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PAPER

Microwave-promoted efficient synthesis of dihydroquinazolines†

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A solvent- and catalyst-free synthesis of dihydroquinazolines is described. 2,4-Disubstituted-1,2-dihydroquinazolines can be readily obtained from 2-aminobenzophenone and aldehydes under microwave irradiation using urea as an environmentally benign source of ammonia, with a small amount of the corresponding quinazolines as the minor product. The reaction is simple, clean and excellent yields are obtained within minutes.

Introduction

Over the last decade, design of the quinazoline scaffold has caught the attention of synthetic chemists because of their immense biological and pharmacological potency. The importance of quinazoline derivatives has been well documented. It is the building block for many naturally occurring alkaloids found across the plant and animal kingdoms and various microorganisms such as *Bouchardatia Neurococca*,[1] *Peganum nigellastrum*,[2] *Bacillus cereus*[3] and *Dichroa febrifuga*.[4] Quinazoline derivatives are known to act as selective inhibitors of the tyrosine kinase activity of the epidermal growth factor receptor (EGFR).[5] They have also shown remarkable activity as anticancer, antitubercular, antibacterial, and antiviral agents.[6] In a recent report, 3,4-dihydroquinazoline derivatives have been found to have excellent T-type calcium channel blocking activity.[7] Development of the quinazoline-based drugs such as gefitinib (Iressa) and erlotinib (Tarceva) has renewed the interest in developing new synthetic strategies for synthesis of quinazoline derivatives.

Although a number of methods for the synthesis of quinazoline derivatives have been reported,[8] most of them suffer from one or more disadvantages like preparation of starting materials *via* multistep synthesis, use of catalyst, ligand or additives, requirement of inert atmosphere and stringent reaction conditions. Vanelle *et al.*[8d] reported a microwave-mediated process for synthesis of quinazolinones in aqueous medium, but suffered from the drawback of preparation of the starting compound using organic solvent. In a recent report, Fu and his coworkers[8c] have synthesised quinazolines from 2-bromobenzaldehydes. However, their method required use of ligand, base, catalyst and inert atmosphere for the transformation to take place. As such, development of mild and rapid approaches to quinazolines, especially under solvent-free conditions, is still desired because of their biological significance.

The most fundamental obstacles in developing technologies are to minimise the energy consumption and to eliminate/minimise the use of hazardous solvents. In this scenario, use of microwave energy to bring about chemical transformations is a suitable alternative, as it takes care of two very essential criteria of synthesis: minimise energy consumption required for heating and time required for the reaction.[9] Moreover, solventless synthesis results in reaction rate enhancements along with differed selectivity compared to conventional conditions.[10] Thus microwave heating coupled with dry reaction media presents a green protocol to carry out organic reactions.

Conventional synthetic approaches towards 1,2-dihydroquinazolines are based on reaction of 2-aminobenzonitriles with Grignard reagents, followed by condensation with an aldehyde.[11a,b] The yield of the reaction was very poor under such conditions due to competitive side reactions. Moreover, inert atmosphere and long reaction time is necessary. In another report, 2-carboxylic acid derivatives of 1,2-dihydroquinazoline[11c] were synthesized from hydroxyglycine and aminobenzophenone wherein the stability of the products were compromised as they tend to decompose in solution.

Results and discussion

In our continued effort towards development of microwave-assisted synthetic methodologies,[12] we describe in this paper an efficient catalyst- and solvent-free protocol for the synthesis of 1,2-dihydroquinazolines under one-pot conditions. Initially, reaction of 2-aminobenzophenone with one equivalent of an aldehyde and 1.5 equivalents of urea were investigated. Formation of 1,2-dihydroquinazolines were observed in excellent yields as the major product with little amount of the aromatic counterpart as the minor product when the reactants were irradiated under MW at 540 W and 130 °C for 4 min. The feasibility of the reaction scheme was tested by using various

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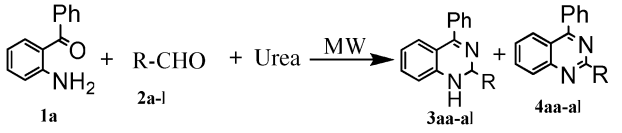
† Electronic supplementary information (ESI) available: Detailed experimental procedure, compound characterization data and NMR spectra. See DOI: 10.1039/c0gc00838a

Table 1 Reaction of different aldehydes with 2-aminobenzophenone and urea[a]



Entry	Aldehyde	Product	Product ratio	Yield (%)[b]
1	C_6H_5–CHO (**2a**)	**3aa/4aa**	85 : 15	82
2	4-CH_3–C_6H_5–CHO (**2b**)	**3ab/4ab**	84 : 16	79
3	4-F–C_6H_5– (**2c**)	**3ac/4ac**	87 : 13	85
4	3-Br–C_6H_5–CHO (**2d**)	**3ad/4ad**	85 : 15	85
5	2-Cl–C_6H_5–CHO (**2e**)	**3ae/4ae**	100 : 0	90
6	CH_3–CHO (**2f**)	**3af/4af**	99 : trace	88
7	$(CH_3)_2$CH–CHO (**2g**)	**3ag/4ag**	99 : trace	90
8	$CH_3(CH_2)_4$–CHO (**2h**)	**3ah/4ah**	99 : trace	90
9	$CH_3(CH_2)_2$–CHO (**2i**)	**3ai/4ai**	99 : trace	85
10	C_6H_5CHCHCHO (**2j**)	**3aj/4aj**	90 : 10	80
11	C_4H_3O–CHO (**2k**)	**3ak/4ak**	80 : 20	82
12	C_4H_3S–CHO (**2l**)	**3al/4al**	80 : 20	83

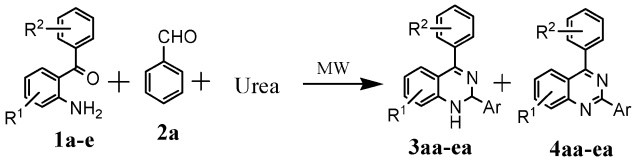
[a] Reaction conditions: **1a** (1 mmol), **2** (1 mmol) and urea (1.5 mmol) were irradiated at 540 W for 4 min in absence of any solvent in a microwave reactor. [b] Isolated yield.

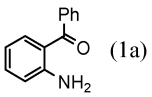
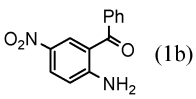
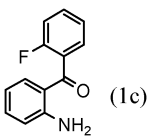
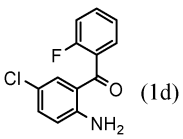
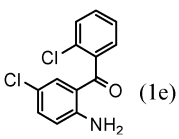
aromatic, aliphatic, heteroaromatic and conjugated aldehydes and the results are summarised in Table 1.

It was observed that the nature of the substituent present in aromatic aldehydes has an impact over the yield of the reaction. The presence of an electron-donating substituent resulted in lowering of the overall yield (Table 1, entry 2), whereas electron-withdrawing substituent increased the yield (Table 1, entry 3–5), relative to benzaldehyde. This may be due to the inductive effect exerted by the substituents on the aldehyde functionality. A positive inductive effect by electron-donating groups lowers the reactivity of the carbonyl carbon of the aldehyde towards nucleophilic attack by the N atom of 2-aminobenzophenone, thereby lowering the rate of the reaction. Electron-withdrawing substituents impart a negative inductive effect, which subsequently increases the reaction rate. However, the nature of the substituent on aromatic aldehydes seems to have no impact on the ratios of the products formed. Quite interestingly, though, the reaction with *o*-chlorobenzaldehyde yielded the dihydroquinazoline as the only product (Table 1, entry 5). Aliphatic aldehydes were reluctant to undergo aromatisation and the dihydro product was formed almost exclusively (Table 1, entry 6–9). This methodology worked equally well with heteroaromatic and conjugated aldehydes and excellent yields were observed (Table 1, entry 10–12).

In the next step we tried to generalise the reaction by varying the 2-aminobenzophenone molecule and the results obtained are summarised in Table 2. The yield of the reaction was found to be excellent in all the cases (Table 2, entry 1–5). Further, the product ratios were also found to be similar with the dihydro compound being the major product. We were delighted to note that 2-aminobenzophenone with substituents on either one or both the phenyl rings underwent the reaction smoothly. The scope and generality of the reaction was studied by reacting 2-aminobenzophenones **1a–e** with a range of aryl aldehydes and the results are summarised in Table 3.

Table 2 Reaction of different 2-aminobenzophenones with benzaldehyde and urea[a]



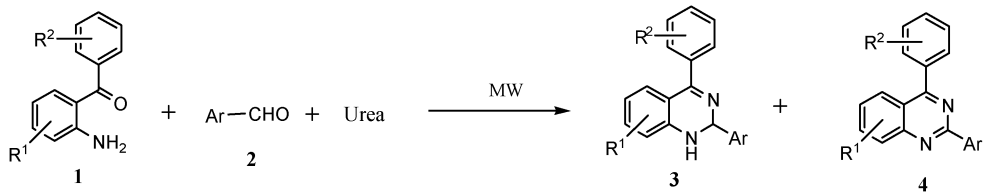
Entry	2-Aminobenzophenone	Product	Product ratio	Yield (%)[b]
1	 (1a)	**3aa/4aa**	85 : 15	82
2	 (1b)	**3ba/4ba**	88 : 12	80
3	 (1c)	**3ca/4ca**	85 : 15	85
4	 (1d)	**3da/4da**	90 : 15	85
5	 (1e)	**3ea/4ea**	87 : 13	78

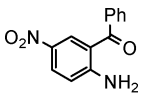
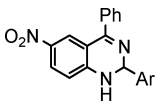
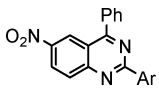
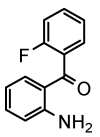
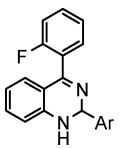
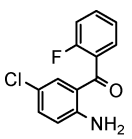
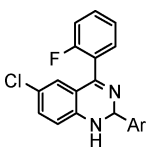
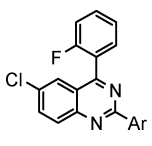
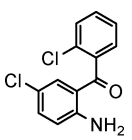
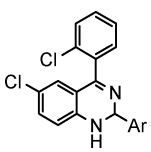
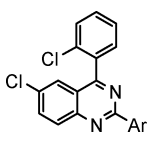
[a] Reaction conditions: **1a** (1 mmol), **2** (1 mmol) and urea (1.5 mmol) were irradiated at 540 W for 4 min in absence of any solvent in a microwave reactor. [b] Isolated yield.

Mechanistically, there are two possible pathways by which the reactants can come together to form the observed products. The ketone group of 2-aminobenzophenone can form an imine [A] with the ammonia generated from urea under MW conditions. The free NH_2 group of [A] can then react with the aldehyde to give intermediate [C], which after cyclisation generates dihydroquinazoline **3**. Aromatisation of **3** yields quinazoline **4** as the minor product (path (a), Scheme 1). Alternatively, the aldehyde can form an imine [B] by reacting with ammonia liberated from urea under MW conditions, which, after simultaneous addition-cyclisation reactions, forms **3** (path (b), Scheme 1).

As ammonium acetate is also a good source of ammonia, we tried our methodology by employing ammonium acetate in place of urea under identical reaction conditions. Accordingly, when 2-aminobenzophenone was reacted with benzaldehyde and ammonium acetate in a microwave reactor under neat conditions in absence of any catalyst, we were happy to note that a mixture of dihydroquinazoline and quinazoline were obtained with yield and product ratios comparable to the reaction with urea (Scheme 2). The only difference in the two processes was that in case of urea the reaction took slightly more time (4 min,

Table 3 Synthesis of 2,4-disubstituted 1,2-dihydroquinazolines **3** and quinazolines **4**[a]



entry	2-Aminobenzophenone	Aldehyde (Ar)	Products		Product Ratio	Yield(%)[b]
	 (1b)					
1		4-CH_3–C_6H_4– (**2b**)	**3bb**	**4bb**	85 : 15	82
2		4-F–C_6H_4– (**2c**)	**3bc**	**4bc**	87 : 13	88
3		2-Cl–C_6H_4– (**2e**)	**3be**	**4be**	90 : 10	90
4		4-CH_3O–C_6H_4– (**2f**)	**3bf**	**4bf**	85 : 15	84
	 (1c)					
5		4-CH_3–C_6H_4– (**2b**)	**3cb**	**4cb**	85 : 15	80
6		4-F–C_6H_4– (**2c**)	**3cc**	**4cc**	82 : 18	90
7		2-Cl–C_6H_4– (**2e**)	**3ce**	**4ce**	99 : 1[c]	90
8		4-CH_3O–C_6H_4– (**2f**)	**3cf**	**4cf**	100 : 0[d]	85
	 (1d)					
9		4-CH_3–C_6H_4– (**2b**)	**3db**	**4db**	80 : 20	87
10		4-F–C_6H_4– (**2c**)	**3dc**	**4dc**	90 : 10	91
11		3-Br–C_6H_4– (**2g**)	**3dg**	**4dg**	90 : 10	90
12		C_4H_3S– (**2l**)	**3dl**	**4dl**	80 : 20	70
	 (1e)					
13		4-CH_3–C_6H_4– (**2b**)	**3eb**	**4eb**	78 : 22	82
14		2-Cl—C_6H_4– (**2e**)	**3ee**	**4ee**	99 : 1[c]	90
15		4-CH_3O–C_6H_4– (**2f**)	**3ef**	**4ef**	82 : 18	83

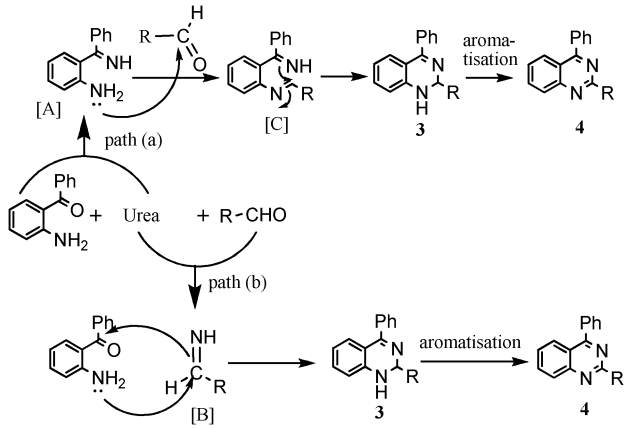
[a] Reaction conditions: **1a** (1 mmol), **2** (1 mmol) and urea (1.5 mmol) were irradiated at 540 W for 4 min in absence of any solvent in a microwave reactor. [b] Isolated yields. [c] Trace amount of quinazoline detected in NMR. [d] No quinazoline product detected in NMR.

Table 1) than that required in case of ammonium acetate (3 min, Scheme 2).

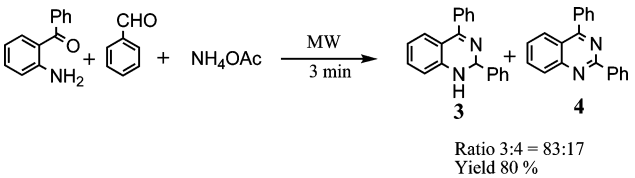
We also carried out the reaction under classical conditions and compared the results with those obtained under microwave conditions. Thus, a mixture of ammonium acetate, 2-aminobenzophenone and benzaldehyde when refluxed in acetic acid for 10 h, yielded dihydroquinazoline and quinazoline in a combined yield of 50% (Scheme 3). Further increase in reaction time resulted in decomposition of products thereby leading to lower yields. This observation made it clear that not only the reaction is promoted by microwave radiation, but also it prevents formation of unwanted side products. This makes our methodology a very clean and green one.

Conclusions

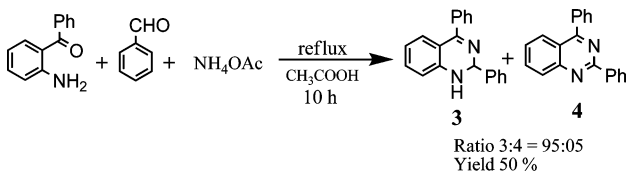
In summary, a range of substituted 2-aminobenzophenones and aldehydes have been shown to undergo a microwave promoted three component, one pot reaction with urea to generate a library of 2,4-disubstituted-1,2-dihydroquinazolines and



Scheme 1 Proposed mechanism for formation of quinazolines **3** and **4**.



Scheme 2 Reaction of 2-aminobenzophenone and benzaldehyde with ammonium acetate.



Scheme 3 Three component reaction of 2-aminobenzophenone, benzaldehyde and ammonium acetate under classical conditions.

2,4-disubstituted quinazolines under catalyst- and solvent-free conditions. This methodology works equally well when ammonium acetate is employed as the source of ammonia instead of urea. This approach offers an environmentally friendly and 'green' alternative towards removing organic solvents from organic synthesis.

Experimental

General experimental

Melting points were measured with a Buchi B-540 melting point apparatus and are uncorrected. IR spectra were recorded on a SHIMADZU FTIR-8400. NMR spectra were recorded on Advance DPX 300 MHz FT-NMR spectrometer using tetramethylsilane (TMS) as an internal standard. Mass spectra were recorded on ESQUIRE 3000 Mass spectrometer. All the commercially available regents were used as received. All experiments were monitored by thin layer chromatography (TLC). TLC was performed on pre-coated silica gel plates (Merck). After elution, plate was visualized under UV illumination at 254 nm for UV active materials. Further visualization was achieved by staining $KMnO_4$ and warming in a hot air oven. Column chromatography was performed on silica gel (100—200 mesh, Merck) using ethyl acetate–hexane as eluent.

Microwave instrumentation

All MW reactions were carried out in a Synthos 3000 (Anton Paar) microwave reactor. The multitude microwave has a twin magnetron (2.45 GHz) with maximum output power of 1400 W. The output power can be controlled in unpulsed control mode over whole power range which is adjustable in 1 W increments. A Motorola 68xxx series microprocessor system control is used to measure temperature, pressure, time and power during the reaction. The temperature and pressure were monitored throughout the reaction by an infrared detector. The temperature can be measured from 0 to 280 °C with uncertainty ±1%. The pressure can be measured from 0 to 86 bar with uncertainty ±0.2 bar.

General procedure for synthesis of quinazolines

(a) Under MW irradiation using urea. 2-Aminobenzophenone **1** (1 mmol), an aldehyde **2** (1 mmol) and urea (1.5 mmol) were irradiated in a closed vessel in absence of any solvent in a Synthos 3000 microwave reactor at 540 W, 140 °C and 10.9 bar for 4 min. The crude product mixture was dissolved in ethyl acetate and directly column chromatographed using 2 : 8 ethyl acetate–hexane as the eluent to get pure 1,2-dihydroquinazoline **3** and quinazoline **4**.

(b) Under MW irradiation using ammonium acetate. 2-Aminobenzophenone **1** (1 mmol), an aldehyde **2** (1 mmol) and ammonium acetate (1.5 mmol) were irradiated in a closed vessel for 2 min in absence of any solvent in a Synthos 3000 microwave reactor at 540 Watt, 130 °C and 15 bar pressure. The crude product mixture was dissolved in ethyl acetate and directly column chromatographed using 2 : 8 ethyl acetate–hexane as the eluent to get pure 1,4-dihydroquinazoline **3** and quinazoline **4**.

(c) Under classical conditions using ammonium acetate. 2-Aminobenzophenone **1** (1 mmol), an aldehyde **2** (1 mmol) and ammonium acetate (1.5 mmol) were refluxed in acetic acid under air for 10 h. The reaction mixture was poured in water, neutralised with potassium bicarbonate solution and extracted with ethyl acetate and dried over anhydrous sodium sulfate. It was filtered and purified by column chromatography using 2 : 8 ethyl acetate–hexane as the eluent to get the products 1,4-dihydroquinazoline **3** and quinazoline **4**.

Acknowledgements

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