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Short Communication

GREEN SYNTHESIS OF 2-ARYL-4-PHENYL-QUINAZOLINE DERIVATIVES PROMOTED BY LACTIC ACID

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An environmentally benign three-component synthetic method is described for the construction of 2-aryl-4-phenylquinazoline derivatives from the reaction between aldehydes, ammonium acetate, and 2-aminobenzophenone in the presence of lactic acid in a solvent-less media. The benefits of the reaction were good yields, a simple procedure, simple starting materials short reaction time, easy work-up, and cleaner reaction profiles.

Keywords: green protocol; quinazoline derivatives; multi-component reaction; lactic acid; solvent-free conditions

ЗЕЛЕНА СИНТЕЗА НА 2-АРИЛ-4-ФЕНИЛХИНАЗОЛИНСКИ ДЕРИВАТИ ПОМОГНАТА СО МЛЕЧНА КИСЕЛИНА

Опишан е еколошко прифатлив трокомпонентен метод на синтеза за добивање 2-арил-4-фенилхиназолински деривати од реакција меѓу алдехиди, амониум ацетат и 2-аминобензофенон во присуство на млечна киселина без растворувач. Погодностите на оваа реакцијата се добри приноси, едноставна постапка, едноставни почетни материјали, кусо време на реакција, лесно обработка и почисти реакциски профили.

Клучни зборови: зелен протокол; хиназолински деривати; мултикомпонентна реакција; млечна киселина; услови без растворувач

1. INTRODUCTION

Nitrogen-containing heterocycles are present in a wide variety of bioactive natural products and biological molecules that may be good drug candidates [1]. Specifically, quinazolines and their derivatives represent a medicinally and pharmaceutically important class of heterocyclic motifs that are found as the core structural skeletons in a variety of drug molecules such as prazosin [2] and lapatinib [3] (Figure 1). They possess a wide range of biological and pharmacological activities, including anticancer [4], antiviral [5], antitubercular [6] and antimalarial properties [7]. Zhang et al. [8] have reported quinazoline synthesis with 2-aminobenzophenones and benzylic amines via SP_3 C-H activation, where I_2 served as a catalyst in the presence of an added oxidant at a relatively high temperature (90 °C) and relatively longer reaction time (12 h). A catalyst and solvent-free microwave assisted improved reaction methodology was recently developed by Prajapati and co-workers for synthesizing dihydroquinazoline derivatives [9]. Although the method is novel and exemplary, it lacks selectivity towards quinazoline derivatives.

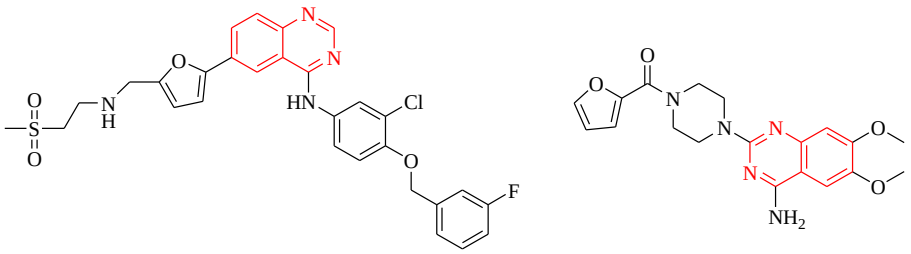
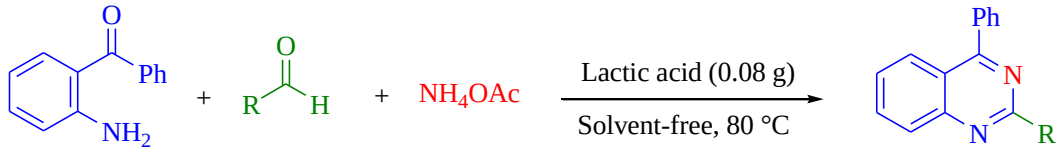


Figure 1. Structures of some biologically active quinazoline cores

Although there are a certain number of methods available for the synthesis of quinazoline derivatives, the reported methods have their demerits and limitations, such as multi-step synthesis, the use of expensive harmful reagents, the application of toxic solvents like toluene and DMSO, a complicated work-up procedure and low yields. Based on their extensive application, it is necessary to further develop more efficient and convenient methods to construct such significant heterocyclic compounds. In this communication, we wish to describe a green one-pot three-component protocol for the synthesis of quinazoline derivatives from the reaction of aldehydes, ammonium acetate and 2-aminobezophenone under thermal conditions in the presence of an efficient, green and inexpensive catalyst of lactic acid under solvent-free conditions (Scheme 1).



Scheme 1. Lactic acid catalyzed synthesis of quinazoline derivatives 4

2. EXPERIMENTAL

The melting points of all compounds were measured on an Electrothermal 9100 apparatus. The ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker DRX-300 Avance instruments with DMSO as the solvent and using TMS as the internal reference at 300 and 75 MHz, respectively. The mass spectra were recorded on an Agilent Technology (HP) mass spectrometer, operating at an ionization potential of 70 eV. All reagents and solvents obtained from Fluka and Merck were used without further purification.

2.1. *General procedure for the synthesis of quinazoline derivatives (4a-k)*

To a round-bottomed flask containing 0.08 g of lactic acid was added 2-aminobenzophenone (1.0 mmol), aldehyde (1.0 mmol) and ammonium acetate (1.0 mmol). The mixture was heated at 80 °C under stirring, while air was bubbled into the reaction. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was cooled to room temperature. Water was added, and the precipitated solid was collected by filtration and washed with water. Then, the residue was recrystallized from EtOH.

2-methoxy-6-(4-phenylquinazolin-2-yl)phenol (**4a**): Yield: 96%; m.p. 210–212 °C; IR (KBr, cm^{-1}): 3436, 2924, 1541, 1455, 1249, 1045, 770, 701; ^{1}H NMR (300 MHz, DMSO-d$_6$): δ = 6.99 (t, 1H, *J* = 8.1 Hz, H$_{aromatic}$), 7.21 (dd, 1H, *J* = 8.1 Hz, *J* = 1.2 Hz, H$_{aromatic}$), 7.72–7.77 (m, 3H, H$_{aromatic}$), 7.78–7.84 (m, 1H, H$_{aromatic}$), 7.95–7.98 (m, 2H, H$_{aromatic}$), 8.12–8.26 (m, 4H, H$_{aromatic}$), 13.95 (s, 1H, OH). ^{13}C NMR (75 MHz, DMSO-d6): δ = 56.35, 115.77, 118.61, 118.69, 119.24, 121.11, 121.26, 127.76, 127.87, 128.83, 129.30, 130.50, 131.10, 135.86, 136.79, 149.10, 149.16, 149.29, 150.97, 160.58, 168.71; MS m/z (%): 77.1 (13), 128.1 (10), 180.1 (12), 255.1 (22), 285.1 (52), 328.2 (100), 328 (M+, 1).

4-bromo-2-(4-phenylquinazolin-2-yl)phenol (**4b**):

Yield: (94 %); m.p. 195–197 °C; IR (KBr, cm^{-1}): 3435, 2924, 1535, 1476, 700, 634; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.07 (d, 1H, *J* = 8.7 Hz, $H_{aromatic}$), 7.64 (dd, 1H, *J* = 8.7 Hz, *J* = 2.7 Hz, $H_{aromatic}$), 7.74–7.78 (m, 3H, $H_{aromatic}$), 7.81–7.86 (m, 1H, $H_{aromatic}$), 7.95 (d, 1H, *J* = 4.2 Hz, $H_{aromatic}$), 7.97 (d, 1H, *J* = 1.8 Hz, $H_{aromatic}$), 7.16 (d, 2H, *J* = 10.2 Hz, $H_{aromatic}$), 8.20 (d, 1H, *J* = 3.3 Hz, $H_{benzylic}$), 8.28 (d, 1H, *J* = 8.4 Hz, $H_{aromatic}$), 8.72 (d, 1H, *J* = 8.4 Hz, $H_{aromatic}$), 13.82 (s, 1H, OH). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 110.71, 120.54, 121.10, 121.40, 127.85, 128.04, 129.25, 129.37, 130.51, 131.21, 131.57, 136.07, 136.62, 159.62, 159.91; MS m/z (%): 77.1 (17), 133.8 (16), 268.1 (19), 296.2 (28), 376 (M+, 100), 378.1 (M+2, 98).

4-Phenyl-2-(p-tolyl)quinazoline (**4c**):
Yield: (92%); m.p. 163–165 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.45 (s, 3H, CH_3), 7.44 (d, 2H, *J* = 7.8 Hz, $H_{aromatic}$), 7.70–7.78 (m, 4H, $H_{aromatic}$), 7.92–7.97 (m, 2H, $H_{aromatic}$), 8.06–8.20 (m, 3H, $H_{aromatic}$), 8.56 (d, 2H, J = 8.1 Hz, $H_{aromatic}$), ^{13}C NMR (300 MHz, DMSO-d_6): δ = 21.55, 121.45, 127.32, 128.22, 128.62, 129.07, 129.13, 129.84, 130.45, 130.59, 134.87, 135.28, 137.47, 141.15, 151.69, 159.55, 168,46.

2-(4-Methoxyphenyl)-4-phenylquinazoline (**4d**):
Yield: (95%); m.p. 159–161 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.86 (s, 3H, OCH_3), 7.12 (d, 2H, *J* = 9 Hz, $H_{aromatic}$), 7.64–7.69 (m, 4H, $H_{aromatic}$), 7.85–7.90 (m, 2H, $H_{aromatic}$), 7.98–8.11 (m, 3H, $H_{aromatic}$), 8.56 (d, 2H, J = 9 Hz, $H_{aromatic}$).

2-(4-Bromophenyl)-4-phenylquinazoline (**4e**):
Yield: (94%); m.p. 140–142 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.68-7.75 (m, 4H, $H_{aromatic}$), 7.79 (d, 2H, J = 8.7 Hz, $H_{aromatic}$), 7.90–7.91 (m, 2H, $H_{aromatic}$), 8.04–8.18 (m, 3H, $H_{aromatic}$), 8.55 (d, 2H, J = 8.4 Hz, $H_{aromatic}$).

2-(4-Chlorophenyl)-4-phenylquinazoline (**4f**):
Yield: (90%); m.p. 193–195 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.48 (d, 2H, *J* = 8.5 Hz, $H_{aromatic}$), 7.54–7.61 (m, 4H, $H_{aromatic}$), 7.87–7.91 (m, 3H, $H_{aromatic}$), 8.12–8.14 (m, 2H, $H_{aromatic}$), 8.65 (d, *J* = 8.0 Hz, 2H, $H_{aromatic}$).

2-(2-Nitrophenyl)-4-phenylquinazoline (**4g**):
Yield: (90%); m.p. 126–128 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.37–7.84 (m, 8H, $H_{aromatic}$), 7.89–8.36 (m, 5H, $H_{aromatic}$).

2-(3-Nitrophenyl)-4-phenylquinazoline (**4h**):
Yield: (89%); m.p. 180–182 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.69–7.93 (m, 7H, $H_{aromatic}$), 8.07–8.24 (m, 3H, $H_{aromatic}$), 8.40–8.43 (m, 1H, $H_{aromatic}$), 9.01 (d, 1H, J = 7.8 Hz, $H_{aromatic}$), 9.312 (t, *J* = 2.1 Hz, 1H, $H_{aromatic}$).

2-(3-fluorophenyl)-4-phenylquinazoline (**4i**):
Yield: (95%); m.p. 198–200 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.39–7.45 (m, 1H, $H_{aromatic}$), 7.60–7.78 (m, 5H, $H_{aromatic}$),7.88–7.93(m, 5H, $H_{aromatic}$), 8.07 (td, 1H, J = 6.9 Hz, J = 1.5 Hz, $H_{aromatic}$), 8.12 (d, *J* = 8.1 Hz, 1H, $H_{aromatic}$), 8.18 (d, *J* = 8.1 Hz, 1H, $H_{aromatic}$), 8.30 (ddd, *J* = 10.5 Hz, *J* = 2.4 Hz, *J* = 1.5 Hz, 1H, $H_{aromatic}$), 8.45 (d, *J* = 7.8 Hz, 1H, $H_{aromatic}$).

3. RESULTS AND DISCUSSION

Based on our long-standing interest in exploring organic synthesis based on green chemistry [11–13], we report herein a three-component reactions of aldehydes, ammonium acetate, and 2- aminobenzophenone for the synthesis of quinazolines, which are core structures in several drug molecules such as gefitinib (Iressa), erlotinib (Tarceva) and actinomycin. This was achieved by using lactic acid as a sustainable bio-based promoter in a solvent-less medium. Considering the good promotion activity as well as the inherent greenness of lactic acid as a nontoxic and bioavailable acid, lactic acid was selected as the candidate for further optimization. To start the work, the model reaction of 2-aminobenzophenone **1**, 4-chlorobenzaldehyde **2**, and ammonium acetate **3** was performed under different reaction conditions (Table 1). As shown in Table 1, the shortest time and best yield were achieved at 80 °C.

Increasing either the amount of catalyst and/or prolonging the reaction time did not improve the yield, while reducing these factors led to a reduction in product yield (Table 1).

To evaluate the substrate scope and limitations of this methodology, we extended our studies with a wide range of substrate combinations. As shown in Table 2, this three-component reaction performed well for most of the substrates. It was found that there was no remarkable electron or position effects from the aromatic aldehydes in this reaction.

The results clearly indicate that the first step of these multicomponent reactions is the condensation of the aldehyde with the 2-aminobenzophenone substrate, a not likely the attack of ammonium acetate (in equilibrium with ammonia) as presumed in the literature [9, 10]. Prajapati and co-workers [9] have identified one of the intermediates, **D** (in Scheme 2), as the major product, which is formed from **C** upon cyclization. According to their proposed mechanism [9, 10], **C** can be formed in two ways, in which the preferred first step was assumed to be the attack of NH_4OAc on the keto group of the benzophenone moiety.

Table 1

Optimization of catalyst for the synthesis of quinazoline derivatives [a]

Entry	Catalyst	Reaction conditions	Time/min	Yield (%)[b]
1	I_2 (10 mol%)	Neat or EtOH, 40 °C	150	95
2	PFPAT (10 mol%)	Toluene, reflux	240	95
3	Maltose–DMU–NH_4Cl (50: 40: 10) (1.5g)	Maltose-DMU-NH_4Cl melt (1.5 g) 90 °C	200	86
4	Lactic acid (0.021g)	Solvent-free 80 °C	90	80
5	Lactic acid (0.042g)	Solvent-free 80 °C	85	84
6	Lactic acid (0.060)	Solvent-free 80 °C	76	89
7	**Lactic acid (0.080)**	**Solvent-free 80 °C**	**60**	**95**
8	Lactic acid (0.11)	Solvent-free 80 °C	55	89

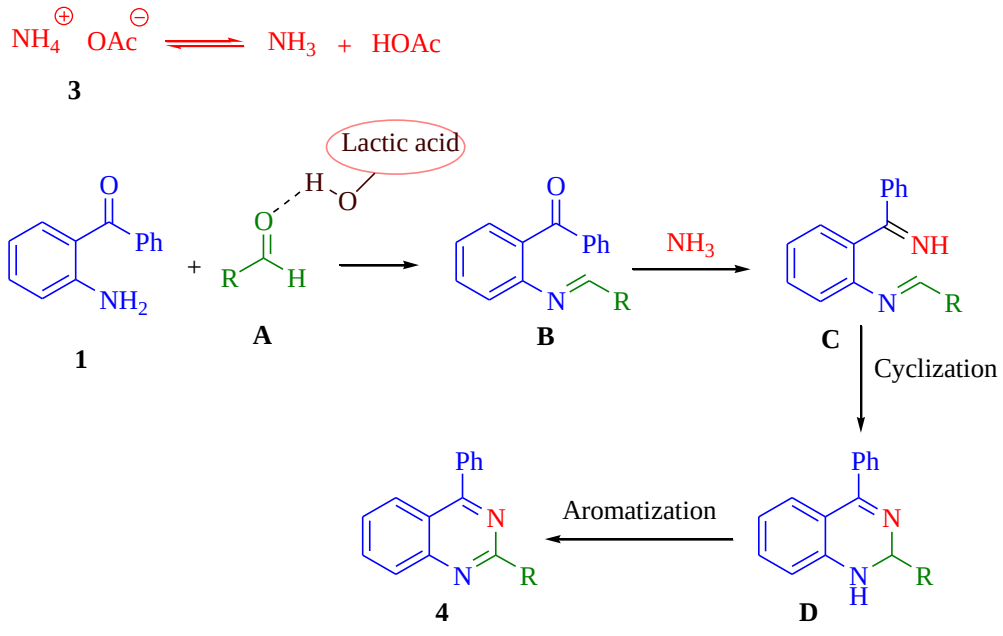
[a] Reaction conditions: 2-aminobenzophenone, ammonium acetate and benzaldehyde in the presence of a catalyst
[b] Isolated yield.

Table 2

Synthesis of quinazoline derivatives

Entry	R	Time (min)	Yield (%)[a]	Product	m.p. (ºC)	Lit. m.p. (ºC)
1	2- OH, 3-OMe - C_6H_3	30	96	**4a**	210–212	[*b*]
2	2- OH,5-Br- C_6H_3	35	94	**4b**	195–197	[*b*]
3	4-Me-C_6H_4	50	92	**4c**	163–165	167–170 [14]
4	4-OMe-C_6H_4	50	95	**4f**	159–161	159–162 [14]
5	4-Br-C_6H_4	45	94	**4g**	140–142	140–145 [14]
6	2-NO_2-C_6H_4	52	90	**4h**	126–128	129.6 [15]
7	3-NO_2-C_6H_4	40	90	**4i**	180–182	181–183 [16]
8	4-Cl-C_6H_4	50	89	**4j**	193–195	193–196 [14]
9	3-F-C_6H_4	35	95	**4k**	198–200	160 [17]

[a] Isolated yield.
[b] The new compounds synthesized in this work. All known products reported previously in the literature were characterized by comparison of m.p., IR and NMR spectra with those of authentic samples



Scheme 2. Suggested mechanism for the synthesis of quinazoline derivatives

4. CONCLUSİON

In conclusion, we have established a new method for the facile preparation of quinazoline derivatives with excellent yield. The present method employs readily available and simple starting materials and proceeds well in green media in the presence of sustainable bio-available lactic acid. Thus, this method offers several advantages including mild reaction conditions, high yields, operational simplicity and clean reaction conditions, which makes it a useful and attractive process for the synthesis of a wide variety of biologically active compounds.

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