Quinolines Formation by Condensation of Heteroaromatic Ketones and 2-Aminobenzophenones under MW Irradiation

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Microwave (MW) irradiation facilitated synthesis provides fast, safe, simple, and green reaction conditions. MW irradiation of 2-aminobenzophenones with heteroaromatic ketones afforded quinolines via Friedlander condensation in high yields with intact halogen substituents for further modifications. Dibenzo[b,f][1,5]diazocines were found as minor products and in some instances as the only products as the result of self-condensation of 2-aminobenzophenones. Different acid catalysts were found to affect these cyclization processes. Mini library of quinolines and dibenzo[b,f][1,5]diazocines were created in order to understand the substituents effect on the reaction. Resultant quinolines and dibenzo[b,f][1,5]diazocines are anticipated to serve as an interesting library for high throughput screening of various biological applications.

Keywords: Quinolines, Friedlander condensation, MW irradiation, Dibenzo[b,f][1,5]diazocines, Self-condensation

Introduction

Quinoline and its derivatives are prevalent in a variety of biological natural and synthetic compounds. Reported biological activities of quinoline derivatives include anticancer, antimycobacterial, antimicrobial, anticonvulsant, antiinflamatory, and cardiovascular properties.[1–3] For example, chloroquine, the most representative drug containing quinoline moiety, has been used to treat malaria for decades.[4] In addition to pharmacological activities, quinoline and its derivatives are widely used in industrial applications such as alkaloids, dyes, rubber chemicals, flavoring agents, corrosion inhibitors, and preservatives.[5] This wide variety of applications prompted the synthesis of quinoline derivatives.

Various synthetic routes have already been proposed along with new methods being extensively investigated.[6–8] Conventionally, quinolines are usually synthesized using large amounts of acid catalysts and highly toxic solvents under harsh conditions (reaction temperature above 180 °C for 24 h or longer). In addition, microwave (MW) irradiation is a promising alternative as it dramatically reduces the reaction time (down to minutes), reduces solvents (or no solvent at all), reduces side reactions, and hence increases yields in contrast to the conventional methods.[9]

In this paper, we report the synthesis of quinoline derivatives via MW irradiation. MW irradiation allowed fast and efficient quinoline formation without the need for any organic solvent or high reaction temperature. During the course of the study, dibenzo[b,f][1,5]diazocines were found to be minor products and in some instances, to be the only product as the result of self-condensation of 2-aminobenzophenones. In order to better understand the self-condensation, the effects of various acid catalysts were investigated.

Experimental

General Procedure for the Synthesis of Quinoline Compounds 3–7. 2-Aminobenzophenone **1** (1 mmol), heteroaromatic ketone **2** (1 mmol), and diphenylphosphate (DPP) (0.5 mmol) were mixed without any organic solvent and the reaction mixture was irradiated in the microwave oven (RE-555 TCW, Samsung, Busan, Korea) for 3 min. Resulting reaction mixture was diluted with 50 mL of ethyl acetate, neutralized with aqueous 10% NaOH and extracted with ethyl acetate three times, washed with water, and dried using $MgSO_4$. Products were purified by column chromatography (ethyl acetate/*n*-hexane = 1/20–1/40 v/v) to give the corresponding quinoline compounds **3–7**. (Analytical data provided in Supporting Information).

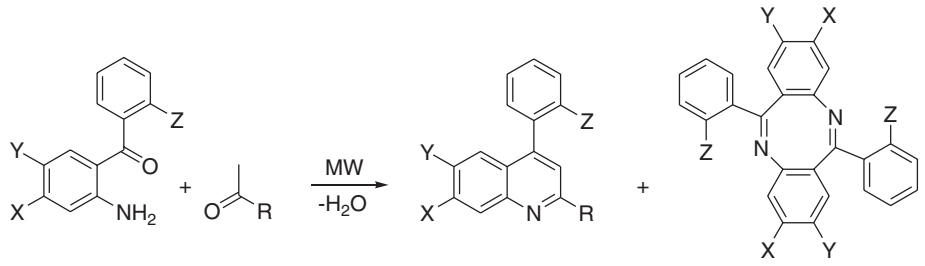
General Procedure for the Synthesis of Dibenzo[b,f][1,5] diazocine Compounds 8–12. 2-Aminobenzophenone **1** (1 mmol) was self-condensed in the presence of catalysts (DPP, hydrogen chloride [HCl], phosphoric acid [H_3PO_4], acetic acid [CH_3COOH], or acetic anhydride [$(CH_3CO)_2O$]) (0.5 mmol) without any organic solvent and the reaction mixture was irradiated in the microwave oven for 3 min. Resulting reaction mixture was diluted with 50 mL of ethyl acetate, neutralized with aqueous 10 % NaOH and extracted with ethyl acetate three times, washed with water, and dried using $MgSO_4$. Products were purified by column chromatography (ethyl acetate/*n*-hexane = 1/20–1/40 v/v) to give the corresponding dibenzo[b,f][1,5]diazocine compounds **8–12**. (Analytical data provided in Supporting Information).

Results and Discussion

Friedlander condensation of 2-aminobenzophenones **1** with various heteroaromatic ketones **2** via MW irradiation was carried out in the absence of any organic solvent. To create a mini library, 2-aminobenzophenones were condensed with acetyl pyridines **2a–c**, 2-acetylfuran **2d**, 2-acetylthiophene **2e**, and 4-methylacetophenone **2f** (structural details provided in Supporting Information). To further broaden the scope of the proposed reaction, various 2-aminobenzophenones with different substituents (*e.g.*, 2-aminobenzophenone **1a**, 2-amino-4-bromobenzophenone **1b**, 2-amino-5-chlorobenzophenone **1c**, 2-amino-2′,5-dichlorobenzophenone **1d**, and 2-amino-5-chloro-2′-fluorobenzophenone **1e**) were tested. These substituents at various positions allow further modification of products for different applications such as conjugation of pharmaceutically relevant moieties. In fact, present reaction conditions using MW irradiation did not affect the halogen substituents at various positions (evidenced by analytical data provided in Supporting Information), which can serve as important platforms for further modifications.

Generally, quinolines were obtained as the major products with good yields in the range of 60–75% (Table 1). There were no noticeable trends in the reaction yields except for

Table 1. Condensation of 2-aminobenzophenones with various heteroaromatic ketones under MW irradiation.



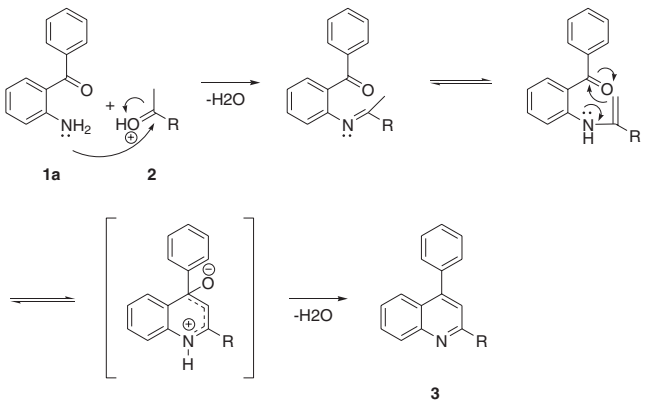
Product	2-Aminobenzophenones 1	*X*	*Y*	*Z*	Heteroaromatic ketones 2	R	Major product **3–7** yield (%)[a]	Minor product yield (%)[a]
3a	**1a**	H	H	H	**2a**	Pyridin-2-yl	71.0	13.2
3b					**2b**	Pyridin-3-yl	74.5	15.6
3c					**2c**	Pyridin-4-yl	71.0	12.3
3d					**2d**	Furan-2-yl	68.0	10.5
3e					**2e**	Thiophen-2-yl	60.0	11.0
4a	**1b**	Br	H	H	**2a**	Pyridin-2-yl	71.0	13.2
4b					**2b**	Pyridin-3-yl	74.3	15.1
4c					**2c**	Pyridin-4-yl	66.5	9.4
4d					**2d**	Furan-2-yl	78.5	11.4
4e					**2e**	Thiophen-2-yl	72.5	15.8
4f					**2f**	2-*p*-tolyl	77.7	9.3
5a	**1c**	H	Cl	H	**2a**	Pyridin-2-yl	70.0	8.9
5b					**2b**	Pyridin-3-yl	72.0	9.4
5c					**2c**	Pyridin-4-yl	66.5	9.4
6a	**1d**	H	Cl	Cl	**2a**	Pyridin-2-yl	71.4	10.2
6b					**2b**	Pyridin-3-yl	37.1	12.0
6c					**2c**	Pyridin-4-yl	62.9	9.4
6d					**2d**	Furan-2-yl	67.8	10.0
6e					**2e**	Thiophen-2-yl	70.4	9.1
6f					**2f**	2-*p*-tolyl	60.1	11.0
7a	**1e**	H	Cl	F	**2a**	Pyridin-2-yl	64.1	13.0
7b					**2b**	Pyridin-3-yl	57.9	10.8
7c					**2c**	Pyridin-4-yl	40.3	9.8
7d					**2d**	Furan-2-yl	74.3	10.3
7e					**2e**	Thiophen-2-yl	66.1	10.7
7f					**2f**	2-*p*-tolyl	56.1	10.7

[a] Isolated yields.

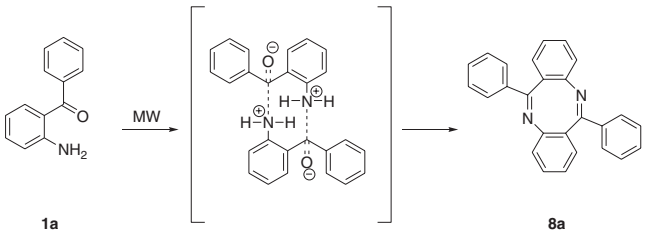
3-acetylpyridine reacted species (*i.e.*, **3b**, **4b**, and **5b**) showing higher yields (74.5, 74.3, and 72.0%, respectively) than 2-acetylpyridine and 4-acetylpyridine reacted species probably due to meta position effect. However, when the Z-substituted 2-aminobenzophenones (*i.e.*, **1d** and **1e**) were reacted with 3-acetylpyridine, resultant products showed exceptionally low yield (37.1% for **6b**) or lower yield (57.9% for **7b**). As a matter of fact, Z-substituted 2-aminobenzophenones (**1d** and **1e**), in general, exhibited lower yields than non-Z-substituted 2-aminobenzophenones (**1a**, **1b**, and **1c**) possibly due to steric hindrance effect. Dipole–dipole interaction along with the increase in the polarity of the system during the progress of the reaction is considered to be the driving force in MW-mediated solvent-free conditions (Scheme 1).[10]

In all cases, dibenzo[b,f][1,5]diazocines were obtained as minor products with relatively low yields in the range of 9–16 % (Table 1). However, when 2-aminobenzophenone **1a** was reacted with 4-acetylmorpholine **2g**, 3-acetyl-2-oxazolidinone **2h**, and 4-acetylimidazole **2i**, 6,12-diphenyldibenzo[b,f][1,5]diazocine **8a** was obtained as the only product with higher yields (34.0, 42.0, and 41.0%, respectively). Morpholine (**2g**), oxazolidinone (**2h**), and imidazole (**2i**) moieties were chosen for applications in biological activity as they are often found in antibacterial drugs,[11,12] but these results suggest that they inhibit the formation of quinolines.

Dibenzo[b,f][1,5]diazocine products are understood to be formed by the self-condensation of 2-aminobenzophenones (Scheme 2). Dibenzo[b,f][1,5]diazocines have drawn the attention of organic chemists since the 1960s due to antiviral, cholesterol-lowering and hormone-like activity.[13,14] Moreover, their reversible conformational changes during electrochemical redox processes make them interesting building blocks for molecular machines and artificial muscles.[15] Conventional synthesis methods preparing dibenzo[b,f][1,5]diazocines required long reflux times,[16,17] which in this paper was dramatically changed to solvent-less, no-heat-required, and 3 min reaction.



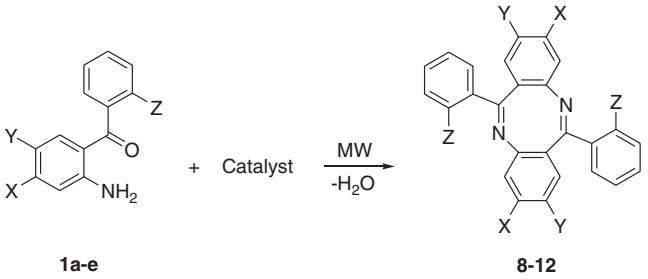
Scheme 1. Friedlander condensation of 2-aminobenzophenone **1** with heteroaromatic ketone **2** to afford quinoline compound **3**.



Scheme 2. Self-condensation of 2-aminobenzophenone 1 to yield dibenzo[b,f][1,5]diazocine compound 8.

Generally, acid catalysts are known to be more effective than base catalysts in Friedlander condensations.[18] Therefore, several acid catalysts of interest (DPP, HCl, H_3PO_4, CH_3COOH, and $(CH_3CO)_2O$) were investigated on the self-condensation of 2-aminobenzophenones (Table 2). Anhydrous DPP afforded dibenzo[b,f][1,5]diazocine products **8** with highest yields (above 70%). For the rest of the acid catalysts, yields of dibenzo[b,f][1,5]diazocine products decreased with decreasing acidity of catalysts. The cyclization reaction was effectively mediated by the presence of DPP. It would be an interesting subject of subsequent study to see if catalysts with lower dibenzo[b,f][1,5]diazocine yields (*i.e.*, CH_3COOH or $(CH_3CO)_2O$) would facilitate higher quinoline yields.

Table 2. Self-condensation of 2-aminobenzophenones with various catalysts under MW irradiation.



		2-Aminobenzophenones				
Product	Catalyst	1	*X*	*Y*	*Z*	Yield (%)[a]
8a	DPP	**1a**	H	H	H	89.4
8d		**1d**	H	Cl	Cl	76.2
8e		**1e**	H	Cl	F	77.5
9a	HCl	**1a**	H	H	H	61.6
9d		**1d**	H	Cl	Cl	56.3
9e		**1e**	H	Cl	F	51.7
10a	H_3PO_4	**1a**	H	H	H	45.7
10d		**1d**	H	Cl	Cl	40.2
10e		**1e**	H	Cl	F	41.8
11a	CH_3COOH	**1a**	H	H	H	18.9
11d		**1d**	H	Cl	Cl	16.7
11e		**1e**	H	Cl	F	14.4
12a	$(CH_3CO)_2O$	**1a**	H	H	H	23.7
12d		**1d**	H	Cl	Cl	15.7
12e		**1e**	H	Cl	F	16.5

[a] Isolated yields.

Conclusion

In conclusion, MW irradiation of 2-aminobenzophenones with heteroaromatic ketones resulted in the formation of quinolines via Friedlander condensation in high yields. MW irradiation facilitated fast, safe, simple, and green reaction conditions. Dibenzo[b,f][1,5]diazocines were found as minor products as the result of self-condensation of 2-aminobenzophenones. Careful selection of acid catalysts is anticipated to affect the side self-condensation and hence increase overall yield of quinolines formation. High throughput screening of resulting quinolines and dibenzo[b,f][1,5]diazocines library for applications in biological activity are underway.

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Supporting Information. Additional supporting information is available in the online version of this article

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