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Microwave-assisted synthesis of aminopyrimidines

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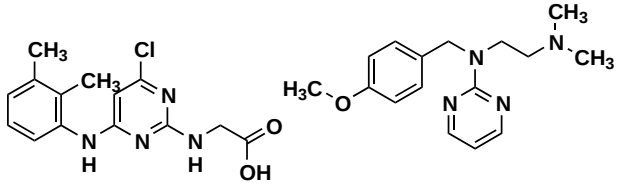
Abstract—Series of mono- or di-substituted aminopyrimidine derivatives were synthesized through microwave-assisted aromatic nucleophilic substitution or Suzuki coupling.

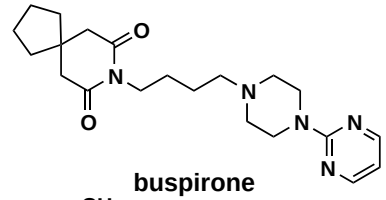
Substituted amino pyrimidine structures are common in marketed drugs, such as anti-atherosclerotic aronixil, anti-histaminic thonzylamine, anti-anxielytic buspirone, anti-psoriatic enazadrem, and other medicinally relevant compounds (Scheme 1).[1]

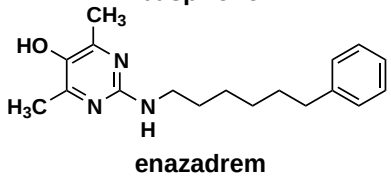
Conventional syntheses include ring formation reactions and thermal nucleophilic aromatic substitution reactions of amines with halogenated pyrimidines.[1,2] Nucleophilic aromatic substitution reactions of electron deficient halogenated pyrimidines are usually rapid and high yielding. However, in the case of electron rich or even neutral halogenated pyrimidines (c.a. with alkyl, alkoxyl or amino substituents), the substitution reactions require prolonged heating for hours or days. Recently, we were interested in a drug discovery lead structure modification which required the efficient synthesis of substituted mono- and di-aminopyrimidines. With regard to convenience, we choose to pursue the direct addition of amines to the easily obtained halopyrimidines (Scheme 2).

Microwave-assisted organic synthesis is an increasingly popular field as indicated by numerous publications in the last few years.[3] Many different types of thermal organic reactions have been accelerated through the use of microwave irradiation.[4] A significant majority of the examples have been carried out using domestic microwave ovens. Due to variations in wattage, field distribution, and vessel construction the experiments are sometimes difficult to reproduce. Commercially available focused-field microwave heating instruments provide safer and more uniform conditions.[5] We chose to use the latter to optimize our required synthesis of aminopyrimidines.[6]

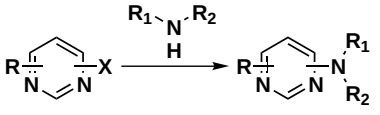
The reactions were carried out in 2-propanol (0.5–3 M) in the presence of diisopropylethylamine (2 equiv.).[7] Most reactions achieved complete conversions within 2 h as shown in Table 1.







Scheme 1.



Scheme 2.

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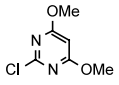
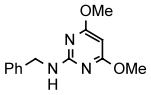
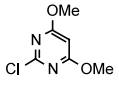
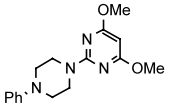
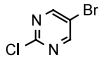
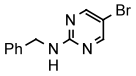
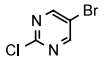
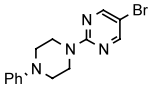
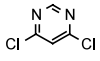
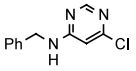
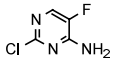
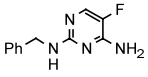
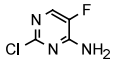
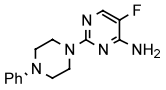
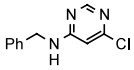
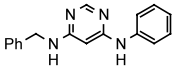
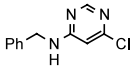
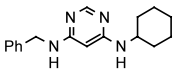
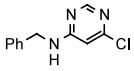
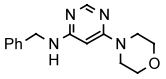
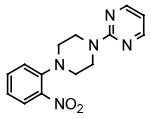
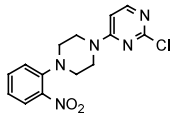
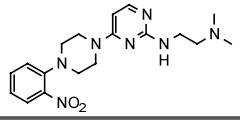
Table 1. Reactions of various halopyrimidines under microwave irradiation

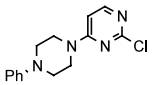
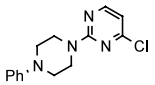
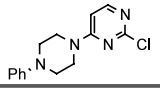
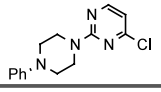
Entry	Halopyrimidines	Product	Time (Min)	Temp. (°C)	Yield[a] (%)
1			40	160	93
2			5	160	97
3			30	160	95
4			5	160	95
5			20	130	94
6			80	160	29 (87)
7			30	160	92
8			25	160	87
9			60	160	58 (92)
10			5	160	92
11			20	160	51 (80)
12			160	170	45 (91)

a. Isolated yield of pure compound. %conversion in parentheses.

Reactions of secondary amines (entries 2, 4, 7, 10) are much faster than primary amines (entries 1, 3, 6, 9, 12) while aniline (entry 8) is somewhere in between. The most difficult reactions were adding a second primary amino group to an aminopyrimidine (entries 6, 9, 12), which resulted only in modest conversion even with prolonged irradiation.

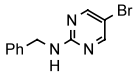
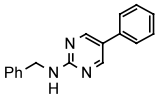
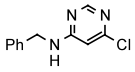
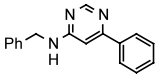
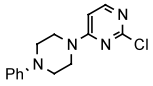
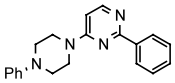
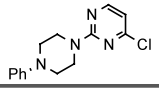
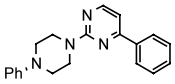
When two halogens are at *meta* positions (2,4- or 4,6-dichloropyrimidine), different amines can be selectively added by purifying the mono-amination intermediates. For the reactions with 4,6-dichloropyrimidine, the first addition (entry 5) is substantially easier than the addition of the second amino group (entries 8, 9, 10). A slight excess of dichloropyrimidine (1.1 equiv.) was used for the first amination and there was no detectable amount of bis-aminated product (entry 5). With 2,4-dichloropyrimidine, we anticipated that both 4- and 2-substituted product would be produced. As listed in Table 2, reaction of 4-phenylpiperazine with 2,4-dichloropyrimidine afforded two separable isomers,[8] whose ratio depends on the solvent used. While it is obvious that 4-position is more active towards substitutions (entries 1, 2), the product ratio could be improved by running the reaction in a more polar solvent to produce much more polar 4-amino isomer (entry 1).

Table 2. Solvent influence of regioselectivity in reactions of 2,4-dichloropyrimidine with phenylpiperazine

Entry	Amination at 4-position	Amination at 2-position	Reaction Conditions	Ratio (4-/2-)	Yield[a] (%)
1			M.W. 130 °C, 10 min i-PrOH	5.5/1	81
2			M.W. 130 °C, 10 min Toluene	1.5/1	75

a. Isolated total yield of pure compounds.

Table 3. Suzuki coupling of various aminopyrimidines with phenyl boronic acid

Entry	Halopyrimidines	Product	Time (Min)	Temperature (°C)	Yield[a] (%)
1			15	140	79
2			10	140	87
3			10	140	79
4			10	140	92

a. Isolated yield of pure compound.

We were curious to see if the halogenated aminopyrimidines were suitable substrates for further arylations by the Suzuki coupling reaction. To the best of our knowledge there has been only one report on the synthesis of C-aryl pyrimidines with halogenated pyrimidines through Suzuki coupling.[9] The reactions under conventional heating take many hours to days and no amine substituted halopyrimidines were reported.[9] The reactions outlined in Table 3 generally achieve complete conversion within 15 min.[10]

In conclusion, we have demonstrated that microwave irradiation can greatly facilitate the synthesis of various substituted aminopyrimidines through nucleophilic aromatic substitutions and Suzuki coupling reactions.

Acknowledgements

The authors are grateful to Dr. Lawrence Marcin for his many suggestions and proof-reading.

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3. For recent reviews, see: (a) Perreux, L.; Loupy, A. *Tetrahedron* **2001**, *57*, 9199–9223; (b) Larhed, M.; Hallberg, A.

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4. Some recent reactions facilitated by microwave irradiations. **Synthesis of heterocycles**: triazoles: (a) Bentiss, F.; Lagrenee, M.; Barby, D. *Tetrahedron Lett*. **2000**, *41*, 1539–1541. Thiazoloquinazolines: (b) Besson, T.; Guillard, J.; Rees, C. W. *Tetrahedron Lett*. **2000**, *41*, 1027–1030. Quinolines: (c) Ranu, B. C.; Hajra, A.; Jana, U. *Tetrahedron Lett* **2000**, *41*, 531–533. Oxazoles: (d) Lee, J. C.; Song, I.-G. *Tetrahedron Lett*. **2000**, *41*, 5891–5894. Imidazoles: (e) Usyatinsky, A. Y.; Khmelnitsky, Y. L. *Tetrahedron Lett*. **2000**, *41*, 5031–5034. **Reaction types**: Asymmetric hydrogen transfer: (f) Lutsenko, S.; Moberg, C. *Tetrahedron: Asymmetry* **2001**, *12*, 2529–2532. Esterifications: (g) Kabza, K. G.; Chapados, B. R.; Gestwicki, J. E.; McGrath, J. L. *J. Org. Chem*. **2000**, *65*, 1210–1214. Sonogashira coupling: (h) Kabalka, G. W.; Wang, L.; Namboodiri, V.; Pagni, R. M. *Tetrahedron Lett*. **2000**, *41*, 5151–5154. Thia-Fries rearrangement: (i) Moghaddam, F. M.; Dakamin, M. G. *Tetrahedron Lett*. **2000**, *41*, 3479–3481. Wittig reaction: (j) Frattini, S.; Quai, M.; Cereda, E. *Tetrahedron Lett*. **2001**, *42*, 6827–6829. Mitsunobu reactions: (k) Steinreiber, A.; Stadler, A.; Mayer, S. F.; Faber, K.; Kappe, C. O. *Tetrahedron Lett*. **2001**, *42*, 6283–6286. Suzuki couplings: (l) Blettner, C. G.; Konig, W. A.; Stenzel, W.; Schotten, T. *J. Org. Chem*. **1999**, *64*, 3885–3890; (m) Villemin, D.; Gomez-Escalonilla, M. J.; Saint-Clair, J.-F. *Tetrahedron Lett*. **2001**, *42*, 635–637; (n) Villemin, D.; Caillot, F. *Tetrahedron Lett*. **2001**, *42*, 639–642.

5. The microwave unit used in our experiments is the Smith Creator® from Personal Chemistry. It continuously adjusts the applied wattage to maintain the desired temperature. Reactions were conducted in their proprietary 5 mL sealed vials.

6. Microwave irradiation was shown to facilitate *meta*-amination of benzenes: Brown, G. R.; Foubister, A. J.; Roberts, C. A.; Wells, S. L.; Wood, R. *Tetrahedron Lett*. **2001**, *42*, 3917–3919.

7. **Typical procedure for the nucleophilic aromatic substitution:** To a solution or suspension of halopyrimidine (0.2–3 M) and amine (2 equiv., 0.9 equiv. when dichloropyrimidines were used) in 2-propanol was added diisopropylethyl amine (2 equiv.). The vial was sealed and heated by microwave at the indicated temperature and time. The mixture was concentrated and purified by flash column chromatography. Analytical data for a representative compound (entry 2 in Table 1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (t, $J=7.8$ Hz, 2H), 6.99 (d, $J=8.3$ Hz, 2H), 6.92 (t, $J=7.4$ Hz, 1H), 5.44 (s, 1H), 3.99 (t, $J=5.0$ Hz, 4H), 3.90 (s, 6H), 3.25 (t, $J=5.0$ Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 160.9, 151.5, 129.2, 120.1, 116.6, 78.3, 53.5, 49.4, 43.9; MS: $[M+H]^+=301$.

8. The regiochemistry of these monoaminated products was unequivocally verified by dehalogenation (10% $Pd/C/H_2$, 55 psi, 15 h) followed by comparison of their NMR data with synthesized materials: (a) the authentic 2-aminated products were synthesized by reaction of the corresponding amine with 2-bromopyrimidine (see entry 11); (b) the authentic 4-aminated products were synthesized by reaction of the corresponding amine with 4,6-dichloropyrimidine (see entry 5) followed by dehalogenation (this represents a unique way of making exclusive 4-aminopyrimidines).

9. Schomaker, J. M.; Delia, T. J. *J. Org. Chem*. **2001**, *66*, 7125–7128.

10. **Typical procedure for the Suzuki coupling:** To a solution or suspension of halopyrimidine and phenylboronic acid (1.4 equiv.) in toluene/ethanol (4/1, 0.13 M) was added $Pd(PPh_3)_4$ (0.04 equiv.) and K_2CO_3 (2.0 M in water). The vial was sealed and heated by microwave at the indicated temperature and time. The mixture was partitioned between CH_2Cl_2 and 1N NaOH. The layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), concentrated and purified by flash column chromatography. Analytical data for a representative product (entry 1 in Table 3): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.41 (br. 2H), 7.46–7.24 (m, 10H), 6.37 (br. 1H), 4.70 (d, $J=5.7$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 161.6, 156.3, 139.0, 135.5, 129.1, 128.7, 127.7, 127.4, 127.3, 125.9, 124.0, 45.8; MS: $[M+H]^+=262$.