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General and Rapid Pyrimidine Condensation by Addressing the Rate Limiting Aromatization

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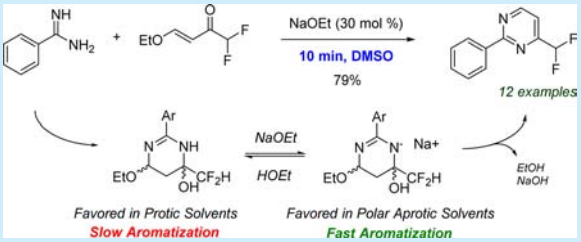
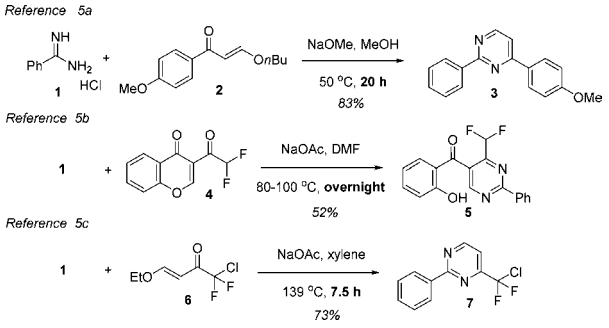
Supporting Information

ABSTRACT: The rate limiting aromatization within the condensation approach toward pyrimidines utilizing amidines and activated olefins was addressed to provide for a general and rapid process. A strong solvent effect was elucidated to affect the rate for the initial alkoxide elimination from the intermediate Michael adduct wherein polar aprotic solvents demonstrate an addition controlled aromatization. Spectroscopic studies support a solvent dependent equilibrium between the amidine and alkoxide base wherein the rate for aromatization is optimal when the equilibrium toward the amidine anion was strongly favored.



The biological importance of the pyrimidine core can be exemplified by the essential vitamin B_1 and its presence in natural products.[1] Furthermore, pharmaceutical applications of the pyrimidine have generated both the blockbuster drugs imatinib and rosuvastatin as well as led to the identification of many potent and promising drug candidates.[2] This interest in pyrimidines provided the impetus for numerous and creative methodologies[3] to construct the pyrimidine including the use of vinamidinium salts.[4] However, the predominately practiced strategy toward the heterocycle relied on the classical condensation approach (Scheme 1) which requires the elimination of alkoxide substituents for aromatization.[5] Although numerous variations are established to affect the condensation,[6,7] basic conditions employing a protic solvent with a reaction time of several hours to days are the most common. Even among the thousands of examples, few mechanistic or optimization studies to address the rate limiting operations are published. Through detailed and exemplary ^{13}C NMR analysis, Katritzky and Yousaf demonstrated both the intermediate formation and subsequent alkoxide elimination were slow operations for the Pinner pyrimidine synthesis between an amidine and β-ketoketones.[8] Application of microwave technology has been applied to afford reasonable reaction times,[9] but no general and time efficient process amenable for a conventional batch process has been reported. General rapid approaches toward pyrimidines which provide high throughput in regard to time and volume[10] would provide value toward library synthesis, discovery optimization, and scaleup. Herein, we report an effective model system to identify conditions to address the rate limiting aromatization and development of a rapid pyrimidine synthesis from amidines and activated olefins.

Scheme 1. Representative Condensation Conditions toward Pyrimidines



The model system to examine the Michael addition approach toward pyrimidines employed the reaction between benzamidine and our recently reported fluorinated butenone **8**.[11] Reversed phase HPLC analysis of the intermediate generated from the reaction between the components under neutral conditions showed multiple broad peaks with a consistent mass indicative of the cyclized adduct **9**. The main limitation with HPLC analysis was the inability to qualitatively determine the rate for both the intermediate formation as well as the subsequent aromatization. Accordingly, a react-IR analysis on the reaction was conducted. Component analysis revealed a rapid and complete Michael addition once the amidine salt was neutralized by sodium ethoxide (Figure 1). Furthermore, this intermediate was relatively stable, and at 35 °C, the intermediate showed minimal decomposition over several hours.[12] The stability and rapid formation was also demon-

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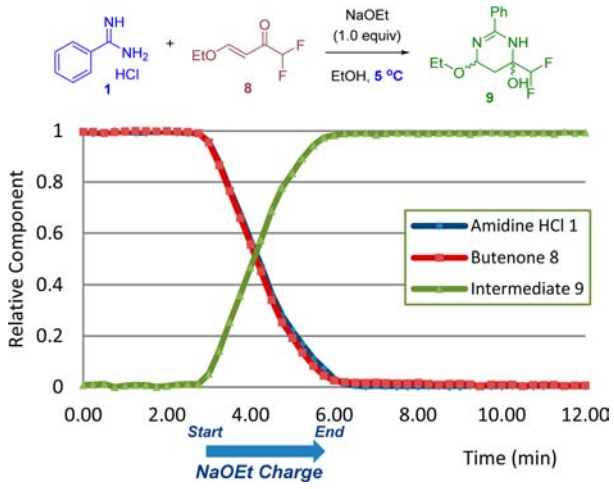

Figure 1. React-IR analysis for the Michael addition conducted with benzamidine **1** (1.02 equiv), butenone **8** (1.0 equiv), and NaOEt (21 wt % in EtOH, 1.0 equiv) in EtOH. Relative component analysis and identities confirmed by HPLC and LC-MS.

strated in DMSO wherein NMR and mass spectroscopic analysis supported the cyclized intermediate **9**[12] consistent with the Katritzky and Yousaf report.[8]

After establishment of a rapid intermediate formation, the rate limiting aromatization was addressed. The most influential parameter examined[12] was the solvent choice under basic conditions. Alcoholic solvents are the most commonly employed solvents for the pyrimidine synthesis. However, the model system under the conventional conditions[5−7] demonstrated a sluggish aromatization and provided only a moderate yield for the pyrimidine (Figure 2). Alternatively, polar aprotic

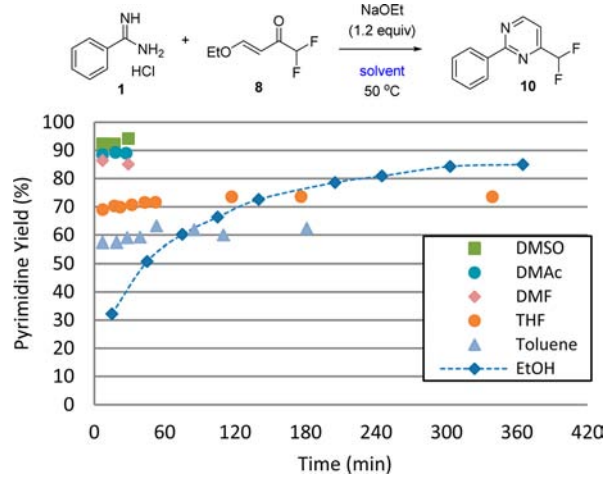

Figure 2. Solvent effect on the pyrimidine aromatization.[12] Reactions conducted with benzamidine **1** (1.02 equiv), butenone **8** (1.0 equiv), and NaOEt (21 wt % in EtOH, 1.0 equiv) in the indicated solvent. Pyrimidine **10** yield determined by HPLC (220 nm) assay utilizing *m*-xylene as an internal standard.

solvents such as DMSO, DMF, or DMAc demonstrated a rapid and essentially addition controlled reaction. Other commonly employed solvents such as THF and toluene also demonstrate a rapid aromatization but provided only poor to moderate yields due to the reaction stalling at partial conversions. The aromatization rate for the pyrimidine formation was also qualitatively assessed through react-IR analysis. The examination subjected the Michael adduct **9** generated from the reaction between the butenone **8** and free base amidine **1b** in DMSO to catalytic sodium ethoxide (Figure 3). Both the

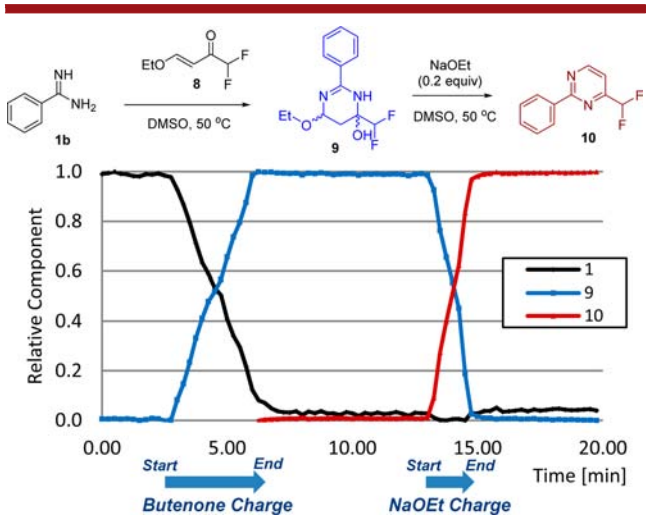

Figure 3. React-IR analysis on the pyrimidine condensation. Reaction conducted with benzamidine **1b** (free base, 1.02 equiv), butanone **8** (1.0 equiv), and NaOEt (21 wt % in EtOH, 0.2 equiv) in DMSO. Relative component analysis and identities confirmed by HPLC and LC-MS.

Michael addition and subsequent aromatization exhibited addition control behavior.[12] Accordingly, the aromatization promoted by the necessary alkoxide eliminations demonstrated a strong rate dependence on the solvent choice under basic conditions.

The developed pyrimidine synthesis from amidines and activated olefins proved general (Table 1). The challenge with a general process was establishing conditions to tolerate the breath and quality of the available activated olefins. A process wherein the Michael addition was initiated prior to the base promoted aromatization proved more robust than conducting both operations concurrently. Accordingly, the olefin was subjected to the free base amidine, either by utilizing the free base or by neutralizing the hydrochloride salt with sodium ethoxide, prior to subjecting the reaction to the basic conditions. To compensate for the activated olefin quality, which was observed to contain impurities that would quench the base, the sodium ethoxide charge to promote the aromatization was adjusted based on the individual reaction from 0.1 to 1.3 equiv. For example, butenones **17** (50 wt %), **19** (80 wt %), and **27** (35 wt %) were able to be directly utilized in the process without purification after appropriate adjustment to the base stoichiometry. Flavone **35** was also competent for the rapid pyrimidine synthesis. Due to the observed slower Michael addition and resulting phenol functional group related to the system, the process was modified by use of an excess of sodium *tert*-butoxide to afford a moderate yield within 15 min (eq 1).

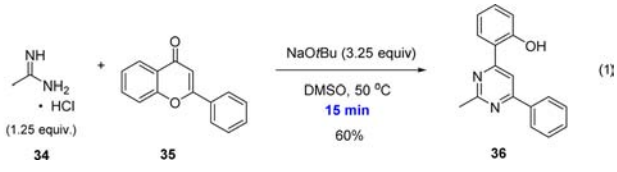

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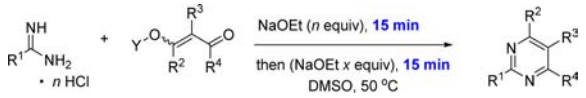
Table 1. Pyrimidine Scope[a]



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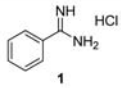
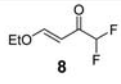
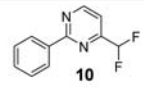
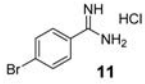
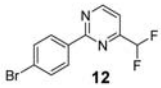
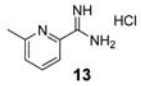
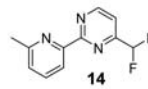
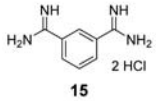
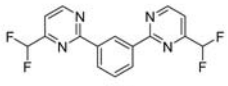
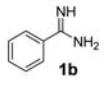
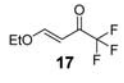
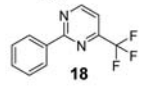
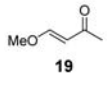
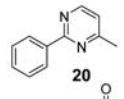
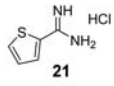
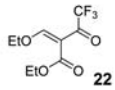
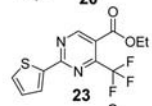
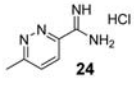
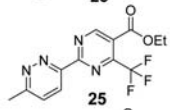
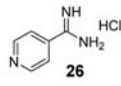
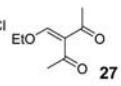
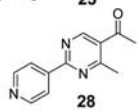
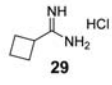
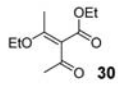
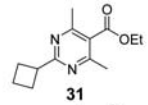
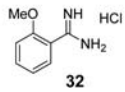
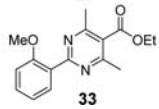
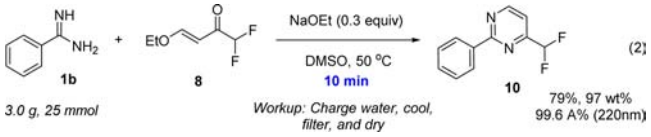
1				97%
2		8		75%
3		8		88%
4		8[c] 		88%
5				86%
6	1b			68%
7				89%
8		22		74%
9				87%
10[d]				82%
11[d]		30		73%

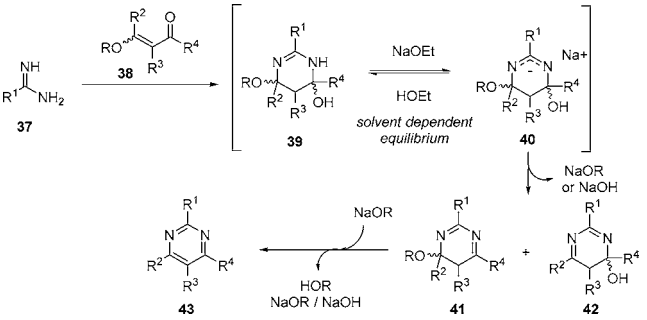
[a]Reactions were conducted by charging NaOEt (21 wt % in EtOH, 0.1 to 1.3 equiv based on individual reaction[12]) to a 15 min aged mixture of NaOEt (21 wt % in EtOH, *n* equiv), electrophile, and amidine *n*-HCl in DMSO at 50 °C. Completion of each reaction was determined by HPLC. [b]Isolated yields. [c]2.94 equiv of butenone **8** utilized. [d]Reaction conducted by aging a mixture of the amidine, electrophile, and NaOEt (21 wt % in EtOH, 1.1 equiv) for 15 min at 50 °C.

The condensation with a water miscible solvent was also amenable for a direct crystallization process. Simple addition of water to the parent reaction between benzamidine **1b** and butenone **8** catalyzed by sodium ethoxide enabled the precipitation of pure pyrimidine **10** with good recovery (eq 2).



A reasonable rationalization for the rapid aromatization observed in the condensation approach toward pyrimidines with an alkoxide base in DMSO relates to the solvent effect driving the acid–base equilibrium to favor the amidine anion and associated increase in the rate for the initial alkoxide elimination (Scheme 2). Based on Katritzky and Yousaf's

Scheme 2. Proposed Mechanism for the Pyrimidine Condensation



analysis[8] and utilization of a system wherein the Michael addition was rapid, the reasonable rate limiting step for the condensation process was the aromatization. Under basic conditions, the elimination would occur through the amidine anion generated from the base wherein the rate is dependent upon the concentration of the anion. Solvent choice is well-known to influence acid–base equilibria as well as dramatically affect reaction rates.[13] The equilibrium between the amidine anion and base may also show a similar solvent dependence. Direct examination of the anionic intermediate **9** was not feasible due to the rapid resulting reaction. However, the free base benzamidine is a reasonable model for the intermediate **9** in acid–base equilibria. The established pK_a values of methanol, *tert*-butanol, and benzamidine in DMSO are 29.0, 32.2,[14] and 26.7,[15] respectively, to support a strong equilibrium toward the amidine anion with alkoxide bases in polar aprotic solvents. The corresponding equilibrium in methanol was qualitatively assessed through spectroscopy. The amidine anion generated in DMSO with sodium *tert*-butoxide was apparent by the respective aromatic proton shielding upon deprotonation through ^{1}H NMR as well as the associated IR absorbance change of the amidine function group (Figures 4 and 5). When the amidine was subjected to sodium *tert*-butoxide in methanol, which generates sodium methoxide, the spectra supported

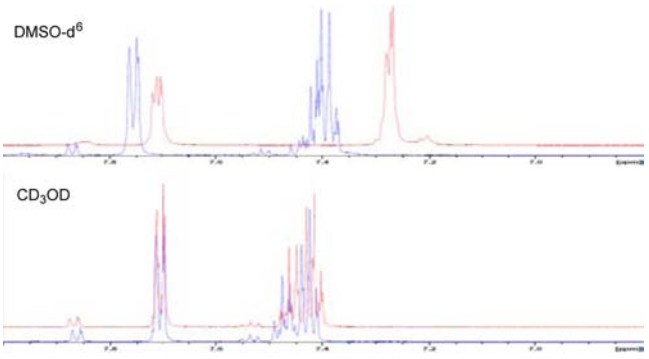


Figure 4. ^{1}H NMR at 500 MHz analysis for the treatment of benzamidine **1b** with (red) and without (blue) sodium *tert*-butoxide (1.1 equiv) in the indicated solvent at ambient temperature.

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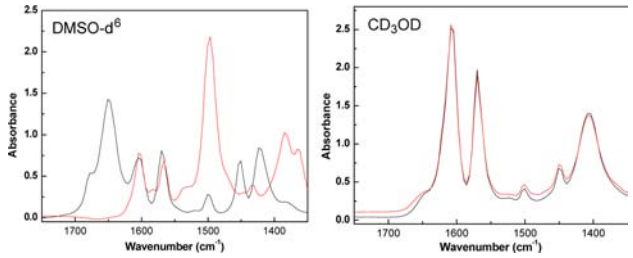

Figure 5. IR analysis for the treatment of benzamidine **1b** with (red) and without (black) sodium *tert*-butoxide (1.1 equiv) in the indicated solvent at ambient temperature.

predominately the free base amidine with little observable amidine anion. Accordingly, the amidine−alkoxide acid−base equilibrium was solvent dependent wherein the amidine anion necessary for the initial alkoxide elimination was strongly favored in DMSO. Other solvent effects[13,16] may also contribute to the reaction rate differences, but the correlation between the anion equilibria and reaction behavior reasonably rationalizes the solvent effect on the rate of the pyrimidine condensation.

In conclusion, the rate limiting aromatization within the condensation approach toward pyrimdines utilizing amidines and activated olefins was addressed to provide for a general and rapid process. Employing polar aprotic solvents with an alkoxide base provided a reaction wherein optimal yields were obtained in DMSO. The process demonstrated a broad tolerance toward the substrates and allowed the generation of a diverse pyrimidine series. Mechanistic analysis on the acid−base equilibrium between an alkoxide base and benzamidine demonstrated a pronounced solvent effect wherein DMSO strongly favors the amidine anion necessary to promote the initial alkoxide elimination. Extension of factors to bias the acid−base equilibria necessary for base promoted condensations should also facilitate other related heterocycle syntheses.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details including additional react-IR experiments, copies of HPLC, ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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