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Microwave-assisted synthesis of 2-aminoquinolines

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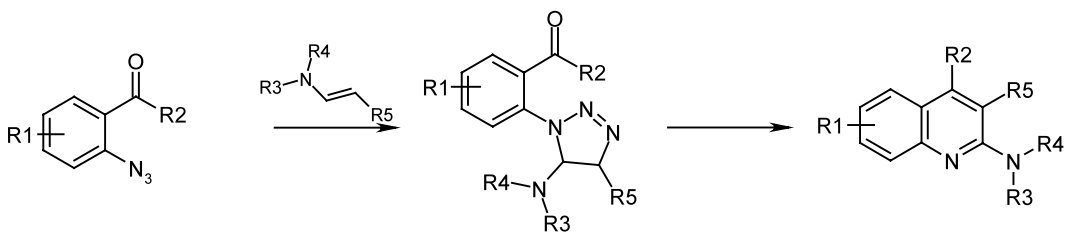
Abstract—An improved method for the synthesis of 2-aminoquinolines utilizing microwave-assisted synthesis is described. The process involves rapid microwave irradiation of secondary amines and aldehydes to form enamines followed by the addition of 2-azidobenzophenones with subsequent irradiation to produce the 2-aminoquinoline derivatives. Purification of the products is accomplished in a streamlined manner using solid-phase extraction techniques to produce the desired products in high yields and purity.

The heterocyclic quinoline scaffold and derivatives occur in a large number of natural products[1] and drug-like compounds.[2] While numerous synthetic approaches have been developed for quinoline synthesis, most are unsatisfactory for combinatorial library production over a wide-range of substitutions and functionalities.[3] In other examples of cycloadditions, microwave irradiation (noted as μW) has had dramatic effects on reaction times, purities, and yields.[4] We have developed a new efficient method for generating 2-aminoquinolines via a three component condensation utilizing microwave irradiation as the heat source. In this method, the initially formed triazoline intermediates undergo a thermal rearrangement and intermolecular base-catalyzed cyclocondensation[5] to produce a quinoline-based pharmacophore combinatorial library (Scheme 1).

We have found that a variety of amines, aldehydes, and 2-azidobenzophenones[6] are readily converted to 2-aminoquinolines in good to excellent yields by using single-mode microwave irradiation[7] (Tables 1 and 2). Although conventional heating methods can be used to synthesize 2-aminoquinolines, only low to moderate yields are obtained even after prolonged heating (entries 1–8). *p*-Xylene and toluene provided the best results under thermal heating conditions (entries 1–3); however, these solvents are poor microwave absorbers so we investigated the use of DMF and DCE as possible solvents. In general, compounds with a high dielectric constant (e.g. water and methanol) generally heat more readily under microwave irradiation, while compounds with lower dielectric constants and/or poor net dipole moments poorly absorb microwaves (e.g. *p*-xylene and dioxane).[4] Direct reaction comparison between thermal and microwave conditions, using identical stoichiometry and sealed reaction vessels (entries 8 and 9) show greatly improved yield for the microwave example. This result may simply be due to the fact that solvents, heated using microwave irradiation, can be heated (or superheated) to a higher temperature which



Scheme 1.

Keywords: microwave-assisted synthesis; 2-aminoquinolines; combinatorial chemistry.

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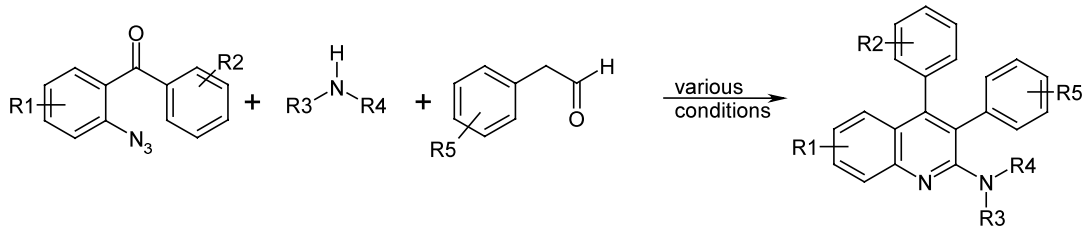
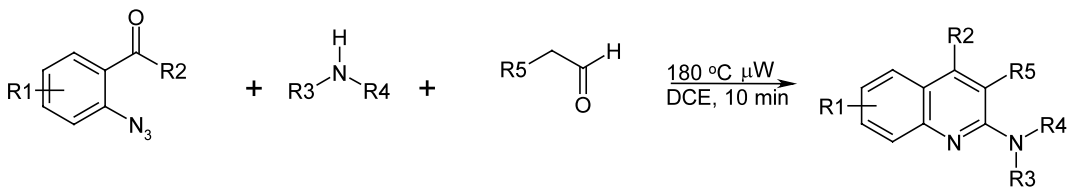
Table 1. Conventional heating versus microwave irradiation



Entry	R1, R2	R3, R4	R5	Temp. (°C)	Solvent	Time	Completion (%)[a]
1	5-Cl	Morpholine	H	Reflux	*p*-Xylene	4 h	52[b]
2	5-Cl	Morpholine	H	110	Toluene	6 h	39[c]
3	5-Cl	Morpholine	H	110	Toluene	24 h	50[c]
4	5-NO_2,H	Cyclohexyl, Me	H	110	Toluene	6 h	10
5	5-NO_2,H	Cyclohexyl, Me	H	110	Toluene	24 h	31
6	5-NO_2,H	Cyclohexyl, Me	H	85	DCE	24 h	11
7	5-NO_2,H	Cyclohexyl, Me	H	150	DMF	24 h	16
8	5-NO_2,H	*N*-Methylpiperazine	H	180[d]	DCE	10 min	31
9	5-NO_2,H	*N*-Methylpiperazine	H	180[e]	DCE	8 min[f]	63
10	5-NO_2,H	*N*-Methylpiperazine	H	180[e]	DCE	10 min[f]	73
11	5-NO_2,H	*N*-Methylpiperazine	H	180[e]	DCE	13 min[f]	29
12	5-NO_2,H	*N*-Methylpiperazine	H	220[e]	DMF	10 min[f]	38

[a] Purity determined by LC–MS analysis of crude products (integration area @ 254 nm) unless otherwise noted.
[b] Reported conditions and yield by E. A. Beccalli and co-workers.[5]
[c] Purity determined by ELSD-MS analysis of crude products (integration area).
[d] Oil bath temperature.
[e] Microwave irradiation done in a PS3 Smith Synthesizer™.
[f] Time includes 3 min required for enamine formation.

Table 2. Reaction validation results



Entry	R1, R2	R3,R4	R5	Yield (%)
1	4-Me, Ph	Me, Bz	4-Ethoxyphenyl	76
2	4-Me, Ph	Me, 3,4-Dimethoxyphenyl	4-Ethoxyphenyl	62
3	4-Me, Ph	Methylisonipecotate	4-Ethoxyphenyl	72
4	4-Me, Ph	4-Furoylpiperazine	4-Ethoxyphenyl	71
5	4-NO_2, Ph	Pyrrolidine	3,4-Dimethoxy Phenyl	100
6	5-Cl,*o*-F Ph	Methylisonipecotate	2-Fluorophenyl	64
7	4-Br,*o*-F Ph	Morpholine	3,4-Dichlorophenyl	57

is known as the nucleation limited boiling point[8] and such superheating may increase overall reaction rates. Furthermore, we have noted that the purity of products resulting from the traditional thermal reactions is also reduced due to the presence of decomposed 2-azidobenozphenone.

Optimized reaction conditions were produced by heating for 10 min in 1,2-dichloroethane (1,2-DCE) at 180°C, which includes 3 min for enamine formation (Table 1, entry 10). The irradiated reaction mixture was filtered through an SCX cartridge with 1,2-DCE as the eluent to remove the impurities followed by 1% HCl/MeOH to release the 2-aminoquinoline. While DMF can be used in this reaction, lower yields are typically observed (Table 1, entry 12) and the reaction workup is significantly more complicated. The differences in yield between entries 10 and 12 maybe due to pressure effects in these reactions.

In conclusion, we have developed a simple, rapid, two-step, one-pot method for the conversion of 2-azidobenzophenones into corresponding 2-aminoquinolines in good to excellent yields using microwave irradiation.

The compounds were further purified using simple SPE purification techniques. Overall we found that this approach accelerated the overall reaction 24 fold. The versatility of this methodology can be extended to develop a streamlined approach to 2-aminoquinoline libraries in a combinatorial fashion.

Typical experimental procedure

In a typical procedure, the enamine was prepared in situ by adding *N*-methylcyclohexylamine (1 mmol) and phenylacetaldehyde (1.1 mmol) to a Smith Process Vial™ (glass vessel) containing 4 mL of DCE. The vial was sealed and the mixture was heated in the Smith Synthesizer™ microwave at 180°C for 3 min, cooled to room temperature, and added to a second capped Smith Process Vial™ containing 2-azido-5-nitrobenzophenone[9] (0.8 mmol). The mixture was then heated a second time in the microwave at 180°C for 7 min and cooled to room temperature. The crude mixture was purified by filtering through a Varian SCX cartridge with DCE or DCM as the eluent to remove the impurities followed by 1% HCl/MeOH to release the 2-aminoquinoline. The 1% HCl/MeOH fractions are combined and the solvent removed on a rotary evaporator to furnish the desired material as a solid.

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6. The azide was prepared by adding $NaNO_2$ (2 equiv.) to a suspension 2-amino-5-nitrobenzophenone (1 equiv.) in TFA (3.5 mL) @ 0°C. After stirring for 20 min NaN_3 (3 equiv.) was added (N_2 evolved). The mixture was stirred for 20 min then quenched by addition of ice/H_2O. Water is added until a light yellow suspension formed, the suspension filtered, washed with water, and dried under vacuum.
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