Research
Volume 11:2,2020
DOI: 10.37421/csj.2020.11.206

Chemical Sciences Journal

Open Access

Visible Light Promoted One-Pot, Three Component Reaction for the Synthesis of quinazolines

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Abstract

Highly efficient one-pot three component approach was developed for the synthesis of biological active quinazoline derivatives. By the application of visible light via SP^3 C-H bond activation, desired products were obtained in high yields. The advantages of this method are application of green chemistry approach, avoidance of toxic organic solvents, easily available starting material, simple operation and shorter reaction times.

Keywords: Visible light • Quinazolines • Solvent-free • Photo catalysis

Introduction

The C-H bonds are abundant in organic compounds, but they do not seem to be operative functional groups owing to the low relativities and high thermodynamic stabilities [1,2]. Therefore, the development a mild and effective organic transformation with clean and renewable energy is of high interest. Solar energy is a unique and renewable resource in nature [3]. Recently, application of visible light in organic transformation was reported by several prominent groups 3 for the formation of new chemical bonds (C–C and C–X). In the past five years, owing to its significant advances in energy-saving and environmentally benign features, visible-light photo redox catalysis has witnessed rapid development and attracted considerable attention in both academia and industry [4]. Quinazoline moiety plays a vital role in pharmacological and medicinal chemistry, which is the building block for several naturally occurring alkaloids [5-9]. Microorganisms [10-15], It shows other remarkable biological activity such as anti-diabetic [16], antihypertensive [17], anticancer [18], antitumor [19], antitubercular [20,21], antibacterial [22], anti-inflammatory [23], antiviral [24], and it also act as selective inhibitors of the tyrosine kinase activity of the epidermal growth factor receptor (EGFR) [25], 3, 4-dihydroquinazoline derivatives shows the excellent T-type calcium channel blocking activity [26,27], it also use as ligand for benzodiazepine and neurotransmitter gamma-aminobutyric acid [GABA] receptors in the central nervous system [CNS] [28], DNA binders [29,30]. In the literature, different methodologies are reported for the synthesis of quinazolines under different reaction condition and reagents, such as Bu_3SnH [31], microwave [32], CsOH [33], Zn $(OTf)_2$ [34], Microwave-NaOH [35], NH_4OAc-H_2O [36], I2 [37]. However many reported methods suffer from drawback such as drastic reaction condition, high temperature, volatile organic solvents, toxic reagents, use of expensive metal catalysts, and long reaction time. All such types of drawbacks prompt researchers to develop alternate route for the synthesis of quinazolines.

The present method

In the present method, quinazoline derivatives have been synthesized using visible light from the reaction of 2- aminobenzophenone, aldehyde and ammonium acetate under catalyst-free and solvent-free conditions. Respective was shown in Figure 1.

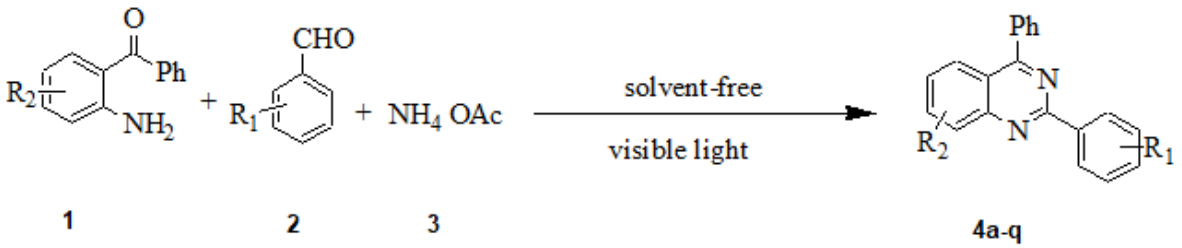

Figure 1. Synthesis of quinazoline derivatives.
R_1= Cl, OH, OMe, Me, NO_2, CN, etc; R_2 = H,

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Received: 16 March, 2020; **Accepted:** 27 April, 2020; **Published:** 04 May, 2020

Reaction conditions

2-aminobenzophenone (1 mmol), benzaldehyde (1 mmol), ammonium acetate (2.5 mmol) was kept under visible light (using an LED bulb (λ max=450 nm) for the appropriate time.

Experimental Section

In a 25 mL round-bottom flask, the mixture of 2-aminobenzophenone (1 mmol), benzaldehyde (1 mmol), ammonium acetate (2.5 mmol) was placed under irradiation using an LED bulb (λ max=450 nm) as the light source for the appropriate time shown in Table 1. The progress of reaction was monitored by TLC (PET ether: ethylacetate 8:2). After completion of reaction, the reaction mixture was cooled at room temperature and crude product was recrystallized by ethyl alcohol.

Spectral data of representative compounds

2, 4-diphenylquinazoline (4a): Yellow solid, m. p:117-119^{0}C; IR (KBr, cm^{-1}): 3410, 1622, 1534, 1445; ^{1}H NMR: (400 MHz, $CDCl_3$): δ = 7.62-7.45 (m, 7H), 7.88-7.83 (m, 3H), 8.12-8.15 (m, 2H), 8.69 (m, 2H);^{13}CNMR: (400 MHz, $CDCl_3$): δ =121.7, 126.9, 127.7, 127.9, 129.9, 132.2, 131.3, 134.4, 136.7, 138.1, 153.2, 160.0, 168.1, MS: m/z =283.

2- (4- nitrophenyl)-4-phenylquinazoline (4b): White solid; m. p: 209^{0}C; IR (KBr, cm^{-1}): 3440, 1609, 1542, 1524, 1339, 837, 772, 706; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.59 (t, J = 4.27 Hz, 4H), 7.20 - 7.30 (m, 3H), 7.41 (t, J = 6.6 Hz, 2H), 7.78 (d, J = 8.3 Hz, 2H), 8.37 (d, J = 8.3, 2H); ^{13}C NMR (400 MHz, $CDCl_3$): δ = 72, 78, 115, 117, 118, 123.1, 130.9, 131.2, 131.9, 134.5, 139.2, 147.3, 148.1, 150.0, 167.1; MS: m/z =330.

2- (2-Nitrophenyl-4-phenylquinazoline (4c): Brown solid; m. p: 127^{0}C; IR (KBr, cm^{-1}):3481, 1614, 1561, 1524, 1347, 862, 787, 713;^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63-7.48 (m, 7H), 7.83-7.74 (m, 2H), 8.14-8.06 (m, 4H); ^{13}C NMR (400 MHz, $CDCl_3$): δ = 118.3, 121.5, 121.8, 122.2, 124.1, 127.2, 128.1, 128.6, 128.9, 129.5, 130.1, 130.2, 132.1, 137.8, 149.1, 149.7, 161.6; MS:m/z =328.

2- (4-chlorophenyl)-4- phenylquinazoline (4e): Yellow solid, m. p: 186^{0}C; IR (KBr, cm^{-1}): 3476, 2918, 2189, 1647, 1577, 874; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.65-6.86 (m, 5H), 7.16-7.91 (m, 4 H), 7.5 (d, J = 9.6 Hz, 2H), 7.68 (d, J = 8.1 Hz, 2H); ^{13}C NMR (400 MHz, $CDCl_3$): δ = 70, 77.1, 77.6, 77.9, 113, 117.2, 117.6, 127.2, 127.8, 127.9, 131.2, 132.5, 138.12, 141.23, 147.11, 166.3; MS: m/z =319.

4-phenyl-2-p-tolyquinazoline (4j): White solid; m. p:166-168^{0}C; IR (KBr, cm^{-1}):3312, 1609, 1569, 1533, 1339, 1070, 771, 697; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.45 (s, 3H), 7.30 (d, J = 7.7 Hz, 2H), 7.69 - 7.47 (m, 4H), 7.78 - 7.65 (m, 3H), 8.11 (t, J = 7.55, 2H), 8.53 (d, J = 8.1 Hz, 2H); ^{13}C NMR (400 MHz, $CDCl_3$): δ = 21.6, 121.3, 125.1, 125.52, 126.8, 126.9, 126.9, 127.4, 128.2, 129.3, 132.8, 133.2, 139.2, 143.7, 151.2, 158.6; MS: m/z = 297.

Results and Discussion

Table 1 shows both the electron-withdrawing and electron donating groups are unaffected on the reaction time and yield of products.

Table 1. Synthesis of quinazoline derivatives by using various benzaldehydes.

S. No	Aldehyde	Product	Time (min)	Yield[a, b]
1	Benzaldehyde	4a	45	86
2	4-Nitro benzaldehyde	4b	51	90
3	2-Nitro benzaldehyde	4c	57	79
4	3-Nitro benzaldehyde	4d	49	87
5	4-Chloro benzaldehyde	4e	40	94
6	3-Chloro benzaldehyde	4f	46	90
7	4-Fluoro benzaldehyde	4g	54	91
8	4-Bromo benzaldehyde	4h	41	92
9	4-Methoxy benzaldehyde	4i	40	95
10	4-Methyl benzaldehyde	4j	38	94
11	3, 4-Dimethoxy benzaldehyde	4k	45	86
12	2-Hydroxy benzaldehyde	4l	57	90
13	3- Hydroxy benzaldehyde	4m	50	82
14	4-Hydroxy benzaldehyde	4n	45	85
15	4-Cyano benzaldehyde	4o	40	89

[a]Isolated yield and [b]Products are characterized by IR, ^{1}H NMR

Initially, we chose 2-aminobenzophenone (1 mmol), benzaldehyde (1 mmol), ammonium acetate (2.5 mmol), as model reaction to assess the solvent efficacy. Variety of organic solvents such as DMSO, MeCN, MeOH, CH2Cl2, EtOAc and toluene were examined. There is no product formation in toluene. When the reaction was performed in MeCN, MeOH it resulted in trace amounts of product and large amount side product formation. In solvents like CH2Cl2, EtOAc and DMSO, lower yield of product was obtained.

So, we performed reaction in solvent-free condition and best result in terms of time and yield was observed.

Our methodology is mild and effective with clean and renewable energy source. The further scope of the substrate was expanded with a variety of aldehydes.

Comparative studies of different reaction conditions, confirm the efficacy of present methodology (Entry 8, Table 2).

Table 2. Comparative studies of catalyst with present methods.

Entry	Catalyst	Loading	Reaction Conditions	Time(h/min)	Solvent
1	Bu_3SnH/Triethyl Borane	0.76/3.6 equiv.	inert	10/	dry toluene
2	Nil	---	300 W h ν at 150°C	10/	Solvent-free
3	Zn $(OTf)_2$	5 mol	reflux	6-12/	toluene
4	Molecular iodine	10 mol	40°C	2.5/	Heat or ethanol
5	CsOH	0.5 mmol	60°C	24/	acetonitrile
6	NaOH	2 mol	Hg Lamp 335 nm	2-5.5/	acetonitrile
7	$HCOONH_4$, PhCOCl, Et_3N	20 equiv.	Microwave, high pressure	/4-20	Nil
8	$HCOONH_4$	2.5 equiv.	Visible light (450 nm)	/30-40	Solvent-free

Conclusion

We have developed highly efficient method for the synthesis of quinazoline derivatives via visible light mediated C-H activation. The advantages of the present method are use of eco-friendly conditions, easily available starting materials; high yields, short reaction time and less energy consume process.

Acknowledgements

Dr. Ravi Varala thanks Dr. Ch. V. Rajasekhar for his kind support and encouragement.

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How to cite this article: Parshuram MP, Vinod TK, Ravi V and Pradip BG. "Visible Light Promoted One-Pot, Three Component Reaction for the Synthesis of quinazolines". Chem Sci J 11 (2020) doi: 10.37421/csj.2020.11.206