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Efficient synthesis of functionalized pyrimidones via microwave-accelerated rearrangement reaction

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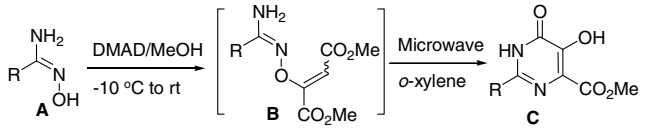
Abstract—An efficient synthesis of functionalized pyrimidones via microwave-accelerated rearrangement reaction of amidoxime DMAD adducts is described. In most cases, the pyrimidone formation was furnished in reasonable yield after 2 min of microwave irradiation.

Substituted pyrimidones of type **C** represent an important class of compounds due to their well-known biological activity.[1] Pyrimidones of this type were recently found to inhibit a series of hepatitis C virus (HCV) NSSB polymerase[2] and have also shown anxiolytic activity.[3] Most synthetic strategies toward these densely functionalized heterocycles are based on two synthetic methods. The first is a three-step sequence that involves two condensations and a deprotected step from commercially available materials.[4] The second method uses a Michael reaction between substituted amidoximes of type **A** with dimethyl acetylenedicarboxylate (DMAD) followed by thermal rearrangement of intermediate **B** (Scheme 1).[5] The Michael reaction/thermal rearrangement sequence typically affords pyrimidones in only 30–40% overall yield in the few examples that have been reported.[2,3,5]

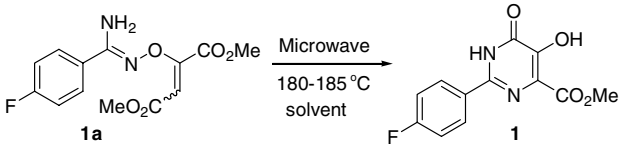
The use of microwave irradiation to assist organic reactions has shown considerable advantages over thermal reactions.[6] Reactions that typically require high temperatures and extended reaction times have been tremendously accelerated using microwave irradiation.[7] Herein, we report on a two-step, one-pot conversion of aldoximes to pyrimidones via a microwave-assisted thermal rearrangement of intermediate B.



Scheme 1.

For reaction optimization studies, we focused on amidoxime DMAD adducts **1a**, which were isolated as a mixture of cis/trans (ratio ca. 6–10:1) crystalline solid

Table 1. Solvent effect for the microwave-assisted rearrangement



Entries	Solvents[a]	Assay yield (%)
1	Neat	52
2	1,2-Dichlorobenzene	62
3	DME	54
4	1,2-Dichloroethane	50
5	1,4-Dioxane	66
6	DMF	38
7	IPA	35
8	Toluene	47
9	Acetonitrile	48
10	*o*-Xylene	68

[a] DME = ethylene glycol dimethyl ether, DMF = *N*,*N*-dimethylformamide; IPA = 2-propanol.

Keywords: Pyrimidone; Hydroxyamidine; Rearrangement; Heterocyclic compounds; Microwave irradiation.
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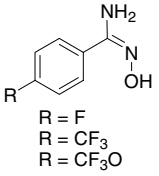
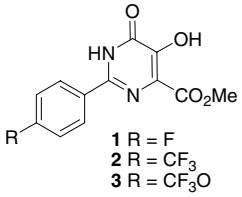
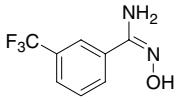
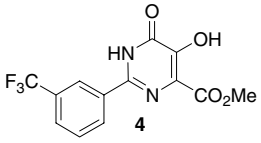
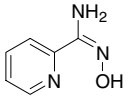
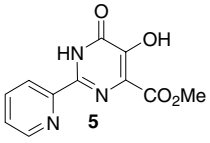
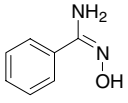
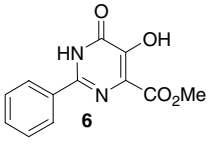
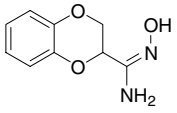
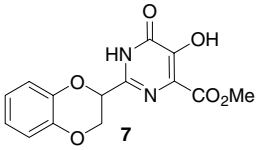
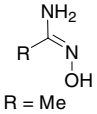
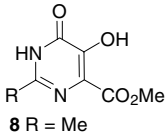
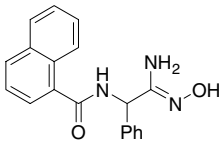
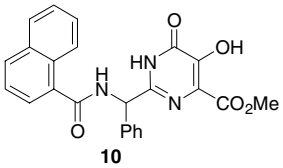
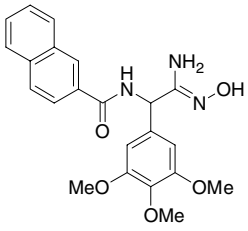
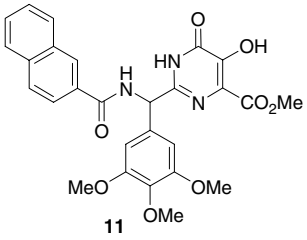
in quantitative yield by treatment of 4-fluoro-*N*′-hydroxybenzenecarboximidamide with DMAD in methanol. Intermediate **1a** was irradiated[8] for 2 min (internal temperatures reached 185 °C) in a variety of solvents and all reactions gave >95% conversion (Table 1). We were also delighted to find that several solvents provided assay yields in >60%.[9]

The desired pyrimidone **1** is isolated by direct precipitation from the crude mixture via filtration to afford 60% isolated yield in >95% purity (entry 1).

The scope of the reaction sequence was investigated and all substrates shown in Table 2 were converted to pyrimidones in reasonable yield over two steps. In practice, the

Table 2. Synthesis of pyrimidones

Entry	Starting material	Product	Conditions	Yield (%)[b]
1 2 3	 R = F R = CF_3 R = CF_3O	 **1** R = F **2** R = CF_3 **3** R = CF_3O	rt to 185 °C over 85 s	60 61 48
4[a]		 **4**	rt to 185 °C over 160 s	50
5		 **5**	rt to 185 °C over 85 s	50
6		 **6**	rt to 182 °C over 85 s	50
7		 **7**	rt to 185 °C over 85 s	59
8 9	 R = Me R = CO_2Et	 **8** R = Me **9** R = CO_2Et	rt to 185 °C over 85 s	48 50
10[a]		 **10**	rt to 185 °C over 120 s	39
11[a]		 **11**	rt to 170 °C over 300 s	67

[a] The hydroxyamidines were prepared by reaction of their corresponding nitrile with 50% aqueous hydroamine in methanol.
[b] Isolated yield.

amidoxime was dissolved in methanol, DMAD (1.05 equiv) was added dropwise at −10 °C, and then slowly allowed to warm to ambient temperature over 6 h (>98% conversion). The reaction mixture was concentrated and then dissolved in *o*-xylene. The solution was microwave irradiated[8] for 1–2 min and the resulting slurry was aged at room temperature for 1 h. The crystalline solid was isolated by filtration, washed with toluene, MTBE, and finally 1:1 methanol/0.5 N HCl. The solid was then dried under vacuum to afford the desired pyrimidone. A variety of substituted aldoximes including aromatic (entries 1–6),[10] and functionalized aliphatic (entries 7–9), and N-protected α-amino amidoximes (entries 10 and 11) were efficiently cyclized to the corresponding pyrimidones in an average isolated yield of 52%.[11]

In conclusion, we have developed a practical and efficient procedure for the rapid construction of highly functionalized pyrimidones via microwave irradiation.

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8. Smith Synthesizer microwave set at 80% of a total output of 1000 W or with the temperature control set to 185 °C.
9. The control experiment using thermal heat: A solution of **1a** (1.00 g) in *o*-xylene (5 mL) was heated in reflux using an oil bath for 3.5 h to give >95% conversion. The assay yield and isolated yield of desired product **1** were 61% and 53%, respectively.
10. The reported yield for Table 1, entry 6 was 44% (crude) or 21% after recrystallization from xylene (see Ref. 5).
11. All new compounds gave satisfactory analytical and spectral data in accordance to their structures. Selected data for compound **1**: ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.05 (dd, $J = 8.7$, 5.5 Hz, 2H), 7.33 (t, $J = 8.7$ Hz, 2H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 166.2, 164.0 (d, $J = 248$ Hz), 159.9, 130.1, 130.0, 130.1 (d, $J = 10$ Hz), 129.0, 116.0 (d, $J = 22$ Hz). Compound **5**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 11.23 (br s, 1H), 10.91 (br s, 1H), 8.61 (br d, $J = 4.5$ Hz, 1H), 8.39 (d, $J = 8.0$ Hz, 1H), 7.88 (td, $J = 8.0$, 1.5 Hz, 1H), 7.44 (dd, $J = 8.0$, 4.5 Hz, 1H), 4.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.8, 156.9, 152.0, 148.7, 147.3, 143.7, 137.6, 126.1, 126.0, 121.4, 53.4.