Microwave-Assisted Combinatorial Synthesis of New 3-Pyrimidin-5-ylpropanamides via a Solvent-Dependent Chemoselective Reaction

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A series of new 3-pyrimidin-5-ylpropanamides was selectively synthesized via a microwave-assisted, chemoselective reaction of arylidene-Meldrum's acid, 6-hydroxypyrimidin-4(3*H*)-one, and structurally diverse amines including (*S* or *R*)-1-phenylethanamine, cyclohexanamine, and cyclopentanamine depended on nature of solvents. In this reaction, the utilization of HOAc as a solvent leads to 3-pyrimidin-5-ylpropanamides, whereas water as reaction media results in the spiro[5.5]undecane-1,5,9-triones from same starting materials. This method has the advantages of short synthetic route, operational simplicity, increased safety for small-scale high-speed synthesis, and minimal environment impact.

Introduction

Selectivity is a key issue to be controlled in organic synthesis. In particular, chemoselectivity is synthetically useful because it gives one of several products selectively from the same substrate without the need to separate the products from the product mixture. It continues to be developed as organic synthesis strives for ever-increasing levels of efficiency. As a result, many studies have focused on the chemoselectivity of reactions.[1] In recent years, many reports have dealt with the control of chemoselectivity reactions with metal catalysts,[1a−e] while solvent-dependent chemoselective reactions have been researched in relatively few papers.[1g−i] Therefore, the development of highly solvent-dependent chemoselective reactions remains a challenge.

It is well-known that heterocycles are abundant in nature and are of great significance to life because their structural subunits exist in many natural products such as vitamins, hormones, antibiotics, and alkaloids, as well as pharmaceuticals, herbicides, dyes, and many more compounds. The pyrimidines and their derivatives as a class of extremely important heterocyclic compounds are used in a wide array of synthetic and industrial applications. They not only are an integral part of the genetic materials, namely, DNA and RNA as nucleotides and nucleosides, but also play critical roles especially in pharmaceutical fields.[2] Some pyrimidine derivatives can give stable and good quality nanomaterials having many important electrical and optical properties,[3] and they can also be also used as functional materials.[4] Therefore, the synthesis of these structures has attracted considerable attention.[5] However, the synthesis of 3-pyrimidin-5-ylpropanamides has not stimulated much interest so far. In this paper, we would like to report a chemoselective reaction of arylidene-Meldrum's acid with 6-hydroxypyrimidin-4(3*H*)-one and structurally diverse amines by controlling the nature of solvents to give 3-pyrimidin-5-ylpropanamides in good to excellent yields (Scheme 1).

Results and Discussion

The choice of an appropriate reaction media is of crucial importance not only for successful microwave-promoted synthesis but also for the effective control of chemoselective

Scheme 1. Chemoselective Synthesis of 3-Pyrimidin-5-ylpropanamides and Spiro[5.5]indecane-1,5,9-triones

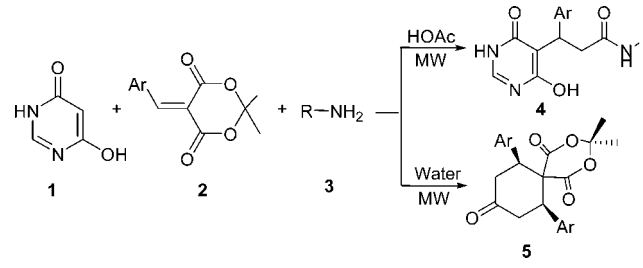

Table 1. Optimization of Chemoselectivity Conditions in the Synthesis of Compounds **4a** and **5a**

			product	
entry	solvent	time (min)	4a	5a
1	ethylene glycol	19	56	13
2	DMF	20	49	23
3	ethanol	22	59	19
4	HOAc	20	84	trace
5	water	22	trace	38

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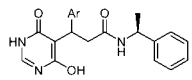
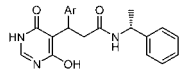
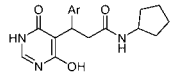
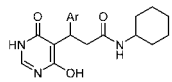
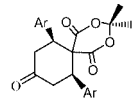
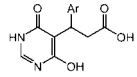
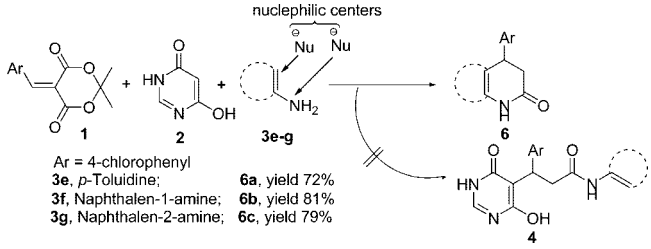
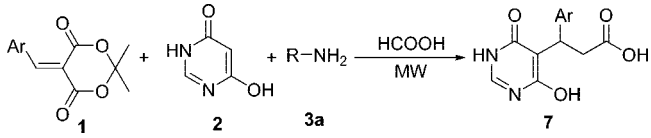
Table 2. Synthesis of Compounds **4**, **5**, and **7** under Microwave Irradiation Conditions

Entry	Product	Ar =	Time / min	Yield / %	Mp / °C
1		**4a**, 4-Tolyl (**1a**)	20	84	263-265
2		**4b**, 4-Methoxyphenyl (**1b**)	18	81	239-240
3		**4c**, 4-Dimethylaminophenyl (**1c**)	22	79	255-257
4		**4d**, 4-Bromophenyl (**1d**)	18	85	278-280
5		**4e**, 4-Fluorophenyl (**1e**)	18	84	285-287
6	**4a-4h**	**4f**, 2,4-Dichlorophenyl (**1f**)	18	85	254-256
7		**4g**, 4-Nitrophenyl (**1g**)	16	89	298-300
8		**4h**, 4-Hydroxy-3-nitrophenyl (**1h**)	16	87	176-178
9		**4i**, 4-Tolyl (**1a**)	22	81	266-268
10		**4j**, 4-Methoxyphenyl (**1b**)	20	75	252-253
11		**4k**, 4-Bromophenyl (**1d**)	18	84	272-274
12		**4l**, 4-Fluorophenyl (**1e**)	18	82	264-266
13	**4i-4n**	**4m**, 4-Nitrophenyl (**1g**)	16	85	285-287
14		**4n**, 4-Hydroxy-3-nitrophenyl (**1h**)	16	82	182-184
15		**4o**, 4-Tolyl (**1a**)	20	87	274-276
16		**4p**, 4-Methoxyphenyl (**1b**)	19	84	251-252
17		**4q**, 4-Bromophenyl (**1d**)	16	91	241-243
18		**4r**, 4-Fluorophenyl (**1e**)	16	87	202-203
19		**4s**, 4-Nitrophenyl (**1g**)	14	85	292-293
20	**4o-4w**	**4t**, 2,4-Dichlorophenyl (**1f**)	14	82	278-280
21		**4u**, 4-Hydroxy-3-nitrophenyl (**1h**)	14	79	260-262
22		**4v**, Benzo[*d*][1, 3]dioxol-5-yl (**1i**)	18	81	269-271
23		**4w**, 3-Nitrophenyl (**1j**)	14	86	216-218
24		**4x**, 4-Tolyl (**1a**)	18	83	261-263
25		**4y**, 4-Methoxyphenyl (**1b**)	18	82	222-224
26		**4z**, 4-Bromophenyl (**1d**)	14	84	209-210
27		**4aa**, 4-Fluorophenyl (**1e**)	14	85	257-259
28		**4bb**, 4-Nitrophenyl (**1g**)	12	81	225-227
29	**4x-4hh**	**4cc**, 2,4-Dichlorophenyl (**1f**)	12	83	276-278
30		**4dd**, 4-Hydroxy-3-nitrophenyl (**1h**)	14	80	238-239
31		**4ee**, Benzo[*d*][1, 3]dioxol-5-yl (**1i**)	16	72	273-275
32		**4ff**, 3-Nitrophenyl (**1j**)	14	86	206-208
33		**4gg**, 2-Chlorophenyl (**1l**)	16	73	240-242
34		**4hh**, Thien-2-yl (**1m**)	18	69	265-267
35		**5a**, 4-Tolyl (**1a**)	22	38	180-182
36		**5b**, 4-Methoxyphenyl (**1b**)	22	35	208-209
37		**5c**, 4-Dimethylaminophenyl (**1c**)	18	39	228-230
38		**5d**, 4-Bromophenyl (**1d**)	16	42	209-210
39		**5e**, Benzo[*d*][1, 3]dioxol-5-yl (**1i**)	16	34	233-235
40	**5a-5g**	**5f**, 4-Chlorophenyl (**1k**)	18	43	211-212
41		**5g**, Thien-2-yl (**1m**)	20	31	191-192
42		**7a**, 4-Tolyl (**1a**)	20	84	265-267
43		**7b**, 4-Fluorophenyl (**1e**)	16	85	248-250
44		**7c**, 2,4-Dichlorophenyl (**1f**)	16	89	>300
45	**7a-7f**	**7d**, Benzo[*d*][1, 3]dioxol-5-yl (**1i**)	18	74	247-249
46		**7e**, 2-Chlorophenyl (**1l**)	18	81	202-204
47		**7f**, 3,4-Dimethoxyphenyl (**1n**)	22	82	255-257

Scheme 2. Synthesis of Quinolin-2(1*H*)-one Derivative **6**



Scheme 3. Synthesis of Pyrimidin-5-ylpropanoic acids **7a**−**7f**



reaction. To choose the optimum solvent, the microwave-assisted reaction of arylidene-Meldrum's acid **1a** (1 mmol) with equimolar 6-hydroxypyrimidin-4(3*H*)-one **2** and (*S*)-1-phenylethanamine **3a** was examined at 100 °C using ethylene glycol, *N*,*N*-dimethylformamide (DMF), and ethanol as solvent. All the reactions were performed under microwave irradiation (initial power 100 W and maximum power 250 W). The results of the screening of solvents are presented in Table 1. It was observed that both 3-pyrimidin-5-ylpropanamides **4a** and spiro[5.5]undecane-1,5,9-triones **5a** could be obtained in the above solvents. When the reaction was carried out in glacial acetic acid (HOAc), the product **4a** was generated in good yield without byproducts, whereas when water was used as a solvent, only spiro[5.5]undecane-1,5,9-triones **5a** was obtained (Table 1). It is worth noting that the reaction could be controlled to exclusively yield **4a** or **5a** by varying reaction media.

Under the conditions described above, the scope of these multicomponent reactions (MCRs) was examined using various easily available starting materials (Table 2). A range of valuable new elaborated structures of **4** were synthesized in good to excellent yields by simply microwave heating an acetic acid solution of structurally diverse arylidene-Meldrum's acid **1**, 6-hydroxypyrimidin-4(3*H*)-one (**2**), and various amines **3**.

Initially, to test the scope of arylidene-Meldrum's acid, 6-hydroxypyrimidin-4(3*H*)-one **2** and (*S*)-1-phenylethanamine **3a** were used as model substrates, and the results (Table 2, entries 1−8) indicated that arylidene-Meldrum's

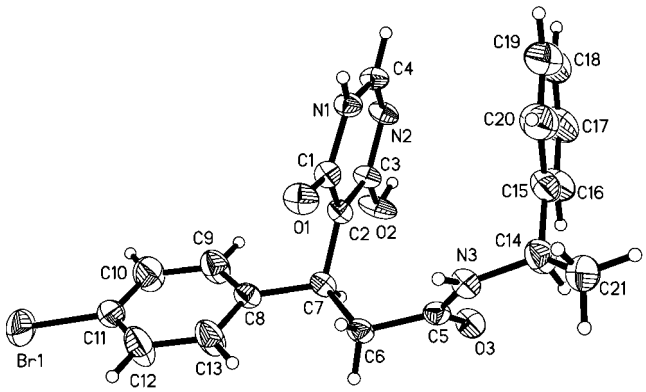


Figure 1. ORTEP drawing of **4d**.

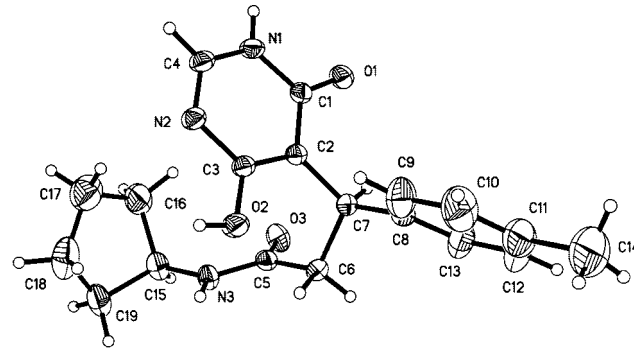


Figure 2. ORTEP drawing of **4o**.

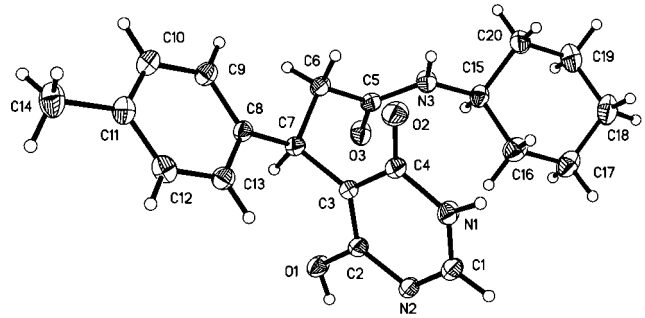


Figure 3. ORTEP drawing of **4x**.

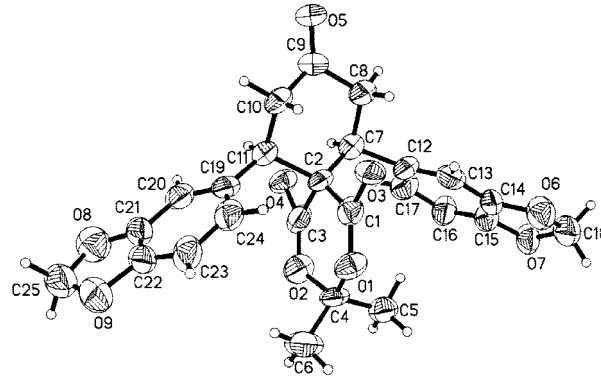
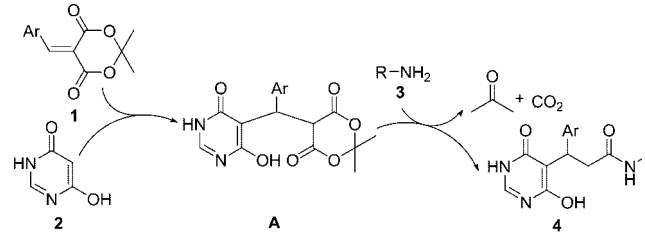


Figure 4. ORTEP drawing of **5e**.

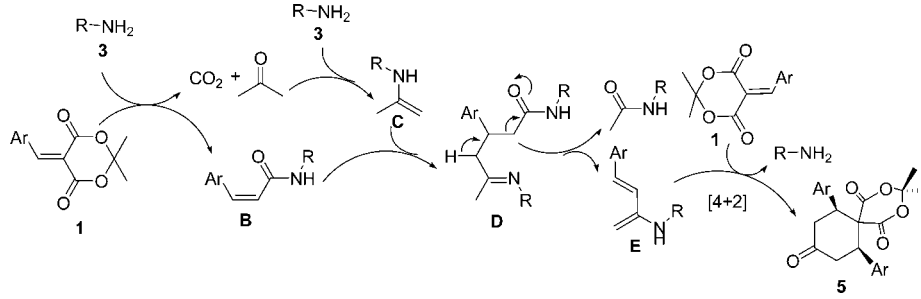
Scheme 4. Possible Reaction Mechanism of Products **4**



acid bearing functional groups such as nitro, bromo, fluoro, or methoxy are suitable for the reaction. We have also observed delicate electronic effects, that is, arylidene-Meldrum's with electron-withdrawing groups (Table 2, entries 4−8) reacted rapidly, while electron-rich groups (Table 2, entries 1−3) decreased the reactivity, requiring longer reaction times.

To expand the scope of amine substrates, we used different arylidene-Meldrum's acids and 6-hydroxypyrimidin-4(3*H*)-one **2** as model substrates and examined various amine including (*R*)-1-phenylethanamine (**3b**), cyclohexanamine (**3c**), and cyclopentanamine (**3d**). In all these cases, the

Scheme 5. Possible Reaction Mechanism of Products **5**



reactions proceeded smoothly to give the corresponding 3-pyrimidin-5-ylpropanamides **4a**−**hh** in good yields of 69−91%. Impressively, the ^{1}H NMR analysis of the products **4a**−**n** indicates the presence of a mixture of two diastereoisomers resulting from generation of a new asymmetric carbon. The ratio of the isomers was close to 1:1 as demonstrated by ^{1}H NMR integration of the crude mixture. Moreover, the heterocyclic arylidene-Meldrum's acid, such as thiophene-2-yl-Meldrum's acid still displayed high reactivity and clean reaction under this standard condition (Table 2, entry 35),. It was important to notice that this protocol could be applied not only to aliphatic amines (Table 2, entries 1−14) but also to alicyclic amines (Table 2, entries 15−35). Unfortunately, when aromatic amines **3e**−**g** were used as precursor instead of aliphatic amines to react with arylidene-Meldrum's acid **1d** and 6-hydroxypyrimidin-4(3*H*)-one **2** in HOAc under microwave heating, we could not get the desired poly-substituted 3-pyrimidin-5-ylpropanamides in any cases. Instead, the quinolin-2(1*H*)-one derivative **6a**−**c** were obtained in good yields (Scheme 2); the synthesis of these structures has been reported.[6] The reason may be that the aromatic amines have two nucleophilic centers, which were simultaneously utilized in one-pot reaction and easily resulted in the quinolin-2(1*H*)-one derivative **6**.

In addition, spirocyclic compounds involving in Meldrum's acid unit are attractive intermediates in the synthesis of natural products and in medicinal chemistry and are the starting materials for the synthesis of exotic amino acids, which are used to modify the physical properties and biological activities of peptides, peptidomimetics, and proteins.[7] Thus, the synthesis of new highly substituted spiro ring system may have potential biologic interest. Impressively, in our reaction progress, spirotriones possessing Meldrum's acid unit was selectively synthesized by screening the reaction media. The treatment of arylidene-Meldrum's acid **1a** with equimolar 6-hydroxypyrimidin-4(3*H*)-one **2** and (*S*)-1-phenylethanamine **3a** in water generate spiro[5.5]undecane-1,5,9-triones **5a** as a single diastereomer in 38% yield. Obviously, 6-hydroxypyrimidin-4(3*H*)-one did not take part in the reaction for spirotriones; (*S*)-1-phenylethanamine has acted not only as a reactant but as a base catalyst. To demonstrate the generality of this methodology, structurally diverse arylidene-Meldrum's acid with electron-withdrawing groups or electron-rich groups on the phenyl ring were employed to react with (*S*)-1-phenylethanamine in water, leading to a series of spiro[5.5]undecane-1,5,9-triones **5** with high syn-selectivities, accompanied with byproduct acetamides. In the further investigation, other amines, for example, (*R*)-1-phenylethanamine, cyclohexanamine, and cyclopentanamine in water can generate same spirocyclic products **5**.

To further investigate this process, reactions of arylidene-Meldrum's acid **1** with 6-hydroxypyrimidin-4(3*H*)-one **2** and amines **3a** were carried out in formic acid (pK_a = 3.77)[8] whose pK_a value was lower than that of acetic acid (pK_a = 4.76).[8] Surprisingly, we could not get the expected product **4**, instead pyrimidin-5-ylpropanoic acids **7** were obtained in good yields (Scheme 3). The results indicated that amine **3a** might have formed ammonium salt by reacting with formic acid, losing the nucleophilicity.

The structures of all of the synthesized compounds were established on the basis of their spectroscopic data. The structures of **4d**, **4x**, **4o**, and **5e** were established by X-ray crystallographic analysis (Figure 1−4, respectively).The IR spectra of compound **4k** showed strong absorptions at 3312 cm^{-1} from NH group and at 1651 cm^{-1} from C═O group. The ^{1}H NMR spectrum of **4k** showed two doublets at δ 1.26 and 1.24, respectively, from the $-CH_3$, a singlet at δ 7.94 from the NH proton (exchanged with D_2O), and two doublets at δ 8.29 and 8.24 from the CH proton in the pyrimidine ring.

A reasonable mechanism for the formation of the product **4** is outlined in Scheme 4. The formation of the product **4** is expected to proceed via initial Michael addition to afford intermediate **A**, which converted to 3-pyrimidin-5-ylpropanamides **4** upon reaction of amines **3**. The formation of the spirotriones **5** is likely to proceed via initial S_NA (nucleophilic acyl substitution) type reaction[9] to yield cinnamamides **B**, which further undergoes in situ Michael addition with enamine **C** to generate intermediate **D**. The 2-amine-1,3-butadiene **E** and amides would be formed by elimination reaction of intermediate **D**, and the following Diels−Alder reaction occurs to complete the final spirotriones **5** (Scheme 5). This hypothesis is also supported by the mechanistic investigation of proline-catalyzed spirotriones formation through the reaction of aldehyde and Meldrum's acid with enones reported by Barbas III et al.[7a,10]

Conclusion

In summary, we have successfully combined the advantages of microwave technology with chemoselective multicomponent reactions to facilitate the rapid construction of 3-pyrimidin-5-ylpropanamide, 3-pyrimidin-5-ylpropanoic acid, and spiro[5.5]undecane-1,5,9-triones skeletons by screening

the nature of solvents from readily obtainable and inexpensive materials. Particularly valuable features of this method included the good to excellent yields and operational simplicity, as well as increased safety for small-scale high-speed synthesis. In addition, this series of new 3-pyrimidin-5-ylpropanamides may prove new classes of biological active compounds for biomedical screening, which is in progress in our laboratory.

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Supporting Information Available. Representative experimental procedures, spectral data of compounds **4a**−**4hh**, **5a**, **5c**, and **7a**−**7f**, and crystallographic information files (CIF) of **4d**, **4x**, **4o**, and **5e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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