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# Observations on the use of microwave irradiation in azaheterocycle synthesis

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ABSTRACT

A comparison of conventional heating and microwave irradiation in the synthesis of azaheterocycles is discussed. Microwave irradiation was found to increase the yields of the desired products, shorten the reaction times, and extended this chemistry to recalcitrant amide substrates and weak nucleophiles.



New and convergent syntheses of azaheterocycles are of continuing importance due to their prominence in natural products, active pharmaceuticals, and functional materials.[1,2] Historically, these classes of azaheterocycle were most frequently prepared by dehydrative cyclization reactions between amine and carbonyl compounds.[1,2] More recently, activated azaheterocycle cross-coupling procedures[3] have proven to be a valuable addendum to methods for azaheterocycle preparation.

Recently, our laboratory discovered a mild and convergent methodology for the synthesis of pyrimidine[4] **1** and pyridine[5] **2** derivatives in a single step from readily available amides[6] and nucleophiles (Fig. 1). The condensation of amides with a variety of nucleophiles in dichloromethane enabled by the action of trifluoromethanesulfonic anhydride[7] ($Tf_2O$) and 2-chloropyridine[8] (2-ClPyr) provided many structurally diverse azaheterocycles at ambient temperature or with mild heating at 45 °C. While recalcitrant amides, including electron deficient *N*-aryl amides, led to low yield of the desired product under thermal heating conditions, they were found to undergo microwave-assisted azaheterocycle formation in satisfactory yields. The advantages in the use of microwave irradiation during these condensation reactions were also found employing both sterically cumbersome amide and nucleophile substrates.[9] Herein, we discuss our observations in the differences in conventional heating and microwave irradiation in the synthesis of azaheterocycles.

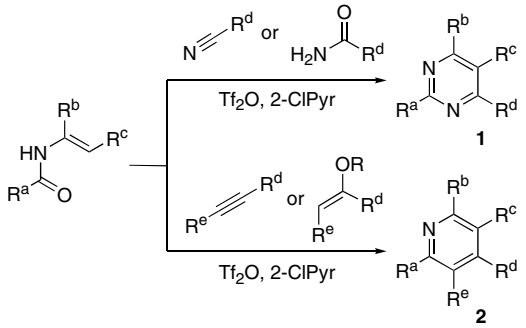
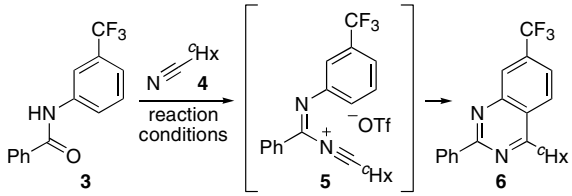



**Figure 1.** Direct synthesis of pyrimidines and pyridines.

Our earlier mechanistic investigation in the synthesis of pyrimidines by *N*-vinyl/*N*-aryl amide activation with $Tf_2O$ and 2-ClPyr suggests formation of a 2-chloropyridinium adduct followed by nucleophilic addition and nitrilium ion formation (e.g., Scheme 1).[4a] Subsequent annulation affords the desired azaheterocycle, in




**Scheme 1.** Reagents and conditions: $Tf_2O$ (1.1 equiv), 2-ClPyr (1.2 equiv), nitrile **4** (1.1 equiv), $CH_2Cl_2$, −78 °C→heating. $^cHx$ = cyclohexyl.

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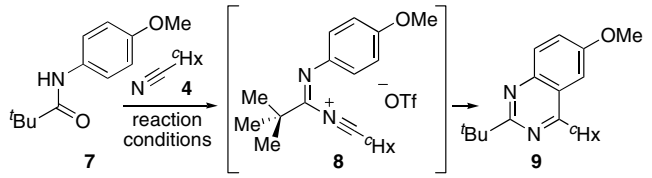
**Table 1**
Synthesis of quinazoline **6**

| Entry | Temp (°C) | Time | Heating method | Yield (%) |
|---|---|---|---|---|
| 1 | 45 | 16 h | Oil bath | 30 |
| 2 | 75 | 30 min | Oil bath | 11 |
| 3 | 75 | 30 min | Microwave reactor | 15 |
| 4 | 140 | 20 min | Oil bath | 27 |
| 5 | 140 | 40 min | Oil bath | 20 |
| *6* | *140* | *20 min* | *Microwave reactor* | *61* |

most instances with either warming to ambient temperature or mild heating at 45 °C. In the case of electron deficient *N*-aryl amides (e.g., **3**, Scheme 1), this condensation required more forcing conditions to proceed effectively. For example, condensation of amide **3** with cyclohexanecarbonitrile (**4**) to give quinazoline **6** (Scheme 1) was found to be exceedingly slow without heating above ambient temperature (16 h, ⩽10%). Even heating at 45 °C for 16 h was found to be not optimal in providing the desired azaheterocycle **6**. Heating at 45 °C over 16 h led to formation of the desired product in 30% yield along with complete consumption of the starting material likely due to competitive decomposition of an activated amide derivative prior to formation of **6** (Table 1, entry 1). Furthermore, short reaction times with heating in an oil bath at higher reaction temperatures (Table 1, entries 2, 4, and 5) were found to result in poor yield of the desired product and complete consumption of starting material. Microwave irradiation with heating to 140 °C for 20 min promoted the formation of the desired azaheterocycle **6** in 61% yield. It is interesting to note that both microwave irradiation with heating at a lower temperature (75 °C for 30 min) and immersion of the reaction flask in an oil bath at 140 °C for 20 or 40 min provided less than optimal results (Table 1).[10]

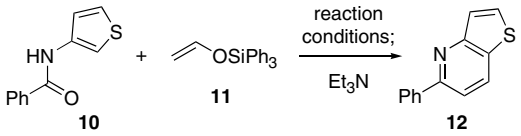
Additionally, sterically hindered substrates such as amide **7** (Scheme 2) were found to proceed sluggishly to the desired product. While prolonged heating in an oil bath at 45 °C led to formation of **9** in only 31% yield (Table 2, entry 1), TLC analysis of the reaction mixture indicated incomplete conversion of amide **7** to the desired azaheterocycle **9**. While the previous example highlighted the difficulty associated with an electron deficient aryl ring, amide **7** highlights the challenges associated with a sterically hindered amide. In this case, the overall reaction progress is stalled possibly due to slower addition of the nucleophile to the neopentyl electrophile and formation of the nitrilium ion intermediate **8** (Scheme 2). Microwave irradiation with heating to 140 °C for 20 min was found to provide the optimal results. While both microwave irradiation and heating at lower temperatures were not effective, given the greater stability of the activated intermediate, immersion of the sealed reaction vessel in an oil bath at 140 °C for 40 min provided similar conversion to the desired product (Table 2, entry 5). Comparison of entries 4 and 6 of Table 2 highlights the greater efficiency in conversion of the starting material to the desired azaheterocycle using microwave irradiation when faced with recalcitrant substrates. Based on these observations, our recommended procedure involves microwave irradiation and heating




**Scheme 2.** Reagents and conditions: $Tf_2O$ (1.1 equiv), 2-ClPyr (1.2 equiv), nitrile **4** (1.1 equiv), $CH_2Cl_2$, −78 °C→heating. $^cHx$ = cyclohexyl.

**Table 2**
Synthesis of quinazoline **9**

| Entry | Temp (°C) | Time | Heating method | Yield (%) |
|---|---|---|---|---|
| 1 | 45 | 16 h | Oil bath | 31 |
| 2 | 75 | 30 min | Oil bath | 11 |
| 3 | 75 | 30 min | Microwave reactor | 14 |
| 4 | 140 | 20 min | Oil bath | 51 |
| 5 | 140 | 40 min | Oil bath | 79 |
| *6* | *140* | *20 min* | *Microwave reactor* | *86* |




**Scheme 3.** Reagents and conditions: $Tf_2O$ (1.1 equiv), 2-ClPyr (1.2 equiv), $CH_2Cl_2$, −78→0 °C; vinyl ether **11** (2.0 equiv), 0→heating; $Et_3N$ (9.5 equiv).

**Table 3**
Synthesis of pyridine **12**

| Entry | Temp (°C) | Time | Heating method | Yield (%) |
|---|---|---|---|---|
| 1 | 45 | 16 h | Oil bath | 44 |
| 2 | 75 | 30 min | Oil bath | 43 |
| 3 | 75 | 30 min | Microwave reactor | 42 |
| 4 | 140 | 20 min | Oil bath | 61 |
| 5 | 140 | 40 min | Oil bath | 70 |
| *6* | *140* | *20 min* | *Microwave reactor* | *76* |

at 140 °C in the most challenging cases. While the majority of *N*-vinyl amides require no heating to form pyrimidine derivatives, quinazolines often require warming above ambient temperature for effective conversion of the starting *N*-aryl amide to the desired product.[4]

In addition to the use of nitriles as σ-nucleophiles, we were pleased to find that our optimal reaction conditions promote annulation of *N*-aryl and *N*-vinyl amides with a variety of π-nucleophiles, providing direct access to quinoline and pyridine derivatives, respectively.[5] Similar to other challenging substrate combinations, the synthesis of pyridine derivative **12** from sensitive amide **10**[4] and triphenylsilyl vinyl ether (**11**) required rapid heating to 140 °C in a microwave reactor for optimal results (Scheme 3, Table 3). Heating of the reaction mixture at lower temperatures even for prolonged periods (Table 3, entries 1–3) was not optimal and led to low conversion to the desired product (along with poor recovery of the starting amide). Again, heating of the reaction mixture in the sealed reaction vessel using microwave irradiation for a short reaction time (20 min) was found to be superior to heating of the reaction mixture by immersion in an oil bath for an equal or longer period (Table 3, entries 4–6).[11]

The examples discussed highlight the advantages in the use of microwave irradiation for the effective condensation of amides with respective nucleophiles in the synthesis of azaheterocycles. Heating the reaction mixtures at 140 °C by microwave irradiation for 20 min was observed to be superior for the synthesis of the desired azaheterocycle as compared to heating in an oil bath.

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10. The following is a representative procedure. 4-Cyclohexyl-2-phenyl-7-trifluoromethylquinazoline (**6**, Scheme 1): Trifluoromethanesulfonic anhydride (82 μL, 0.50 mmol, 1.1 equiv) was added via syringe over 1 min to a stirred mixture of amide **3** (120 mg, 0.450 mmol, 1 equiv) and 2-chloropyridine (51 μL, 0.54 mmol, 1.2 equiv) sealed under argon in dichloromethane (1.5 mL) at −78 °C. After 5 min, the reaction mixture was placed in an ice-water bath and warmed to 0 °C, cyclohexanecarbonitrile (**4**) (54 mg, 0.50 mmol, 1.1 equiv) was added via syringe, and the resulting solution was allowed to warm to ambient temperature for 5 min before the reaction vessel was placed into a microwave reactor and heated to 140 °C. After 20 min, the reaction vessel was removed from the microwave reactor and allowed to cool to ambient temperature before aqueous sodium hydroxide solution (1 mL, 1 N) was introduced to neutralize the trifluoromethanesulfonate salts. Dichloromethane (5 mL) was added to dilute the mixture and the layers were separated. The organic layer was washed with brine (2 mL), dried over anhydrous sodium sulfate, and filtered. The volatiles were removed under reduced pressure and the residue was purified by flash column chromatography (eluent: 5% EtOAc in hexanes; $SiO_2$: 15 × 1.5 cm) on neutralized silica gel to give the quinazoline **6** as a white solid (97 mg, 61%). $^1$H NMR (500 MHz, $CDCl_3$, 20 °C) $\delta$: 8.72–8.69 (m, 2H, Ar*H*), 8.40 (s, 1H, Ar*H*), 8.29 (d, 1H, $J$ = 8.7 Hz, Ar*H*), 7.74 (d, 1H, $J$ = 8.7 Hz, Ar*H*), 7.59–7.54 (m, 3H, Ar*H*), 3.60 (tt, 1H, $J$ = 11.4, 3.4 Hz, $^cC_6H_{11}$), 2.10–1.86 (m, 7H, $^cC_6H_{11}$), 1.64–1.53 (m, 2H, $^cC_6H_{11}$), 1.45 (qt, 1H, $J$ = 12.7, 3.0 Hz, $^cC_6H_{11}$). $^{13}$C NMR (125 MHz, $CDCl_3$, 20 °C) $\delta$: 175.4, 161.3, 150.6, 138.1, 134.8 (q, $J$ = 33 Hz), 131.1, 131.0, 128.9, 128.8, 127.7 (q, $J$ = 4.3 Hz), 125.7, 123.8 (q, $J$ = 271 Hz), 123.1, 122.3 (q, $J$ = 4.1 Hz), 42.0, 32.3, 26.7, 26.3. FTIR (neat) cm$^{-1}$: 2929 (s), 2857 (m), 1575 (s), 1549 (s), 1499 (m), 1344 (s), 1126 (s). HRMS (ESI): calcd for $C_{21}H_{20}F_3N_2$ $[M+H]^+$: 357.1579, found: 357.1587. TLC (20% EtOAc/hexanes), $R_f$: 0.74 (UV, CAM).
11. The addition of triethylamine prior to reaction workup completes the elimination of triphenylsilanol and aromatization of the initial condensation product, facilitating the isolation of the desired product.