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A New Multicomponent Reaction Catalyzed by a Lewis Acid Catalyst: Convenient Synthesis of Polyfunctional Tetrahydropyrimidines

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After publication of this Full Paper,[1] *the authors learned, through X-ray crystal structure analysis, that the structures of the products were incorrectly deduced. As such, the names of the given products were also incorrect. The authors therefore retract this Full Paper and apologize for any inconvenience this may have caused.*

The Autors

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A New Multicomponent Reaction Catalyzed by a Lewis Acid Catalyst: Convenient Synthesis of Polyfunctional Tetrahydropyrimidines

Min Zhang[a] and Huan-Feng Jiang*[a]

Keywords: Lewis acids catalysis / Multicomponent reactions / One-pot synthesis / Tetrahydropyrimidine / Heterocycles

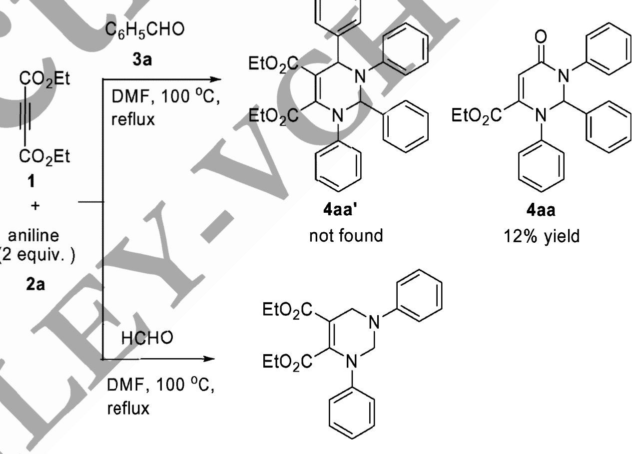
A novel and convenient one-pot synthesis of polyfunctional tetrahydropyrimidine analogues through a Lewis acid catalyzed multicomponent reaction is disclosed. This domino reaction proceeds smoothly in moderate-to-good yields with formation of four C–N bonds in one step. The products are interesting nitrogen heterocycles that contain α- and β-amino acid blocks. (© Wiley-VCH Verlag GmbH & Co. KGaA, 69451 Weinheim, Germany, 2008)

Introduction

Recently, one-pot multicomponent reactions (MCRs) have emerged as a powerful tool in organic synthesis because of the significant advantages they offer, such as the construction of complex molecules from readily available building blocks, higher yields than almost any sequential synthesis of the same target, a single purification step, and easy adaptation to combinatorial synthesis.[1] In the past several years, the new methodologies developed for MCRs to create C–N bonds have become extremely popular as they represent a very efficient entry into different classes of important nitrogenated heterocycles.[2] In this context, we have very recently developed MCR processes for the synthesis of N- or N,O-heterocyclic compounds,[3] which are found in various biologically active natural compounds and in designed medicinal agents.[4,5] Encouraged by these results, we further investigated MCRs in order to construct a new architecture of nitrogen heterocycles by using different reaction conditions, and we present herein an unexpected MCR involving the use of a Lewis acid catalyst that leads to polyfunctional tetrahydropyrimidine analogues.

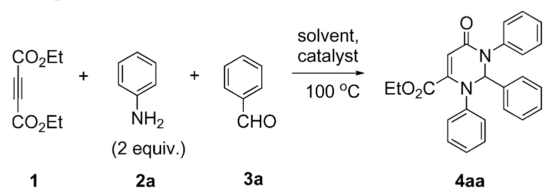
Results and Discussion

We initially subjected diethyl but-2-ynedioate (**1**), aniline (**2a**), and benzaldehyde (**3a**) to our previously reported reaction conditions (DMF, 100 °C, reflux) (Scheme 1).[3a] Unexpectedly no desired product **4aa′** was detected. However, to our surprise, a new nitrogenated cyclic framework of type



Scheme 1. A novel self-mediated bulkiness phenomenon.[3a]

Table 1. Optimization of the reaction conditions for the MCRs.[a]



Entry	Solvent	Catalyst [mol-%]	t [h]	% Yield[b]
1	DMF	–	24	12
2	solvent-free	–	24	3
3	toluene	–	24	15
4	MeCN	–	24	9
5	DMSO	–	24	6
6	dioxane	–	24	10
7	NEt_3	–	8	complex
8	toluene	NaOAc (10)	8	complex
9	toluene	K_2CO_3 (10)	8	complex
10	toluene	KOH (10)	8	complex
11	toluene	$ZnCl_2$ (10)	12	73
12	toluene	$ZnSO_4$ (10)	12	56
13	toluene	$CuBr_2$ (10)	12	37
14	toluene	$ZnCl_2$ (10)	12	78
15	toluene	$ZnCl_2$ (10)	24	76

[a] All reactions were carried out in sealed tubes. [b] Isolated yields.

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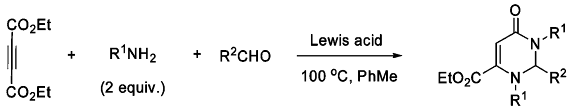
Supporting information for this article is available on the WWW under http://www.eurjoc.org or from the author.

Table 2. One-pot synthesis of polyfunctional tetrahydropyrimidines by the MCR.[a]



1 + **2a–2f** + **3a–3e** → **4aa–4afe**

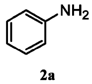
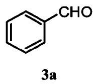
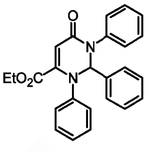
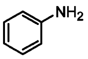
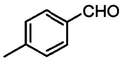
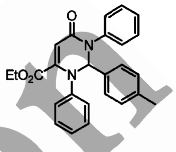
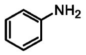
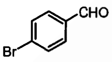
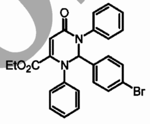
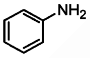
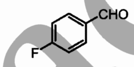
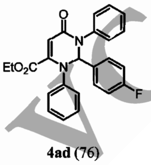
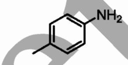
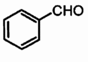
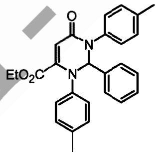
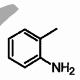
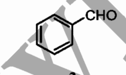
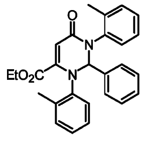
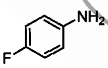
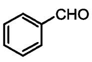
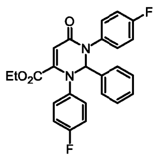
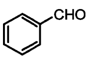
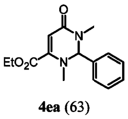
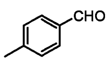
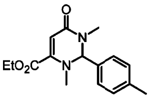
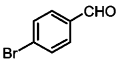
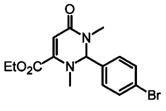
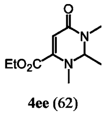
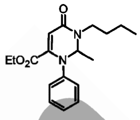
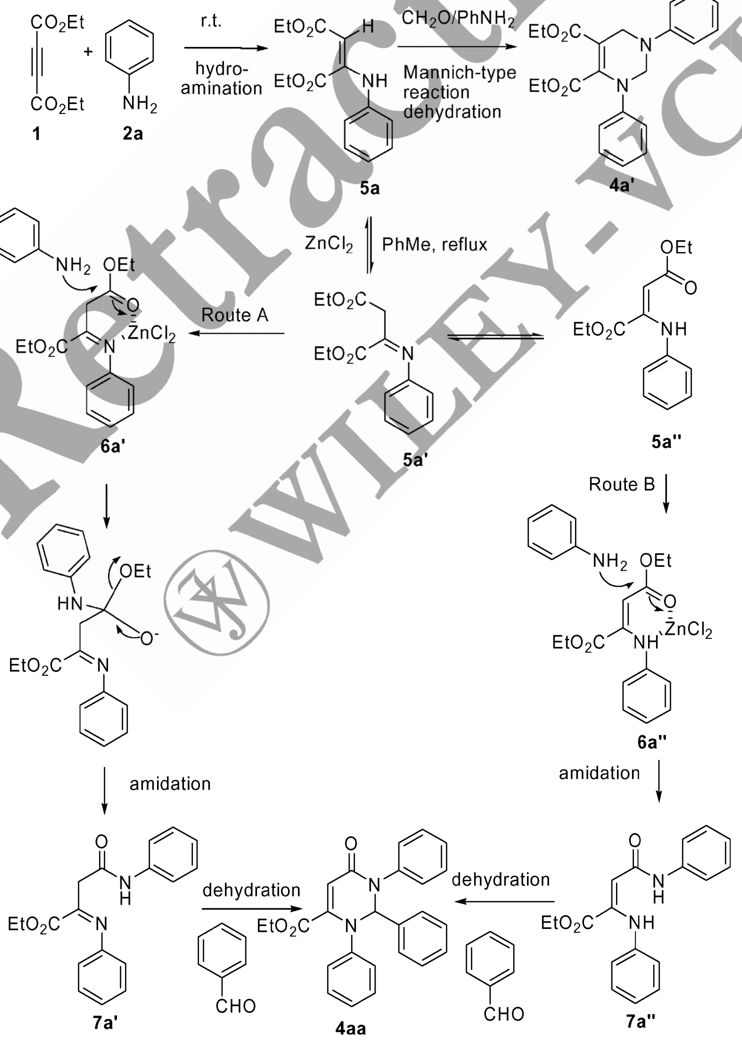
Entry	Amine	Aldehyde	t [h]	Product (% yield)[b]
1	 **2a**	 **3a**	12	 **4aa** (78)
2	 **2a**	 **3b**	12	 **4ab** (71)
3	 **2a**	 **3c**	12	 **4ac** (32)
4	 **2a**	 **3d**	12	 **4ad** (76)
5	 **2b**	 **3a**	12	 **4ba** (71)
6	 **2c**	 **3a**	12	 **4ca** (32)
7	 **2d**	 **3a**	12	 **4da** (47)
8	CH_3NH_2 **2e**	 **3a**	5	 **4ea** (63)
9	CH_3NH_2 **2e**	 **3b**	5	 **4eb** (67)

Table 2. *(Continued)*

Entry	Amine	Aldehyde	*t* [h]	Product (% yield)[b]
10	CH_3NH_2 **2e**	 **3c**	5	 **4ec** (62)
11	CH_3NH_2 **2e**	CH_3CHO **3e**	3	 **4ee** (62)
12[c]	**2a** + *n*-$C_4H_9NH_2$ **(2f)**	CH_3CHO **3e**	3	 **4afe** (82)

[a] All the reaction were carried out in sealed tubes. [b] Isolated yields. [c] Although we tried to change the order of addition of the two amines under the same conditions, only the first drops of aniline resulted in the desired product **4afe**, and a very complicated reaction system was obtained if *n*-$C_4H_9NH_2$ was added first.



Scheme 2. Plausible mechanism for this MCR.

4aa was furnished in low yield (12%), which was confirmed by ^{1}H and ^{13}C NMR measurements after purification by preparative TLC on silica gel. By comparing the structure of **4aa** with those of **4aa′** and **4a′**, it was noted that although they were all six-membered tetrahydropyrimidine rings, the obtained product was dependent on steric hindrance to some extent. The reaction of the aldehyde with a bulky group might favor the formation of less substituted cyclic compounds. On the other hand, this result also revealed that the switch in product selectivity is perhaps controlled by a crucial factor, which has led to a new synthetic MCR strategy for the convenient one-pot synthesis of new polyfunctional 1,2,3,6-tetrahydropyrimidines through a different intramolecular cyclization pathway.

As shown in Table 1, the reaction was performed with various solvents and under solvent-free conditions and resulted in low yields (Table 1, entries 1–7), although toluene proved to be the best (entry 3). A very complicated reaction system was found when bases were added (entries 8–10). To solve the problem, we turned to Lewis acids. The reaction yields could be dramatically increased by using different kinds of Lewis acids, such as $ZnCl_2$, $ZnSO_4$, and $CuBr_2$, and clearly zinc chloride was the most suitable one for the cyclization reaction (entries 11–15).

A series of amines **2a**–**f** and aldehydes **3a**–**e** were subjected to the above optimized reaction conditions to broaden the scope of the MCR (Table 2). We were pleased to find that all the reactions proceeded smoothly and the desired products were afforded in moderate-to-good yields. The steric hindrance effects of the substituents on the aromatic rings have a certain influence on the yields: *o*-substituted aromatic amine (Table 2, entry 6) provided a relatively low yield compared with those of others. However, the electronic effects of the substituents on the aromatic amines or aldehydes (entries 1 and 3–5) did not significantly influence the yields. The reaction time for the aliphatic primary amines (entries 8–12) was shorter than those of the aromatic primary amines, which indicated that the activity of the aliphatic amines is higher.

Scheme 2 shows a plausible mechanism for this MCR. We inferred that the present methodology comprises the relay process of the following domino sequences: (1) A two-component hydroamination to form intermediate **5a**; (2) a Lewis acid promoted two-component ester amidation to give intermediate **6a′** or **6a′′** by route A or B; (3) a two-component amine/aldehyde dehydration/cyclization process to produce new compound **4aa**.

We examined this MCR step by step and found that intermediate **5** could be obtained even at room temperature.[6] The isolated **5** could react smoothly with formaldehyde and aniline at 100 °C to form **4a′**.[3a] When formaldehyde was replaced by benzaldehyde, the reaction was accomplished only in the presence of the Lewis acid.[7] This result clearly shows that the Lewis acid is crucial for the MCR of diethyl but-2-ynedioate (**1**), aniline (**2a**), and benzaldehyde (**3a**). We guessed that the Lewis acid plays a dual role as an efficient promoter for the isomerization of **5a** and the amidation of **5a′** or **5a′′**. Intermediate **7a′** or **7a′′** was converted into product **4aa** in the presence of **3a** by dehydration/cyclization.

Conclusions

An efficient Lewis acid catalyst for a novel type of multicomponent reaction that leads to polyfunctional 1,2,3,6-tetrahydropyrimidine analogues was found. This Lewis acid catalyzed cascade process proceeds smoothly in moderate-to-good yields with the formation of four C–N bonds in one operation. The products obtained in our experiments are interesting nitrogen heterocyclic molecules that contain α- and β-amino acid blocks. Our strategy allows the introduction of different substituents into the 1,2,3-positions of the pyrimidine ring. Thus, the present cascade process allows the assembly of a wide range of polysubstituted tetrahydropyrimidines from readily available starting materials. Further studies and applications of this cascade reaction are ongoing in our laboratory and will be published in due course.

Experimental Section

General: All reactions were performed at 100 °C in sealed tubes containing a magnetic stirring bar. ^{1}H and ^{13}C NMR spectra were recorded using a Bruker Avance 400 MHz NMR spectrometer. The chemical shifts are referenced to signals at 7.24 and 77.0 ppm, respectively, of the chloroform solvent with TMS as the internal standard. IR spectra were obtained either as potassium bromide pellets or as liquid films between two potassium bromide pellets with a Bruker Vector 22 spectrometer. Mass spectra were recorded on a Shimadzu GCMS-QP5050A spectrometer at an ionization voltage of 70 eV equipped with a DB-WAX capillary column (internal diameter: 0.25 mm, length: 30 m). Elemental analyses were performed with a Vario EL elemental analyzer. TLC was performed by using commercially prepared 100–400 mesh silica gel plates (GF254) and visualization was effected at 254 nm. All the other chemicals were purchased from Aldrich Chemicals.

Typical Procedure for the One-Pot Synthesis of 1,2,3,6-Tetrahydropyrimidine Analogues by Three-Component Reactions: Benzaldehyde (127 mg, 1.2 mmol), toluene (3 mL), and zinc chloride (14 mg, 0.1 mmol) were added successively to a stirring mixture of diethyl but-2-ynedioate (**1**, 170 mg, 1 mmol) and aniline (186 mg, 1 mmol). The mixture was stirred at 100 °C for 12 h, and TLC of the mixture showed only traces of intermediate **5**. The reaction mixture was diluted with diethyl ether (15 mL) and dried with anhydrous $MgSO_4$. Then the mixture was filtered and washed with diethyl ether (5 mL × 5). The combined organic solvents were evaporated in vacuo and the crude product was purified by preparative TLC with hexane/ethyl acetate (10:1) as the eluent to afford the desired product **4ab** (252 mg, 78%) as a yellowish solid, which was further recrystallized from hexane/dichloromethane for elemental analysis; m.p. 166–169 °C. IR (KBr): $\tilde{\nu}_{max}$ = 3062, 2982, 1709, 1694, 1596, 1534, 1498, 1454, 1370, 1243, 1077, 1035, 901, 831 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.17 (br. s, 1 H), 7.46–7.26 (m, 7 H), 7.22–7.06 (m, 8 H), 5.80 (s, 1 H), 3.99 (q, J = 7.2 Hz, 2 H), 0.98 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.3, 164.1, 141.9, 138.7, 136.7, 136.5, 128.8, 128.4, 128.3, 128.1, 127.6, 125.6, 124.6, 122.7, 109.8, 63.2, 60.2, 13.7 ppm. MS (EI): m/z (%) = 398 (48) [M]$^{+}$, 325 (100), 297 (26). $C_{25}H_{22}N_2O_3$

(398.45): calcd. C 75.36, H 5.57, N 7.03; found C 74.92, H 5.54, N 7.07.

Supporting Information (see also the footnote on the first page of this article): Analytical and spectroscopic data for compounds **4aa**–**4afe** for this article is available.

Acknowledgments

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[6] A mixture of diethyl but-2-ynedioate (**1**) (170 mg, 1 mmol), aniline (**2a**) (93 mg, 1 mmol), and DMF (2 mL) was stirred at room temperature for 30 min. After completion of the reaction and purification by preparative TLC, intermediate **5** was obtained as a pure compound.

[7] Intermediate **5** can react with benzaldehyde and aniline in the presence of $ZnCl_2$ in toluene at 100 °C to form product **4aa**.

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