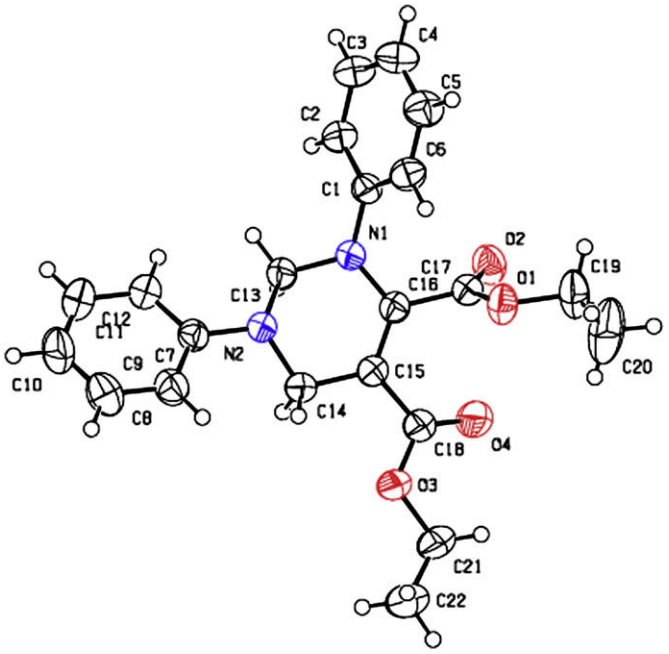
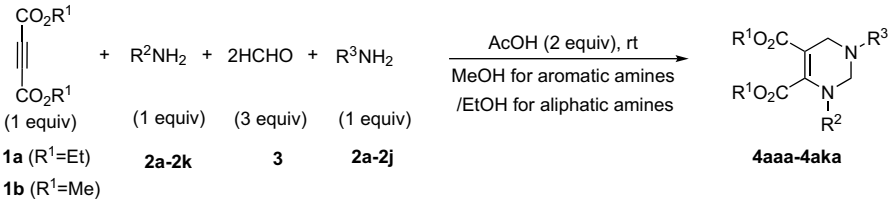


Figure 2. The single crystal X-ray structure of **4aaa**.[16]

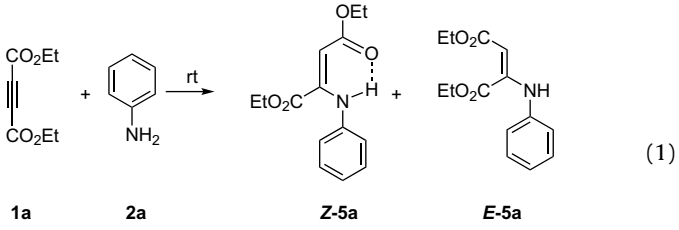
Table 2
Scope of one-pot synthesis of tetrahydropyrimidines **4**[a]



Entry	R^1	R^2	R^3	t (min)	Product	Yield[b] (%)
1	Et **a**	C_6H_5 **2a**		30 (180)[c]	**4aaa**	98 (89)[c]
2	Et **a**	$C_6H_5CH_2$ **2b**		15 (60)[c]	**4abb**	90 (92)[c]
3	Et **a**	*n*-C_4H_9 **2c**		15 (60)[c]	**4acc**	97 (96)[c]
4	Et **a**	4-$CH_3C_6H_4$ **2d**		30 (180)[c]	**4add**	95 (86)[c]
5	Et **a**	4-FC_6H_4 **2e**		30 (180)[c]	**4aee**	94 (88)[c]
6	Et **a**	2-$CH_3C_6H_4$ **2f**		30	**4aff**	92
7	Et **a**	CH_2=$CHCH_2$ **2g**		30	**4agg**	90
8	Et **a**	C_6H_{11} **2h**		15	**4ahh**	95
9	Et **a**	C_6H_5 **2a**	$C_6H_5CH_2$ **2b**	15 (60)[c]	**4aab**	90 (93)[c]
10	Et **a**	$C_6H_5CH_2$ **2b**	C_6H_5 **2a**	30 (60)[c]	**4aba**	89 (86)[c]
11	Et **a**	C_6H_5 **2a**	n-C_4H_9 **2c**	15 (60)[c]	**4aac**	92 (90)[c]
12	Et **a**	C_6H_5 **2a**	4-$CH_3C_6H_4$ **2d**	30 (180)[c]	**4aad**	94 (83)[c]
13	Et **a**	C_6H_5 **2a**	4-FC_6H_4 **2e**	30 (180)[c]	**4aae**	86 (80)[c]
14	Et **a**	C_6H_5 **2a**	2-$CH_3C_6H_4$ **2f**	30 (360)[c]	**4aaf**	93 (62)[c]
15	Et **a**	C_6H_5 **2a**	$HOCH_2CH_2$ **2i**	180	**4aai**	90
16	Et **a**	C_6H_5 **2a**	3-$CH_3C_6H_4$ **2j**	30 (180)[c]	**4aaj**	93 (82)[c]
17	Me **b**	C_6H_5 **2a**		30	**4baa**	98
18	Me **b**	$C_6H_5CH_2$ **2b**		15	**4bbb**	90
19	Me **b**	4-FC_6H_4 **2e**		30	**4bee**	94
20[d]	Et **a**	4-NO_2 C_6H_4 **2k**	C_6H_5 **2a**	6h	**4aka**	92

[a] Reactions were run with **1** (1 mmol), **2** with R^2 (1 mmol), 38% **3** (3 mmol), **2** with R^3 (1 mmol), and AcOH (2 mmol) in 6 mL MeOH or EtOH at room temperature for desired time.
[b] Isolated yields.
[c] The data in parentheses refer to that in our previous report.[12a]
[d] The reaction was run at 50 °C.

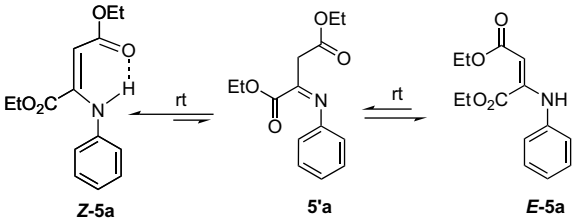
(λ_{max}), color, and the R_f value on TLC. The λ_{max}, color, and the R_f value for one isomer were 320 nm, deep yellow, and 0.5 (*n*-hexane/ethyl acetate=10:1), respectively; and those for the other were 298 nm, almost colorless, and 0.2, respectively. According to Refs. 17–19 and the properties of the two products, it is not difficult to conclude that the former is diethyl 2-(phenylamino) fumarate ***Z*-5a**,[18] and the latter is diethyl 2-(phenylamino) maleate ***E*-5a**.[19]



Solvent	Yield(%)	Ratio of *Z*/*E*
MeOH	> 99	77:23 (HPLC and ^{1}H NMR)
DMF	> 99	2:98 (HPLC)

(1)

Although the R_f values of two isomers are quite different, it is difficult to obtain pure ***Z*-** and ***E*-5a** because an equilibrium (Eq. 2) was reached between them through active imine **5′a**[20] during isolated processes. The equilibrium indicates that ***Z*-5a** has much lower molecular inner energy than ***E*-5a** does. However, in non-proton solvents ***E*-5a** was relatively stable. Therefore, the yield and spectra of ***E*-5a** could be obtained only from the analysis of the resulting reaction product mixture in non-proton deuterio solvents by HPLC and ^{1}H NMR.



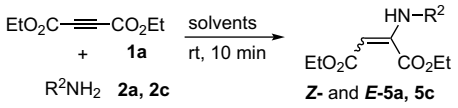
[a] Ratio determined by ^{1}H NMR

(2)

Then we investigated the solvent influence on the hydroamination stereoselectivity of **1a** and aromatic amine **2a**. The results in Table 3 showed that ***Z*-5a** was formed as major product when the hydroamination of **1a** and **2a** was carried out in proton solvents (Table 3, entries 1–4) or in the mixtures of proton and non-proton solvents (Table 3, entries 6 and 7). ***E*-5a** was, however, formed as main product in non-proton solvents (Table 3, entries 5, 9, and 14). The experimental results also showed that the amount of water in DMSO or in DMF could remarkably influence the hydroamination stereoselectivity (Table 3, entries 8 and 10–13), which is expected because water also is a proton solvent.

Solvent effect on the hydroamination stereoselectivity of **1a** and aliphatic amine **2c** was also investigated (Table 3, entries 15–21). In this case, although the stereoselectivity of the reactions in non-proton solvents was high with the ratios of *E*/*Z* more than 92:8 (Table 3, entries 18 and 21), poor stereoselectivity in proton solvents was observed with the ratios of *Z*/*E* less than 63:27 (Table 3,

Table 3
Influence of solvents on the ratios of ***Z*-** and ***E*-5a** and **5c**[a]



Entry	R^2	Solvents	Z/E[b]
1	C_6H_5 **2a**	EtOH	72:28
2[c]	C_6H_5 **2a**	MeOH	77:23 (77:23)[d]
3	C_6H_5 **2a**	AcOH	95:5
4	C_6H_5 **2a**	MeOH+AcOH (1:1)	83:17
5	C_6H_5 **2a**	DMF	2:98
6	C_6H_5 **2a**	DMF+MeOH (1:1)	74:26
7	C_6H_5 **2a**	DMF+AcOH (1:1)	89:11
8	C_6H_5 **2a**	DMF+ H_2O (3:1)	44:56
9[c]	C_6H_5 **2a**	DMSO-d_6	5:95 (4:96)[d]
10	C_6H_5 **2a**	DMSO+H_2O (7:1)	19:81
11[c]	C_6H_5 **2a**	DMSO-d_6+ D_2O (4:1)	33:67 (25:75) [d]
12	C_6H_5 **2a**	DMSO+H_2O (3:1)	37:63
13	C_6H_5 **2a**	DMSO+H_2O (1:1)	Reactants not dissolving
14	C_6H_5 **2a**	EtOAc	12:88
15	*n*-C_4H_9 **2c**	EtOH	53:47
16	*n*-C_4H_9 **2c**	MeOH	63:37
17	*n*-C_4H_9 **2c**	AcOH	Trace products
18	*n*-C_4H_9 **2c**	DMF	3:93
19	*n*-C_4H_9 **2c**	DMF+ H_2O (3:1)	42:58
20	*n*-C_4H_9 **2c**	DMF+AcOH (1:1)	Trace products
21[c]	*n*-C_4H_9 **2c**	DMSO-d_6	4:96 (3:97)[d]

[a] Reactions were run with **1a** (0.1 mmol) and **2a** or **2c** (0.1 mmol) in solvents (1 mL) at room temperature for 10 min in greater than 98% yields except entry 16 (80% yield).
[b] Ratios determined by HPLC (λ=275/298 nm for aliphatic/aromatic *E*-isomer, 300/320 nm for aliphatic/aromatic *Z*-isomer, MeOH/H_2O=80:20, 1 mL·min^{-1}, C_{18}/C_8, 2 μl sample).
[c] The concentration of substrates in this reaction was 0.2 mol L^{-1}.
[d] Ratios determined by ^{1}H NMR.

entries 15 and 16). Compared with the hydroamination of **1a** and aromatic amine **2a**, the water in non-proton solvents could also affect the stereoselectivity to a large extent (Table 3, entry 19). However, AcOH, which could highly increase the yield of ***Z*-5a** with the ratio of *Z*/*E* up to 95:5 in the hydroamination of **1a** and aromatic **2a**, hindered the reaction of **1a** and aliphatic amine **2c** because **2c** rapidly reacted with AcOH to form a salt. Therefore, it is expected that the *Z*/*E* hydroamination stereoselectivities of **1a** and aliphatic amines in proton solvents are lower than that of **1a** and aromatic amines.

2.4. Influence of reactant concentrations and substrate structures on the hydroamination stereoselectivity

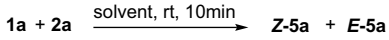
Subsequently, the influence of reactant concentrations and substrate structures on the hydroamination of **1a** and **2** was investigated. In this study, reactant concentrations were proved to have an influence on the stereoselectivity of hydroamination of **1a** and **2a** in DMF to some extent (Table 4, entries 2–5), but almost no influence on that in MeOH (Table 4, entries 6–9). In the meantime, aromatic amines presented more influence on the stereoselectivity of the hydroamination in proton solvents than aliphatic amines did (Table 5).

It is worth mentioning that similar equilibriums to Eq. 2 were observed between ***Z*-** and ***E*-5b–c**, which may explain why the synthesis of only *Z*-isomers of those compounds has been reported.[18b–c]

2.5. The possible routes of the hydroamination in proton or non-proton solvents

Looking comparatively into these aforementioned investigations, we found that proton and non-proton solvents played

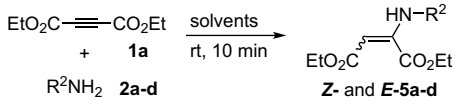
Table 4
Influence of reactant concentrations on the ratio of ***Z*/*E***[a]



Entry	Solvents	**1a** (mol L^{-1})	Z/E[b]
1	Solvent-free	0.1	30:70
2	DMF	1	13:87
3	DMF	0.4	7:93
4	DMF	0.2	5:95
5	DMF	0.1	2:98
6	MeOH	1	77:23
7	MeOH	0.4	77:23
8	MeOH	0.2	78:22
9	MeOH	0.1	77:23

[a] Reactions were run with **1a** (0.1–1 mmol) and equiv of **2a** in solvents (1 mL) at room temperature for 10 min in greater than 98% yields.
[b] Ratios determined by HPLC (λ=298 nm for *E*-isomer, 320 nm for *Z*-isomer, MeOH/H_2O=80:20, 1 mL min^{-1}, C_{18}/C_8, 2 μl sample).

Table 5
Influence of substrate structures on the ratios of Z/E[a]



Entry	R^2	Solvent	Z/E[b]
1	C_6H_5 **2a**	DMSO-d_6	5:95 (4:96)[c]
2	C_6H_5 **2a**	EtOH	65:35
3	$C_6H_5CH_2$ **2b**	DMSO-d_6	7:93 (7:93)[c]
4	$C_6H_5CH_2$ **2b**	EtOH	44:56
5	*n*-C_4H_9 **2c**	DMSO-d_6	4:96 (7:93)[c]
6	*n*-C_4H_9 **2c**	EtOH	53:47
7	4-$CH_3C_6H_4$ **2d**	DMSO-d_6	8:92 (3:97)[c]
8	4-$CH_3C_6H_4$ **2d**	EtOH	58:42

[a] Reactions were run with **1a** (0.2 mmol) and **2a–d** (0.2 mmol) in solvents (1 mL) at room temperature for 10 min in greater than 98% yields.
[b] Ratios determined by HPLC (λ=275/298 nm for aliphatic/aromatic *E*-isomer, 300/320 nm for aliphatic/aromatic *Z*-isomer, MeOH/H_2O=80:20, 1 mL min^{-1}, C_{18}/C_8, 2 μl sample).
[c] Ratios determined by ^{1}H NMR.

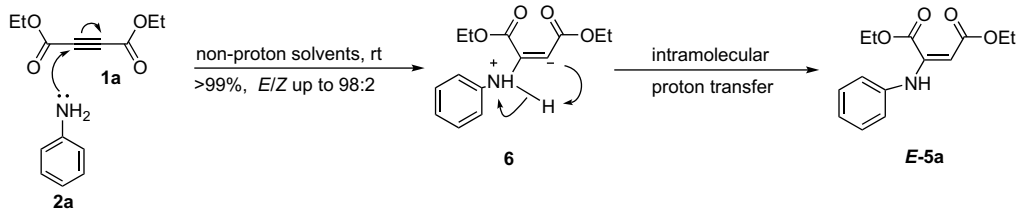
key roles on the hydroamination stereoselectivity of **1a** and **2** although reactant concentrations and substrate structures could influence the stereoselectivity to some extent.

When the hydroamination of **1a** and **2a** was carried out in non-proton solvents, the nitrogen atom of **2a** attacked the alkyne carbon of **1a** and formed a carbanion, and then in intermediate **6** (Scheme 1) occurred an intramolecular proton transfer, which led to ***E*-5a** as a major product at a ratio of *E*/*Z* up to 98:2, while in proton solvents appeared an intermolecular proton transfer from proton solvents to intermediate **7** (Scheme 2), which gave ***Z*-5a** at a ratio of *Z*/*E* up to 95:5.

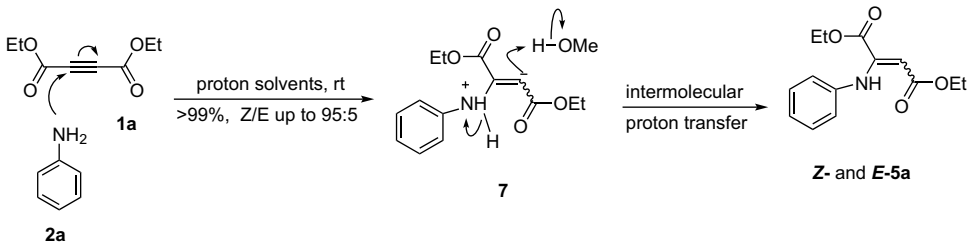
2.6. Aza–ene-type reaction of enamines 5a with aniline and formaldehyde

There are two models for the reactions of *N*-monosubstituted enamines and imines. The first one is Mannich-type reaction, which was proved by Möhrle and Reinhardt[7] (reaction A in Scheme 3). The second is aza–ene-type reaction, which was reported by Terada and co-workers[21] (reaction B in Scheme 3).

Experimental facts and theoretical calculation proved that the reactions of **5a** with **8** or **2a** and **3** proceeded via aza–ene-type pathway. As shown in Scheme 4, aza–ene type led to intermediate **9′**, but Mannich-type reaction led to intermediates ***Z*-** and ***E*-9**. The results calculated using density functional theory, B3LYP/6–31G, proved that the order of molecular energy for the minimum-energy



Scheme 1. Possible route of hydroamination of **1a** and **2a** in non-proton solvents.

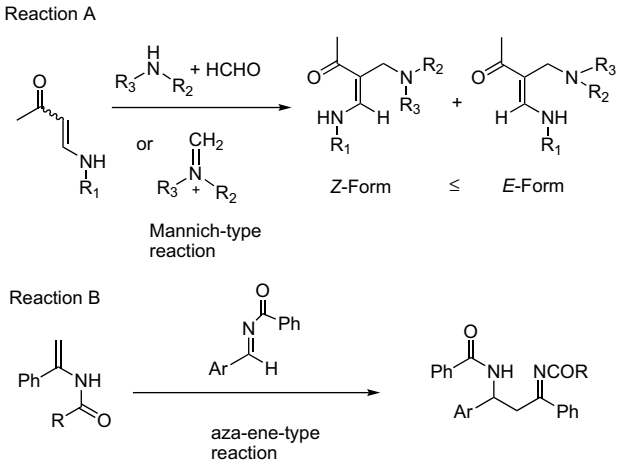


Scheme 2. Possible route of hydroamination of **1a** and **2a** in proton solvents.

conformations of the three isomers is $E_{9'}>E_{E\text{-}9}>E_{Z\text{-}9}$, that is, $E_{9'}-E_{Z\text{-}9}$= 38.0 kJ mol^{-1} and $E_{E\text{-}9}-E_{Z\text{-}9}$=13.8 kJ mol^{-1}. If the reaction proceeded via Mannich-type-reaction model, **10** and **4aaa** (Scheme 4) would be obtained with the ratio of **10** larger than that of **4aaa** because the value of $E_{Z\text{-}9}$ is lower than $E_{E\text{-}9}$. The MCR of **1a**, **2a**, and **3**, however, in MeOH using AcOH as catalyst produced **4aaa** in 98% yield (Table 2, entry 1) although the ratio of the intermediates, ***Z***- and ***E*-5a**, was 77:23 (Table 3, entry 2), which proved that both of ***Z***- and ***E*-5a** could lead to the formation of the same product **4aaa**. In contrast, aza–ene-type reaction could best elucidate the experimental facts because more active **9′** could instantly and completely convert into **4aaa** in the presence of formaldehyde. On the other hand, the high activity of N–H in ***Z***- and ***E*-5a** (the δ values in ^{1}H NMR spectra for ***Z***- and ***E*-5a** are 9.59 and 9.31 ppm, respectively) interprets the feasibility of the formation of C=N bond.

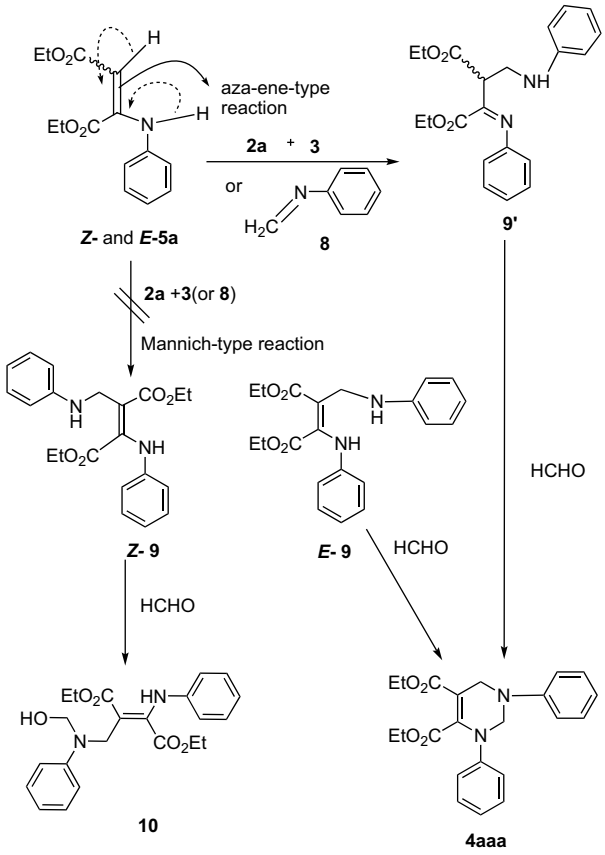
2.7. Overall mechanism for the MCRs pathway

According to the results mentioned above, we tried to propose a suitable reaction mechanism (route II in Scheme 5) for the proton-promoted MCRs in MeOH/EtOH that was different from the one of the heat-promoted MCRs in DMF reported in Ref. 12a (route I in Scheme 5).

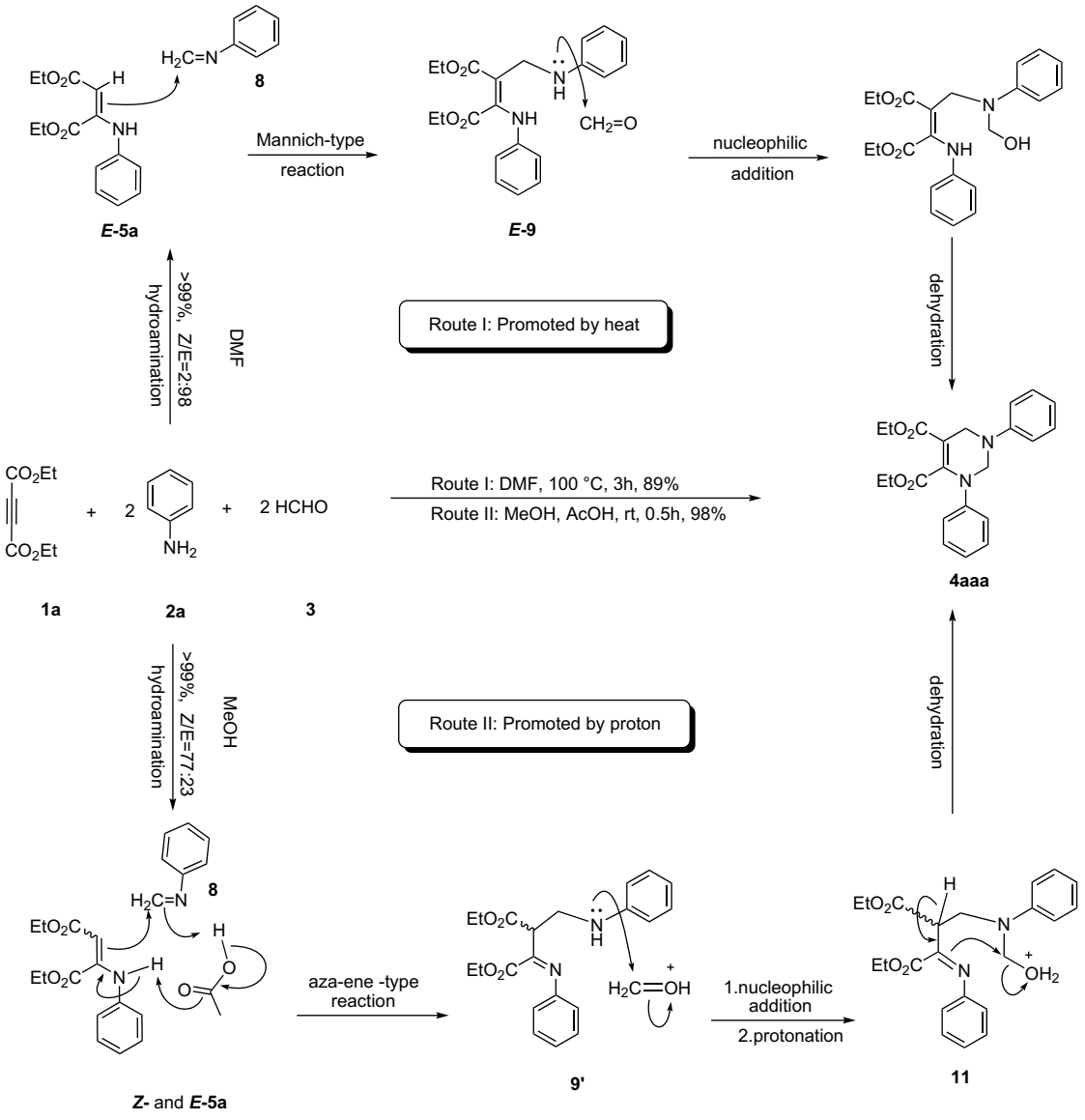


Scheme 3. Some reactions of *N*-monosubstituted enamines and imines.

In route I, the MCRs started with the hydroamination of **2a** to **1a** in DMF, a non-proton solvent, to afford ***E*-5a** with high stereoselectivity, subsequently under heat-promoted conditions followed by a domino process including Mannich-type reaction, nucleophilic addition, and dehydration–cyclization.[12a]



Scheme 4. The reaction of **5a** and **8** (or **2a** and **3**) in MeOH.



Scheme 5. Possible mechanisms for the domino MCRs.

The MCRs in route II, however, underwent the following domino process: hydroamination, aza–ene-type reaction, nucleophilic addition, and dehydration–cyclization. The aza–ene-type reaction afforded intermediate **9′**, followed by intermediate **11** via nucleophilic addition of **9′** to formaldehyde and protonation. Then the dehydration of **11** gave the only product **4aaa**, which best interprets why the one-pot synthesis of **4** could produce good to excellent yields although the formation of intermediate *Z*- and *E*-enamines was influenced by solvents, reactant concentrations, and substrate structures. In addition, two fundamental mechanisms of acid catalysis, the mechanisms of specific acid catalysis and general acid catalysis reported by Mark and Eric[22] were used to make clear why AcOH could dramatically accelerate the rate of the MCRs and decrease its reaction temperature. It was obvious that AcOH efficiently promoted the MCRs via the two mechanisms: the mechanism of reversible protonation of the electrophile (herein such as **3** and **11**) in a pre-equilibrium step prior to nucleophilic attack (*the mechanism of specific acid catalysis*) and the mechanism of proton transfer to the transition state (such as the transition states derived from **5a** and **8**) in the rate-determining step (*the mechanism of general acid catalysis*).

3. Conclusion

In this study, we have developed an efficient and practical one-pot synthesis of polysubstituted tetrahydropyrimidines via the proton-promoted MCRs. Compared to our previous work, the proton-promoted MCRs proceed at lower temperature, in shorter reaction times, and have simpler experimental workup procedures providing improved yields of products especially when amines are aromatic ones.

Furthermore, via the studies of intermediates, ***Z*-** and ***E*-5a**, we came to the following findings: (a) the hydroamination stereoselectivity of **1** and **2** is influenced by solvents, reactant concentrations, and substrate structures, and mainly controlled by solvents: *Z*-isomers in proton solvents and *E*-isomers in non-proton solvents; (b) an equilibrium exists between *Z*- and *E*-isomers. Although *E*-isomers are comparatively stable in non-proton solvents, mostly or even almost completely converted to *Z*-isomers during isolating process; (c) both *Z*- and *E*-enamine intermediates led to the same desired products.

According to the experimental facts and the theoretic calculation results, we proposed mechanisms for the proton-promoted

MCRs, which proceeded through a domino hydroamination, aza–ene-type reaction, nucleophilic addition, and dehydration–cyclization sequence, and well explained why AcOH could dramatically accelerate the MCRs, respectively. The probe into the activity against human hepatoma cell line HepG2 and structure–activity relationship of polysubstituted tetrahedropyrimidines is ongoing in our laboratory.

4. Experimental

4.1. General

All reactions were performed at room temperature under air atmosphere in a round bottom flask equipped with magnetic stir bar. All melting points were taken on an XT-4 micro melting point apparatus and were uncorrected. ^{1}H NMR (400 MHz) and ^{13}C NMR (100.6 MHz) spectra were recorded using a Bruker Avance 400 MHz NMR spectrometer and, respectively, referenced to 7.27 and 77.0 ppm for chloroform-*d* or 2.50 and 39.9 ppm for dimethyl sulfoxide-d_6 with TMS as internal standard. Mass spectra were recorded on an API 4000QTRAP. IR spectra were obtained as potassium bromide film with a Brucker Vector 22 spectrometer. Analytical HPLC was performed using a Dinex INC Summit 680 with a reversed-phase Kromasil BT011943 column (250 mm×4.6 mm) and a UV detector (275, 285, 298/300, and 320 nm) at 30 °C. TLC was performed using commercially prepared 100–400 mesh silica gel plates (GF_{254}), and visualization was effected at 254 and 365 nm.

All other reagents were purchased commercially and used without further purification.

4.2. General procedure for the synthesis of 4

The mixture of MeOH or EtOH (3 mL), **1** (1 mmol), and **2** (1 mmol), which was kept at room temperature for 5–10 min, was dropwise added into the mixture of MeOH or EtOH (3 mL), 38% formaldehyde **3** (240 mg, 3 mmol), **2** (1 mmol), and acetic acid (120 mg, 2 mmol), followed with stirring at room temperature for desired time (monitored by TLC). After completion of the reactions, the product mixture was purified by preparative TLC with *n*-hexane/ethyl acetate (10:1 to 2:1) as eluent to afford the desired products **4** in 86–98% yields.

The following compounds given in Table 2 were prepared according to the general procedure.

*4.2.1. Diethyl 1,2,3,6-tetrahydro-1,3-diphenylpyrimidine-4,5-dicarboxylate (**4aaa**)*[12a]

Yellow solid, mp 85–86 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.24–6.89 (m, 10H, CH_{ar}), 4.90 (s, 2H, 2-H), 4.25 (s, 2H, 6-H), 4.20 (q, *J*=7.2 Hz, 2H, CH_2), 4.00 (q, *J*=7.2 Hz, 2H, CH_2), 1.26 (t, *J*=7.2 Hz, 3H, CH_3), 0.97 (t, *J*=7.2 Hz, 3H, CH_3) ppm.

*4.2.2. Diethyl 1,3-dibenzyl-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate (**4abb**)*[12a]

Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.30–7.15 (m, 10H, CH_{ar}), 4.35 (q, *J*=7.2 Hz, 2H, CH_2), 4.16 (s, 2H, 2-H), 4.11 (q, *J*=7.2 Hz, 2H, CH_2), 3.82 (s, 2H, $PhCH_2$), 3.60 (s, 2H, $PhCH_2$), 3.56 (s, 2H, 6-H), 1.30 (t, *J*=7.2 Hz, 3H, CH_3), 1.21 (t, *J*=7.2 Hz, 3H, CH_3) ppm.

*4.2.3. Diethyl 1,3-dibutyl-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate (**4acc**)*[12a]

Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ=4.32 (q, *J*=7.2 Hz, 2H, CH_2), 4.06 (q, *J*=7.2 Hz, 2H, CH_2), 3.92 (s, 2H, 2-H), 3.45 (s, 2H, 6-H), 2.98 (t, *J*=7.6 Hz, 2H, 1′-H), 2.48 (t, *J*=7.6 Hz, 2H, 1″-H), 1.49–1.16 (m, 14H, 2′/3′/2″/3″-H, CH_3), 0.91–0.84 (m, 6H, CH_3) ppm.

*4.2.4. Diethyl 1,2,3,6-tetrahydro-1,3-di-p-tolylpyrimidine-4,5-dicarboxylate (**4add**)*[12a]

Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.05–6.81 (m, 8H, CH_{ar}), 4.82 (s, 2H, 2-H), 4.20 (s, 2H, 6-H), 4.16 (q, *J*=7.2 Hz, 2H, CH_2), 4.00 (q, *J*=7.2 Hz, 2H, CH_2), 2.28 (s, 3H, $PhCH_3$), 2.24 (s, 3H, $PhCH_3$), 1.24 (t, *J*=7.2 Hz, 3H, CH_3), 0.99 (t, *J*=7.2 Hz, 3H, CH_3) ppm.

*4.2.5. Diethyl 1,3-bis(4-fluorophenyl)-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate (**4aee**)*[12a]

Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ=6.92–6.90 (m, 8H, CH_{ar}), 4.78 (s, 2H, 2-H), 4.18 (s, 2H, 6-H), 4.17 (q, *J*=7.2 Hz, 2H, CH_2), 3.99 (q, *J*=7.2 Hz, 2H, CH_2), 1.25 (t, *J*=7.2 Hz, 3H, CH_3), 0.99 (t, *J*=7.2 Hz, 3H, CH_3) ppm.

*4.2.6. Diethyl 1,2,3,6-tetrahydro-1,3-di-o-tolylpyrimidine-4,5-dicarboxylate (**4aff**)*

Orange oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.26–6.88 (m, 8H, CH_{ar}), 4.53 (d, *J*=11.6 Hz, 1H, 2-H^a), 4.37 (d, *J*=11.6 Hz, 1H, 2-H^b), 4.18 (q, *J*=7.2 Hz, 2H, CH_2), 4.10–4.05 (m, 2H, 6-H), 3.95 (q, *J*=7.2 Hz, 2H, CH_2), 2.23 (s, 3H, $PhCH_3$), 2.16 (s, 3H, $PhCH_3$), 1.25 (t, *J*=7.2 Hz, 3H, CH_3), 0.90 (t, *J*=7.2 Hz, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=165.9 (CO), 164.0 (CO), 148.3 (C-1′), 147.9 (C-4), 141.5 (C-1″), 136.7 (C-3′), 132.7 (C-3″), 131.2 (C-5′), 130.9 (C-5″), 129.2 (C-2′), 128.0 (C-2″), 126.7 (C-4′), 126.3 (C-4″), 124.3 (C-6′), 121.4 (C-6″), 97.8 (C-5), 69.4 (C-2), 61.4 (CH_2), 60.0 (CH_2), 48.8 (C-6), 18.1 ($PhCH_3$), 18.0 ($PhCH_3$), 14.3 (CH_3), 13.5 (CH_3) ppm; IR (cm^{-1}): ν_{max}=3058, 2980, 1740, 1692, 1597, 1493, 1457, 1372, 1258, 1227,1191, 1107, 761, 722; MS (ESI): *m*/*z* 840 ($2M+Na^+$, 92), 818 ($2M+H^+$, 85), 409 ($M+H^+$, 92), 290 (100). Anal. Calcd for $C_{24}H_{28}N_2O_4$: C, 70.57; H, 6.91; N, 6.86. Found: C, 70.38; H, 6.81; N, 6.73.

*4.2.7. Diethyl 1,3-diallyl-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate (**4agg**)*

Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ=5.86–5.69 (m, 2H, CH), 5.21–5.12 (m, 4H, $=CH_2$), 4.31 (q, *J*=7.2 Hz, 2H, CH_2), 4.06 (q, *J*=7.2 Hz, 2H, CH_2), 3.89 (s, 2H, 2-H), 3.58 (d, *J*=6 Hz, 2H, CH_2), 3.48 (s, 2H, 6-H), 3.14 (d, *J*=6.4 Hz, 2H, CH_2), 1.32 (t, *J*=7.2 Hz, 3H, CH_3), 1.18 (t, *J*=7.2 Hz, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=166.2 (CO), 164.8 (CO), 147.7 (C-4), 134.9 (C-2′), 133.2 (C-2″), 118.4 (C-3′), 118.2 (C-3″), 92.2 (C-5), 66.1 (C-2), 61.8 (CH_2), 59.5 (CH_2), 55.8 (C-1′), 53.1 (C-1″), 48.2 (C-6), 14.3 (CH_3), 13.9 (CH_3) ppm; IR (cm^{-1}): ν_{max}=3078, 2980, 1739, 1689, 1585, 1470, 1371, 1287, 1242, 1218, 1175, 1109, 1042, 996, 761, 743; MS (ESI): *m*/*z* 309 ($M+H^+$, 100), 240 (96). Anal. Calcd for $C_{16}H_{24}N_2O_4$: C, 62.32; H, 7.84; N, 9.08. Found: C, 62.43; H, 7.91; N, 9.13.

*4.2.8. Diethyl 1,3-dicyclohexyl-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate (**4ahh**)*

Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ=4.32 (q, *J*=7.2 Hz, 2H, CH_2), 4.06 (q, *J*=7.2 Hz, 2H, CH_2), 3.93 (s, 2H, 2-H), 3.48 (s, 2H, 6-H), 3.01–2.96 (m, 1H, CH), 2.45–2.44 (br s, 1H, CH), 1.90–1.88 (br s, 2H, 2″-H), 1.80–1.75 (m, 6H, 2′-H, 2″-H), 1.60–1.57 (m, 2H, 3″-H), 1.37–1.12 (m, 16H, CH_3, 3′-H, 4′-H, 3″-H, 4″-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=166.0 (CO), 165.3 (CO), 148.6 (C-4), 92.7 (C-5), 61.5 (C-2), 59.7 (CH_2), 59.6 (CH_2), 59.2 (C-1′), 58.8 (C-1″), 45.5 (C-6), 31.1 (C-2′/6′), 30.2 (C-2″/6″), 25.9 (C-4′), 25.7 (C-4″), 25.4 (C-3′/5′), 25.1 (C-3″/5″), 14.3 (CH_3), 13.9 (CH_3) ppm; IR (KBr): ν_{max}=3462, 2931, 2855, 1740, 1688, 1585, 1447, 1371, 1287, 1250, 1168, 1107,759 cm^{-1}; MS (ESI): *m*/*z* 393 ($M+H^+$, 93), 282 (100). Anal. Calcd for $C_{22}H_{36}N_2O_4$: C, 67.32; H, 9.24; N, 7.14. Found: C, 67.45; H, 9.40; N, 7.01.

*4.2.9. Diethyl 1-benzyl-1,2,3,6-tetrahydro-3-phenylpyrimidine-4,5-dicarboxylate (**4aab**)*[12a]

Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.30–7.13 (m, 10H, CH_{ar}), 4.34 (s, 2H, 2-H), 4.14 (q, *J*=7.2 Hz, 2H, CH_2), 4.06 (q, *J*=7.2 Hz,

2H, CH_2), 3.81 (s, 2H, $PhCH_2$), 3.72 (s 2H, 6-H), 1.22 (t, J=7.2 Hz, 3H, CH_3), 1.02 (t, J=7.2 Hz, 3H, CH_3) ppm.

4.2.10. Diethyl 3-benzyl-1,2,3,6-tetrahydro-1-phenylpyrimidine-4,5-dicarboxylate (**4aba**)[12a]

Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.29–7.17 (m, 7H, CH_{ar}), 6.89–6.80 (3H, CH_{ar}), 4.41 (s, 2H, 2-H), 4.31 (q, J=7.2 Hz, 2H, CH_2), 4.22 (s, 2H, $PhCH_2$), 4.19 (q, J=7.2 Hz, 2H, CH_2), 4.10(s, 2H, 6-H), 1.30–1.26 (m, 6H, CH_3) ppm.

4.2.11. Diethyl 1-butyl-1,2,3,6-tetrahydro-3-phenylpyrimidine-4,5-dicarboxylate (**4aac**)[12a]

Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.30–7.10 (m, 5H, CH_{ar}), 4.36 (s, 2H, 2-H), 4.13 (q, J=7.2 Hz, 2H, CH_2), 4.01 (q, J=7.2 Hz, 2H, CH_2), 3.64 (s, 2H, 6-H), 2.61 (t, J=7.2 Hz, 2H, 1′-H), 1.43–1.39 (m, 2H, 2′-H), 1.32–1.26 (m, 2H, 3′-H), 1.22 (t, J=7.2 Hz, 3H, 4′-H), 0.98 (t, J=7.2 Hz, 3H, CH_3), 0.85 (t, J=7.2 Hz, 3H, CH_3) ppm.

4.2.12. Diethyl 1,2,3,6-tetrahydro-3-phenyl-1-p-tolylpyrimidine-4,5-dicarboxylate (**4aad**)[12a]

Yellow solid, mp 83–84 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.26–6.80 (m, 9H, CH_{ar}), 4.85 (s, 2H, 2-H), 4.21(s, 2H, 6-H), 4.19 (q, J=7.2 Hz, 2H, CH_2), 4.00 (q, J=7.2 Hz, 2H, CH_2), 2.23 (s, 3H, $PhCH_3$), 1.25 (t, J=7.2 Hz, 3H, CH_3), 0.97 (t, J=7.2 Hz, 3H, CH_3) ppm.

4.2.13. Diethyl 1-(4-fluorophenyl)-1,2,3,6-tetrahydro-3-phenylpyrimidine-4,5-dicarboxylate (**4aae**)[12a]

White solid, mp 86–87 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.27–6.89 (m, 9H, CH_{ar}), 4.85 (s, 2H, 2-H), 4.21 (s, 2H, 6-H), 4.19 (q, J=7.2 Hz, 2H, CH_2), 4.01 (q, J=7.2 Hz, 2H, CH_2), 1.27 (t, J=7.2 Hz, 3H, CH_3), 0.98 (t, J=7.2 Hz, 3H, CH_3) ppm.

4.2.14. Diethyl 1,2,3,6-tetrahydro-3-phenyl-1-o-tolylpyrimidine-4,5-dicarboxylate (**4aaf**)[12a]

White solid, 91–92 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.22–6.96 (m, 9H, CH_{ar}), 4.61 (s, 2H, 2-H), 4.17 (q, J=7.2 Hz, 2H, CH_2), 4.06 (s, 2H, 6-H), 4.04 (q, J=7.2 Hz, 2H, CH_2), 2.20 (s, 3H, $PhCH_3$), 1.24 (t, J=7.2 Hz, 3H, CH_3), 0.99 (t, J=7.2 Hz, 3H, CH_3) ppm.

4.2.15. Diethyl 1,2,3,6-tetrahydro-1-(2-hydroxyethyl)-3-phenylpyrimidine-4,5-dicarboxylate (**4aai**)[12a]

Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.27–7.07 (m, 5H, CH_{ar}), 4.36 (s, 2H, 2-H), 4.09 (q, J=7.2 Hz, 2H, CH_2), 3.98 (q, J=7.2 Hz, 2H, CH_2), 3.63 (s, 2H, 6-H), 3.58 (t, J=4.2 Hz, 2H, 1′-H), 3.04 (br s, 1H, OH), 2.77 (t, J=4.2 Hz, 2H, 2′-H), 1.19 (t, J=7.2 Hz, 3H, CH_3), 0.95 (t, J=7.2 Hz, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=165.9 (CO), 163.8 (CO), 145.7 (C-1″), 143.5 (C-4), 129.2 (C-3″/5″), 126.4 (C-4″), 125.2 (C-2″/6″), 97.7 (C-5), 71.0 (C-2), 61.5 (CH_2), 60.0 (CH_2), 58.8 (C-2′), 54.2 (C-1′), 48.4 (C-6), 14.2 (CH_3), 13.4 (CH_3) ppm; IR (KBr): ν_{max}=3702, 3432, 2981, 2936, 1740, 1692, 1580, 1496, 1373, 1251, 1209, 1124, 1028, 763, 699 cm^{-1}; MS (ESI): m/z 719 (2M+Na$^+$, 12), 371 (M+Na$^+$, 50), 349 (M+H$^+$, 35), 276 (100). Anal. Calcd for $C_{18}H_{24}N_2O_5$: C, 62.05; H, 6.94; N, 8.04. Found: C, 62.37; H, 6.71; N, 8.01.

4.2.16. Diethyl 1,2,3,6-tetrahydro-3-phenyl-1-m-tolylpyrimidine-4,5-dicarboxylate (**4aaj**)[12a]

Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.32–6.72 (m, 9H, CH_{ar}), 4.90 (s, 2H, 2-H), 4.27 (s, 2H, 6-H), 4.22 (q, J=7.2 Hz, 2H, CH_2), 4.04 (q, J=7.2 Hz, 2H, CH_2), 2.26 (s, 3H, $PhCH_3$), 1.30 (t, J=7.2 Hz, 3H, CH_3), 1.03 (t, J=7.2 Hz, 3H, CH_3) ppm.

4.2.17. Dimethyl 1,2,3,6-tetrahydro-1,3-diphenylpyrimidine-4,5-dicarboxylate (**4baa**)

Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.27–7.16 (m, 5H, CH_{ar}), 6.99–6.96 (m, 2H, CH_{ar}), 6.91–6.86 (m, 3H, CH_{ar}), 4.90 (s, 2H, 2-H), 4.25 (s, 2H, 6-H), 3.72 (s, 3H, CH_3), 3.56 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=166.1 (CO), 164.5 (CO), 148.1 (C-1′), 146.5 (C-1″), 143.5 (C-4), 129.3 (C-3′/5′/3″/5″), 126.5 (C-4′), 124.5 (4″), 121.2 (C-2′/6′), 117.8 (2″/6″), 100.5 (C-5), 68.8 (C-2), 52.5 (CH_3), 51.5 (CH_3), 47.5 (C-6) ppm; IR (KBr): ν_{max}=3463, 2949, 1742, 1700, 1579, 1497, 1436, 1368, 1260, 1235, 1115, 1041, 997, 949, 761, 696 cm^{-1}; MS (ESI) m/z 391 (M+K$^+$, 73), 375 (M+Na$^+$, 48), 353 (M+H$^+$, 58), 248 (100). Anal. Calcd for $C_{20}H_{20}N_2O_4$: C, 68.17; H, 5.72; N, 7.95. Found: C, 68.01; H, 5.80; N, 7.78.

4.2.18. Dimethyl 1,3-dibenzyl-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate (**4bbb**)

Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.31–7.15 (m, 10H, CH_{ar}), 4.15 (s, 2H, 2-H), 3.90 (s, 3H, CH_3), 3.83 (s, 2H, 2-H), 3.64 (s, 3H, CH_3), 3.59 (s, 2H, CH_2), 3.54 (s, 2H, 6-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=166.9 (CO), 165.6 (CO), 148.1 (C-4), 137.9 (C-1″), 136.1 (C-1′), 128.7 (C-2′/6′), 128.3 (C-2″/6″), 128.0 (C-3′/5′/3″/5″), 127.2 (C-4′/4″), 92.1 (C-5), 65.9 (C-2), 56.9 (PhC′H$_2$), 54.2 (PhC″H$_2$), 52.9 (CH_3), 51.1 (CH_3), 48.2 (C-6) ppm; IR (KBr): ν_{max}=3062, 2982, 2936, 2903, 1739, 1695, 1583, 1461, 1371, 1260, 1229, 1209, 1108, 1042, 760, 696 cm^{-1}; MS (ESI): m/z 419 (M+K$^+$, 50), 403 (M+Na$^+$, 27), 381 (M+H$^+$, 73), 262 (100). Anal. Calcd for $C_{22}H_{24}N_2O_4$: C, 69.46; H, 6.36; N, 7.36. Found: C, 69.25; H, 6.43; N, 7.15.

4.2.19. Dimethyl 1,3-bis(4-fluorophenyl)-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate (**4bee**)

Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ=6.92–6.88 (m, 8H, CH_{ar}), 4.78 (s, 2H, 2-H), 4.18 (s, 2H, 6-H), 3.72 (s, 3H, CH_3), 3.55 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=166.0 (CO), 164.3 (CO), 161.0 (d, J=960 Hz, 1C, CF), 158.0 (d, J=960 Hz, 1C, CF), 146.7 (C-1′), 144.6 (C-4), 139.4 (C-1″), 127.3 (C-3′), 127.2 (C-5′), 120.1 (C-3″/5″), 116.2 (C-2′), 116.0 (C-6′), 115.9 (C-2″), 115.7 (C-6″), 99.6 (C-5), 70.4 (C-2), 52.5 (CH_3), 51.6 (CH_3), 47.7 (C-6) ppm; IR (KBr): ν_{max}=3420, 1735, 1650, 1558, 1541, 1509, 1457, 1085, 987 cm^{-1}; MS (ESI): m/z 411 (M+Na$^+$, 23), 389 (M+H$^+$, 100). Anal. Calcd for $C_{20}H_{18}F_2N_2O_4$: C, 61.85; H, 4.67; F, 9.78; N, 7.21. Found: C, 61.67; H, 4.71; F, 9.69; N, 7.28.

4.2.20. Diethyl 1,2,3,6-tetrahydro-3-(4-nitrophenyl)-1-phenylpyrimidine-4,5-dicarboxylate (**4aka**)

Yellow crystal; 138–139 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.12–8.09 (m, 2H, CH_{ar}), 7.19–6.81 (m, 7H, CH_{ar}), 4.98 (s, 2H, 2-H), 4.28 (s, 2H, 6-H), 4.24 (q, J=8 Hz, 2H, CH_2), 4.12 (q, J=8 Hz, 2H, CH_2), 1.31 (t, J=8 Hz, 3H, CH_3), 1.12 (t, J=8 Hz, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=165.1 (CO), 163.5 (CO), 150.0 (C-1″), 147.5 (C-1′), 144.1 (CNO_2), 143.2 (C-3), 129.3 (C-3′/5′), 124.9 (C-3″/5″), 122.5 (C-2′/6′), 121.6 (C-2″/6″), 117.7 (C-4′), 109.3 (C-5), 68.9 (C-2), 62.1 (CH_2), 60.9 (CH_2), 48.0 (C-6), 14.2 (CH_3), 13.6 (CH_3) ppm; IR (KBr): ν_{max}=3444, 1736, 1695, 1587, 1498, 1340, 1257, 1228, 1109, 944, 856, 737, 695, 528 cm^{-1}; MS (ESI): m/z 448 (M+Na$^+$, 80), 426 (M+H$^+$, 85), 321 (100). Anal. Calcd for $C_{22}H_{23}N_3O_6$: C, 62.11; H, 5.45; N, 9.88. Found: C, 62.67; H, 5.51; N, 9.79.

4.3. Preparation and spectroscopic data of diethyl 2-(phenylamino) fumarate (*Z*-5a)

Diethyl but-2-ynedioate **1a** (170 mg, 1 mmol) and aniline **2a** (93 mg, 1 mmol) were added into MeOH (5 mL) at room temperature for 10 min, followed by purification by preparative TLC with *n*-hexane and ethyl acetate (10:1) as eluent to afford ***Z*-5a** as yellow oil, 210 mg, 80% yield; ^{1}H NMR (400 MHz, DMSO-d_6): δ=9.59 (s, 1H, NH), 7.28 (t, J=7.6 Hz, 2H, CH_{ar}), 7.06 (t, J=7.6 Hz, 1H, CH_{ar}), 6.29 (d, J=8.0 Hz, 2H, CH_{ar}), 5.22 (s, 1H, 3-H), 4.14–4.06 (m, 4H, CH_2), 1.21 (t, J=7.2 Hz, 3H, CH_3), 1.01 (t, J=7.2 Hz, 3H, CH_3); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.68 (s, 1H, NH), 7.30–7.25 (m, 2H, CH_{ar}), 7.09 (t, J=7.6 Hz,

1H, CH_{ar}), 6.93 (d, J=7.6 Hz, 2H, CH_{ar}), 5.39 (s, 1H, 3-H), 4.24−4.13 (m, 4H, CH_2), 1.31 (t, J=7.2 Hz, 3H, CH_3), 1.10 (t, J=7.2 Hz, 3H, CH_3); MS (ESI): m/z 286($M+Na^+$, 20), 264($M+H^+$, 42), 94 (100). Anal. Calcd for $C_{28}H_{34}N_2O_8$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.76; H, 6.43; N, 5.28.

4.4. General procedure for the ratio analysis of intermediates *Z*- and *E*-5a–d

Diethyl but-2-ynedioate **1a** (0.1–1 mmol) and equiv of **2a**–**2d** were added to solvents (1 mL) and then kept at room temperature for 10 min to give the hydroamination products: ***Z***- and ***E*-5a**–**d**. Then the ratios of *Z*- and *E*-isomers were determined by HPLC analysis (using MeOH/H_2O=80:20 as eluent, a C_{18} or C_8 column as stationary phase, 275, 285, 298/300, and 320 nm as detecting wavelength, 1.0 mL min^{-1} as flow rate, 30 °C as column temperature, and 2 μL as the mount of each sample). And the concentration of each sample was diluted with MeOH to 0.001 mol L^{-1} before HPLC analysis. If using DMSO-d_6 or deuteriomethanol as solvent, the isomer ratios were determined by HPLC and ^{1}H NMR.

The ratios of *Z*- and *E*-enamine isomers in Tables 3–5 were determined according to the general procedure. The following are the ratios of ***Z***- and ***E*-5a**–**d** in deuteriosolvents in Table 3 and 5 determined by HPLC and ^{1}H NMR.

*4.4.1. The ratio of diethyl 2-(phenylamino)but-2-enedioate (**Z**- and **E-5a**) in CD_3OD*

Diethyl but-2-ynedioate **1a** (34 mg, 0.2 mmol) and aniline **2a** (18.6 mg, 0.2 mmol) were added to CD_3OD (1 mL) and gave a 77:23 mixture of *Z*- and *E*-isomers (determined by ^{1}H NMR). HPLC (λ=298/300 for *E*-isomer and 320 nm for *Z*-isomer, C_{18}): major isomer (***Z*-5a**), t_R=12.8 min; minor isomer (***E*-5a**), t_R=7.0 min; ^{1}H NMR (400 MHz, CD_3OD), *Z*-isomer: δ=7.28–7.26 (m, 2H, CH_{ar}), 7.18–7.15 (m, 1H, CH_{ar}), 6.93–6.90 (m, 2H, CH_{ar}), 4.20–4.09 (m, 4H, CH_2), 1.22 (t, J=7.2 Hz, 3H, CH_3), 1.07 (t, J=7.2 Hz, 3H, CH_3) ppm; *E*-isomer: δ=7.35–7.30 (m, 2H, CH_{ar}), 7.15–7.09 (m, 3H, CH_{ar}), 4.30 (q, 7.2 Hz, 2H, CH_2), 4.07 (q, 7.2 Hz, 2H, CH_2), 1.34 (t, J=7.2 Hz, 3H, CH_3), 1.21 (t, J=7.2 Hz, 3H, CH_3) ppm.

*4.4.2. The ratio of diethyl 2-(phenylamino)but-2-enedioate (**Z**- and **E-5a**) in DMSO-d_6*

Diethyl but-2-ynedioate **1a** (34 mg, 0.2 mmol) and aniline **2a** (18.6 mg, 0.2 mmol) were added into DMSO-d_6 (1 mL) and gave a 4:96 mixture of *Z*- and *E*-isomers (determined by ^{1}H NMR). HPLC (λ=298/300 for *E*-isomer and 320 nm for *Z*-isomer, C_8): major isomer (***E*-5a**), t_R=4.5 min; minor isomer (***Z*-5a**), t_R=8.0 min; ^{1}H NMR (400 MHz, DMSO-d_6), *E*-isomer: δ=9.27 (s, 1H, NH), 7.35–7.31 (m, 2H, CH_{ar}), 7.13–7.07 (m, 3H, CH_{ar}), 5.08 (s, 1H, 3-H), 4.19 (q, J=7.2 Hz, 2H, CH_2), 3.95 (q, J=7.2 Hz, 2H, CH_2), 1.22 (t, J=7.2 Hz, 3H, CH_3), 1.09 (t, J=7.2 Hz, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ=167.0 (CO), 165.3 (CO), 150.4 (C-2), 139.5 (C-1′), 129.9 (C-3′/5′), 124.9 (C-4′), 122.3 (C-2′/6′), 86.5 (C-3), 61.9 (CH_2), 59.2 (CH_2), 14.8 (CH_3), 14.1 (CH_3).

*4.4.3. The ratio of diethyl 2-(phenylamino)but-2-enedioate (**Z**- and **E-5a**) in DMSO-d_6 and D_2O (4:1)*

Diethyl but-2-ynedioate **1a** (34 mg, 0.2 mmol) and aniline **2a** (18.6 mg, 0.2 mmol) were added to DMSO-d_6 and D_2O (0.8 mL+0.2 mL) and gave a 25:75 mixture of *Z*- and *E*-isomers (indicated by ^{1}H NMR). HPLC (λ=298/300 for *E*-isomer and 320 nm for *Z*-isomer, C_8): major isomer (***E*-5a**), t_R=4.3 min; minor isomer (***Z*-5a**), t_R=7.9 min; ^{1}H NMR (400 MHz, DMSO-d_6 and D_2O), ***Z*-5a**: δ=7.32–7.12 (m, 2H, CH_{ar}), 7.12–7.00 (m, 3H, CH_{ar}), 4.07–4.05 (m, 4H, CH_2), 1.38 (t, J=7.2 Hz, 3H, CH_3), 0.98 (t, J=7.2 Hz, 3H, CH_3) ppm; ***E*-5a**: δ=7.34–7.30 (m, 2H, CH_{ar}), 7.12–7.05 (m, 3H, CH_{ar}), 4.16 (q, J=7.2 Hz, 2H, CH_2), 3.92 (q, J=7.2 Hz, 2H, CH_2), 1.20 (t, J=7.2 Hz, 3H, CH_3), 1.07 (t, J=7.2 Hz, 3H, CH_3) ppm.

*4.4.4. The ratio of diethyl 2-(benzylamino)but-2-enedioate (**Z**- and **E-5b**) in DMSO-d_6*

Diethyl but-2-ynedioate **1a** (34 mg, 0.2 mmol) and phenylmethanamine **2b** (21.4 mg, 0.2 mmol) were added to DMSO-d_6 (1 mL) and gave a 7:93 mixture of *Z*- and *E*-isomers (indicated by ^{1}H NMR). HPLC (λ=275 for *E*-isomer and 300 nm for *Z*-isomer, C_8), major isomer (***E*-5b**), t_R=4.2 min; minor isomer (***Z*-5b**), t_R=8.6 min; ^{1}H NMR (400 MHz, DMSO-d_6): *Z*-isomer: δ=4.90 ppm (s, 1H, 3-H), other δ values of *Z*-isomer could not be read as the signals were too weak; *E*-isomer: δ=7.90 (t, J=5.6 Hz, 1H, NH), 7.38−7.25 (m, 5H, CH_{ar}), 4.46 (s, 1H, 3-H), 4.28–4.16 (m, 4H, CH_2), 3.92 (q, J=7.2 Hz, 2H, $PhCH_2$), 1.25 (t, J=7.2 Hz, 3H, CH_3), 1.10 (t, J=7.2 Hz, 3H, CH_3) ppm.

*4.4.5. The ratio of diethyl 2-(butylamino)but-2-enedioate (**Z**- and **E-5c**) in DMSO-d_6*

Diethyl but-2-ynedioate **1a** (34 mg, 0.2 mmol) and butan-1-amine **2c** (14.6 mg, 0.2 mmol) were added to DMSO-d_6 (1 mL) and gave a 7:93 mixture of *Z*- and *E*-isomers (indicated by ^{1}H NMR). HPLC (λ=275 nm for *E*-isomer and 300 nm for *Z*-isomer, C_8); major isomer (***E*-5c**): t_R=4.6 min; minor isomer (***Z*-5c**), t_R=9.6 min; ^{1}H NMR (400 MHz, DMSO-d_6); *Z*-isomer: δ=4.77 ppm (s, 1H, 3-H), other δ values of *Z*-isomer could not be read for the signals were too weak; *E*-isomer: δ=7.31 (t, J=4.8 Hz, 1H, NH), 4.42 (s, 1H, 3-H), 4.19 (q, J=7.2 Hz, 2H, CH_2), 3.92 (q, J=7.2 Hz, 2H, CH_2), 2.89 (q, J=7.2 Hz, 2H, 1′-H), 1.46–1.09 (m, 10H, 2′/3′-H, CH_3), 0.86 (t, J=7.2 Hz, 3H, CH_3) ppm.

*4.4.6. The ratio of diethyl 2-(p-tolylamino)but-2-enedioate (**Z**- and **E-5d**) in DMSO-d_6*

Diethyl but-2-ynedioate **1a** (34 mg, 0.2 mmol) and *p*-toluidine **2d** (21.4 mg, 0.2 mmol) were added to DMSO-d_6 (1 mL) and gave a 3:97 mixture of *Z*- and *E*-isomers (indicated by ^{1}H NMR). HPLC (λ=300 nm for *E*-isomer and 320 nm for *Z*-isomer, C_8): major isomer (***E*-5d**), t_R=5.2 min; minor isomer (***Z*-5d**), t_R=10.2 min; ^{1}H NMR (400 MHz, DMSO-d_6), *Z*-isomer: δ=9.57 (s, 1H, NH), 5.17 ppm (s, 1H, 3-H), other δ values of *Z*-isomer could not be read for the signals were too weak; *E*-isomer: δ=9.18 (s, 1H, NH), 7.17–7.10 (m, 2H, CH_{ar}), 7.08–7.02 (m, 2H, CH_{ar}), 5.00 (s, 1H, 3-H), 4.22 (q, J=7.2 Hz, 2H, CH_2), 3.96 (q, J=7.2 Hz, 2H, CH_2), 2.24 (s, 3H, $PhCH_3$), 1.26 (t, J=7.2 Hz, 3H, CH_3), 1.12 (t, J=7.2 Hz, 3H, CH_3) ppm.

Acknowledgements

The authors thank the National Natural Science Foundation of China (nos. 20772034, 20625205, 20572027, and 20332030) and Guangdong Natural Science Foundation (no. 07118070) for financial support of this work.

References and notes

1. For examples, see: (a) Tozkoparan, B.; Yarim, M.; Saraç, S.; Ertan, M.; Kelicen, P.; Altinok, G.; Demirdamar, R. *Arch. Pharm.* **2000**, *333*, 415–420; (b) Gazivoda, T.; Plevnik, M.; Plavec, J.; Kraljevic, S.; Kralj, M.; Pavelic, K.; Balzarini, J.; Clercq, E. D.; Mintasa, M.; Silvana, R. *Bioorg. Med. Chem.* **2005**, *13*, 131–139; (c) Srivastav, N. C.; Manning, T. D.; Kunimoto, Y.; Kumar, R. *Bioorg. Med. Chem.* **2007**, *15*, 2045–2053; (d) Sondhi, S. M.; Jain, S.; Dinodia, M.; Shuklab, R.; Raghubir, R. *Bioorg. Med. Chem.* **2007**, *15*, 3334–3344.
2. (a) Dunbar, P. G.; Durant, G. J.; Rho, T.; Ojo, B.; Huzl, J. J.; Smith, D. A.; A El-Assadi, M.; Sbeih, S.; Ngur, D. O.; Periyasamy, S.; Hoss, W.; Messer, W. S. *J. Med. Chem.* **1994**, *37*, 2774–2782; (b) Jung, M. H.; Park, J.; Yang, K. J.; Lee, M. S. *Arch. Pharm. Pharm. Med. Chem.* **2001**, *334*, 79–85.
3. De Lucca, G. V.; Liang, J.; De Lucca, I. *J. Med. Chem.* **1999**, *42*, 135–152.
4. Muravyova, E. A.; Desenko, S. M.; Musatov, V. I.; Knyazeva, I. V.; Shishkina, S. V.; Shishkin, O. V.; Chebanov, V. A. *J. Comb. Chem.* **2007**, *9*, 797–803.
5. Nair, A. C.; Jayatilleke, P.; Wang, X.; Miertus, S.; Welsh, W. J. *J. Med. Chem.* **2002**, *45*, 973–983.
6. (a) Zamri, A.; Sirockin, F.; Abdallah, M. A. *Tetrahedron* **1999**, *55*, 5157–5170; (b) Shutalev, A. D.; Fesenko, A. A.; Cheshkov, D. A.; Goliguzov, D. V. *Tetrahedron Lett.* **2008**, *49*, 4099–4101.
7. Möhrle, H.; Reinhardt, H. W. *Arch. Pharm.* **1981**, *314*, 767–778.
8. Cho, H.; Shima, K.; Hayashimatsu, M.; Ohnaka, Y.; Mizuno, A.; Takeuchi, Y. *J. Org. Chem.* **1985**, *50*, 4227–4230.

9. Chanda, K.; Dutta, M. C.; Karim, E.; Vishwakarma, J. N. *J. Heterocycl. Chem.* **2004**, *41*, 627–631.
10. Zhao, F.; Liu, J. *J. Fluorine Chem.* **2004**, *125*, 1491–1496.
11. For recent examples on multicomponent reactions, see: (a) Tietze, L. F.; Sommer, K. M.; Zinngrebe, J.; Stecker, F. *Angew. Chem., Int. Ed.* **2005**, *44*, 257–259; (b) Miyamoto, H.; Okawa, Y.; Nakazaki, A.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 2274–2277; (c) Komagawa, S.; Saito, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 2446–2449; (d) Siamaki, A. R.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2006**, *128*, 6050–6051; (e) Yoshida, H.; Fukushima, H.; Ohshita, J.; Kunai, A. *J. Am. Chem. Soc.* **2006**, *128*, 11040–11041; (f) Ohno, H.; Ohta, Y.; Oishi, S.; Fujii, N. *Angew. Chem., Int. Ed.* **2007**, *46*, 2295–2298; (g) Bonne, D.; Dekhane, M.; Zhu, J. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 2485–2488; (h) Pinto, A.; Neuville, L.; Zhu, J. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 3291–3295; (i) Song, S. D.; Song, L. P.; Dai, B. F.; Yi, H.; Jin, G. F.; Zhu, S. Z.; Shao, M. *Tetrahedron* **2008**, *64*, 5728–5735; (j) Li, D. M.; Song, L. P.; Li, X. F.; Xing, C. H.; Peng, W. M.; Zhu, S. Z. *Eur. J. Org. Chem.* **2007**, 3520–3525; (k) Li, X. F.; Song, L. P.; Xing, C. H.; Zhao, J. W.; Zhu, S. Z. *Tetrahedron* **2006**, *62*, 2255–2263.
12. (a) Zhang, M.; Jiang, H.; Liu, H.; Zhu, Q. *Org. Lett.* **2007**, *9*, 4111–4113; (b) Cao, H.; Wang, X.; Jiang, H.; Zhu, Q.; Zhang, M.; Liu, H. *Chem.—Eur. J.* **2008**, *14*, 11623–11633.
13. (a) Pihko, P. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2062–2064; (b) Bolm, C.; Rantanen, T.; Schiffers, I.; Zani, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 1758–1763; (c) Connon, S. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 3909–3912.
14. (a) Akiyama, T.; Takaya, J.; Kagoshima, H. *Tetrhedron Lett.* **2001**, *42*, 4025–4028; (b) Bahmanyar, S.; Houk, K. N. *Org. Lett.* **2003**, *5*, 1249–1251; (c) Mitsumori, S.; Zhang, H.; Cheong, P. H.; Houk, K. N.; Tanaka, F.; Barbas, C. F. *J. Am. Chem. Soc.* **2006**, *128*, 1040–1041; (d) Cheong, P. H.; Zhang, H.; Thayumanavan, R.; Tanaka, F.; Houk, K. N.; Barbas, C. F. *Org. Lett.* **2006**, *8*, 811–814; (e) Lou, S.; Dai, P.; Schaus, S. E. *J. Org. Chem.* **2007**, *72*, 9998–10008.
15. Um, I. H.; Lee, E. J.; Min, J. S. *Tetrahedron* **2001**, *57*, 9585–9589.
16. CCDC-701656 (for **4aaa**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
17. For the synthesis and properties of similar *Z*- and *E*-isomers see: Huisgen, R.; Herbig, K.; Siegl, A.; Huber, H. *Chem. Ber.* **1966**, *99*, 2526–2545.
18. For the synthesis of ***Z*-5a–d**, see: (a) Maulding, D. R. U.S. Patent 4,814,486, 1989; (b) Iwanami, Y. *Nippon Kagaku Zasshi* **1961**, *82*, 634–637; (c) Iwanami, Y. *Nippon Kagaku Zasshi* **1962**, *83*, 593–597.
19. References that reported *E*-**5a** as an intermediate: (a) Elango, V.; Larkin, D. R.; Fritch, J. R.; Bodman, M. P.; Mueller, W. H.; Gupton, B. F.; Saukaitis, J. C. U.S. Patent 5,405,987, 1995; (b) Surrey, A. R.; Cutler, R. A. *J. Am. Chem. Soc.* **1946**, *68*, 514–517.
20. Toppet, S.; Van Loock, E.; L'Abbe, G.; Smets, G. *Chem. Ind.* **1971**, *25*, 703.
21. Terada, M.; Machioka, K.; Sorimachi, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 2254–2257.
22. Mark, S. T.; Eric, N. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520–1543.