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Efficient synthesis of quinazoline derivatives catalyzed by flourinated alcohol

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Abstract A facile and efficient protocol is reported for the synthesis of quinazoline derivatives via a one-pot multicomponent reaction of 2-amino-5-chlorobenzophenone, aromatic aldehydes and ammonium acetate using 1,1,1,3,3,3-hexafluoroisopropanol (HFIP). The use of HFIP both as the solvent and catalyst has significant advantages, including avoiding the use of an acidic catalyst and ease of product isolation.

Keywords Quinazoline · One-pot synthesis · 1,1,1,3,3,3-Hexafluoroisopropanol

Introduction

Multicomponent reactions (MCRs) are some of the most efficient methods for the synthesis of heterocyclic compounds. These reactions offer remarkable advantages, allowing the formation of several bonds in a single operation without isolating the intermediates. Furthermore, MCRs have other benefits such as bond-forming efficiency and atom economy which conform with green chemistry principles [1–3]. Heterocycles have attracted much attention due to their pharmaceutical properties and high degree of structural diversity [4, 5]. Among the six-membered nitrogen-containing heterocycles, quinazolines occur widely in numerous natural products and synthetic pharmaceutical materials. Since many of these heterocyclic systems exhibit biological and pharmaceutical functions such as antihypertonic, antitumor, antipyretic, diuretic, antihistamine, analgesic, antibiotic, antidefibrillatory, and antidepressant and are used as vasodilating agents, these compounds have become important heterocycles in pharmacy [6–8]. These derivatives also act as selective

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JAK2, PDE5, and epidermal growth factor receptors (EGFR) and inhibitors of tyrosine kinase activity [9–11]. Also, the quinazoline core structure exists in many natural and pharmaceutical compounds and it is used in several drugs such as gefitinib (Iressa), erlotinib (Tarceva), actinomycin and Prazosin (Fig. 1) [12–17].

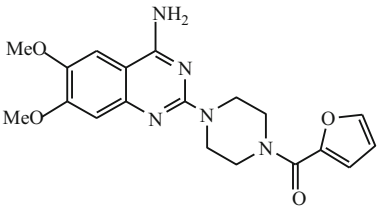
Also, a new series of quinazoline was discovered wherein these derivatives act as CC chemokine receptor-4 (CCR4) antagonists. Several CCR4 antagonists with inhibitory potential have been reported in the literature (Fig. 2) [18, 19].

Several synthetic methods have been developed for the construction of quinazoline derivatives from suitable precursors [20–39]. Also, several protocols have been developed via reaction of aromatic aldehyde, 2-amino-5-chlorobenzophenone and ammonium acetate in the presence of various catalysts and solvents such as I_2 in ethanol [40], low-melting maltose–dimethylurea (DMU)–NH_4Cl mixture as a solvent [41], pentafluorophenylammonium triflate (PFPAT) in toluene [42], $CuFe_2O_4$ nanoparticles in water [43], 1-methylimidazoliumtriflouroacetate ([Hmim]TFA) under aerobic conditions [44], magnetic ionic liquid bmim[$FeCl_4$] [45], $CuCl_2.2H_2O$ in ethanol [46], ceric ammonium nitrate (CAN)-TBHP in acetonitrile [47], and 4-(*N*,*N*-dimethylamino)pyridine (DMAP) in ethanol [48].

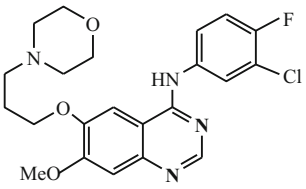
In addition to the benefits of the above procedures, some of them have certain limitations such as cumbersome chromatographic separation procedures [41, 47], the use of hazardous and volatile solvents (ethanol [40, 44, 46], toluene [42], acetonitrile [47]), high heating (90 °C [41], 110 °C [42], 80 °C [43, 44], 80 °C [46, 47]), tedious work-up conditions (ethyl acetate [43, 47], diethyl ether [45]), long reaction time (0.5–3.5 h [40], 4 h [42], 2 h [44], 1.5–3.5 h [45], 4 h [46], 7–7.5 h [47], 1–2.5 h [48] and low yields (79–93% [41], trace–95% [42], 78–93% [47]).

In continuation of our previous studies on developing improved methodologies for organic reactions [49–61], herein we describe the synthesis of quinazoline derivatives in presence of fluorinated alcohol (Scheme 1).

The most commonly used and cheapest fluorinated alcohols are 2,2,2-trifluoroethanol (TFE) and 1,1,1,3,3,3-hexafluoroisopropanol (HFIP), which are available on a commercial scale [62, 63]. These fluorinated alcohols (TFE, bp = 73.8 °C and HFIP, bp = 58.8 °C) have unique properties such as a strong hydrogen bond donating capability, mild acidic character (TFE, pKa = 12.4 and HFIP, pKa = 9.3) and low nucleophilicity of which the most important one is hydrogen bond donating ability [64]. This property is not only apparent from



Prazosin



Iressa

Fig. 1 Quinazolines as core structures in pharmaceuticals

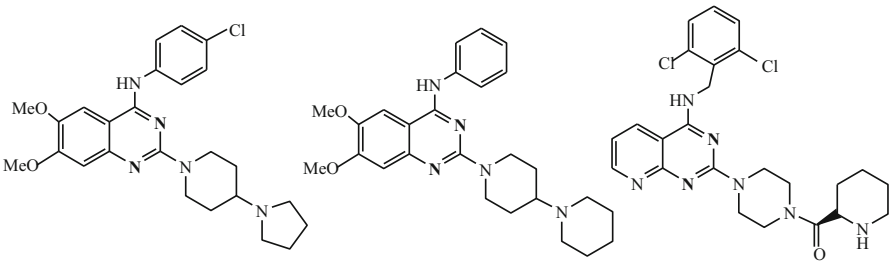
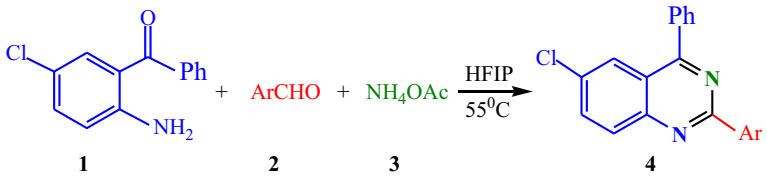


Fig. 2 Some 4-substituted quinazoline derivatives with CCR4 inhibitory activities



Scheme 1 One-pot synthesis of various quinazoline derivatives using HFIP

spectral studies and calorimetric measurments but also by the isolation of extremely stable complexes with a number of nucleophilic species [65–67]. This property makes them powerful solvents for formation of persistent carbocations and cationic radicals [68].

In view of the above-mentioned properties we became interested in using HFIP for the synthesis of quinazoline derivatives. To the best of our knowledge, the use of HFIP in the synthesis of quinazolines has not been previously reported.

Experimental

Apparatus and analysis

Melting points were determined in open capillary tubes in a Stuart BI Branstead Electrothermal apparatus (cat no: IA9200) and are uncorrected. ^{1}H NMR spectra were obtained by use of a Bruker 300-MHz spectrometer in DMSO-d_6 or $CDCl_3$ as solvent and with TMS as internal reference. All reagents were purchased from Merck and Sigma-Aldrich and used without further purification. Infrared (IR) spectra were recorded on a Shimadzu 435-U-04 spectrophotometer (KBr pellets).

General procedure for the synthesis of quinazolines

To a mixture of 2-amino-5-chlorobenzophenone (1 mmol), substituted benzaldehyde (1 mmol), and ammonium acetate (5 mmol), HFIP (0.5 mL) was added and the mixture stirred and boiled under reflux in an oil bath for the appropriate time (see Table 1). The reaction was monitored by thin-layer chromatography (TLC;

Table 1 Synthesis of quinazoline derivatives catalyzed by 1,1,1,3,3,3-hexafluoroisopropanol (HFIP)

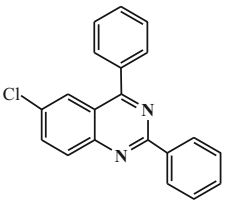
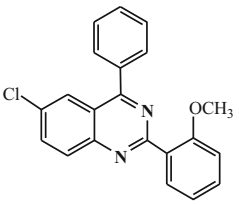
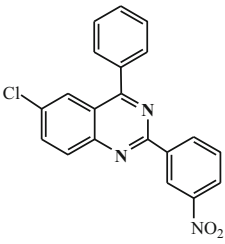
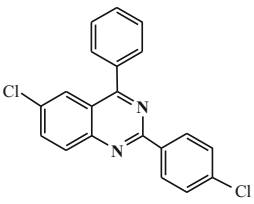
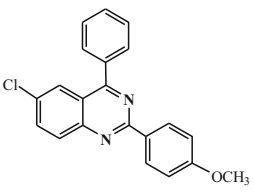
Entry	Quinazoline **(4a–l)**	Yield (%)	Time (min)	Mp (°C)	
				Found	Literature
1	 **4a**	88	90	186–187	185 Dabiri et al. [44]
2	 **4b**	86	90	148–150	144–146 Saeed et al. [46]
3	 **4c**	90	70	182–184	184–187 Saeed et al. [46]
4	 **4d**	90	60	189–190	188–190 Saeed et al. [46]
5	 **4e**	90	50	158–160	159–162 Saeed et al. [46]

Table 1 continued

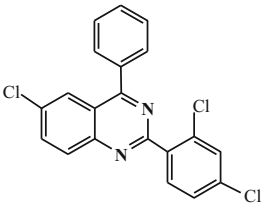
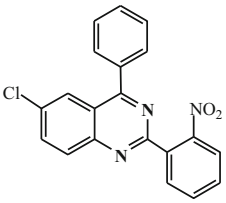
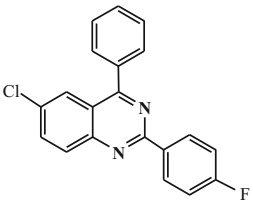
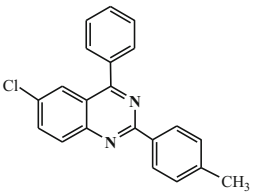
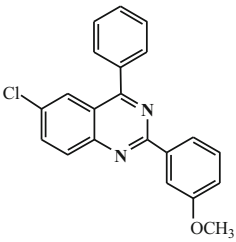
Entry	Quinazoline **(4a–l)**	Yield (%)	Time (min)	Mp (°C)	
				Found	Literature
6	 **4f**	86	70	161–162	162 Dabiri et al. [44]
7	 **4g**	86	80	123–125	125–127 Saeed et al. [46]
8	 **4h**	90	80	191–193	193 Dabiri et al. [44]
9	 **4i**	85	100	209–211	210–212 Saeed et al. [46]
10	 **4j**	90	60	162–164	163–164 Saeed et al. [46]

Table 1 continued

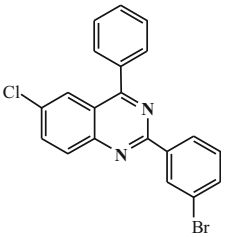
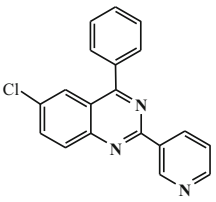
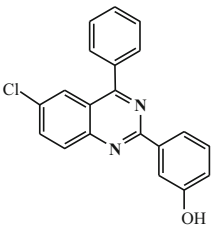
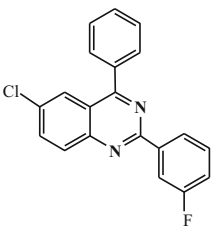
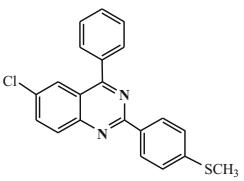
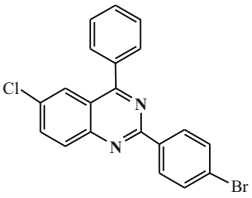
Entry	Quinazoline **(4a–l)**	Yield (%)	Time (min)	Mp (°C)	
				Found	Literature
11	 **4k**	92	30	174–176	178 Dabiri et al. [44]
12	 **4l**	91	70	174–175	173 Dabiri et al. [44]
13	 **4m**	85	90	107–108	105–106 Saeed et al. [46]
14	 **4n**	89	80	173–175	174–175 Zhang et al. [41]
15	 **4o**	84	90	173–174	171–172 Saeed et al. [46]

Table 1 continued

Entry	Quinazoline (**4a–l**)	Yield (%)	Time (min)	Mp (°C)	
				Found	Literature
16	 **4p**	92	30	191–193	194–195 Zhang et al. [41]

n-hexane:ethyl acetate, 9:1). After completion of the reaction, the reaction mixture was poured onto crushed ice and the solid product was filtered, washed with H_2O (10 mL) and dried. The crude product was recrystallized from ethanol (96%) to give pure quinazolines (**4a–p**).

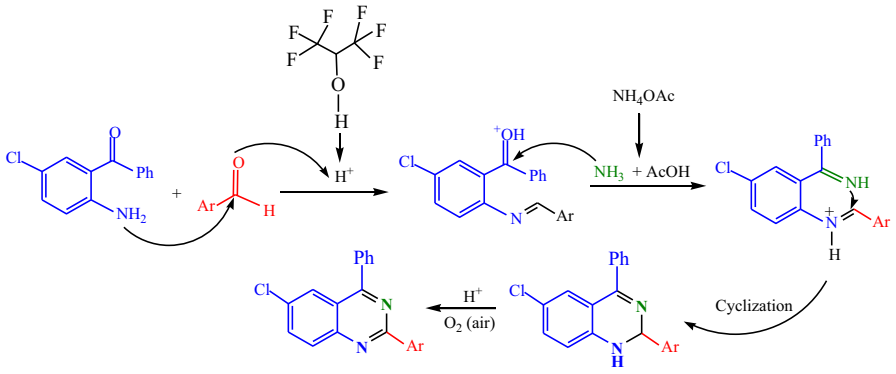
6-Chloro-2,4-diphenylquinazoline (Table 1, entry 1) IR (KBr) cm^{-1}: 3042, 1530, 1473, 1170, 844, 689. ^{1}HNMR (300 MHz, $CDCl_3$); δ 8.62–8.64 (m, 2H), 8.07–8.10 (m, 2H), 7.77–7.89 (m, 3H), 7.59–7.60 (m, 3H) 7.50–7.52 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$); 122.17, 125.77, 128.58, 128.65, 128.75, 130.04, 130.22, 130.76, 130.86, 132.59, 134.50, 137.07, 137.75, 150.48, 160.45, 167.52.

6-Chloro-2-(4-chlorophenyl)-4-phenylquinazoline (Table 1, entry 4) IR (KBr) cm^{-1}: 1527, 1392, 1081, 725; ^{1}H NMR (300 MHz, $CDCl_3$); δ 8.60 (d, 2H), 8.06 (d, 2H), 7.85–7.80 (m, 3H), 7.61–7.59 (m, 3H), 7.47 (d, 2H); ^{13}C NMR (75 MHz, $CDCl_3$); 122.17, 125.83, 128.77, 129.99, 130.31, 130.78, 132.87, 134.64, 136.24, 136.34, 136.95, 150.31, 159.41, 167.64.

6-Chloro-2-(4-methoxyphenyl)-4-phenylquinazoline (Table 1, entry 5) IR (KBr) cm^{-1}: 1610, 1529, 1250, 1025, 830, 700. ^{1}H NMR (300 MHz, $CDCl_3$); δ 8.62 (d, 2H), 8.01–8.04 (m, 2H), 7.74–7.84 (m, 3H), 7.59–7.61 (m, 3H), 7.02 (2H), 3.88 (s, 3H)^{13}C NMR (75 MHz, $CDCl_3$); 55.37, 113.89, 121.86, 125.75, 128.69, 130.00, 130.12, 130.34, 130.47, 130.63, 132.01, 134.36, 137.19, 150.56, 160.26, 161.95, 167.37.

Results and discussion

Our initial effort commenced with the reaction of benzaldehyde (1 mmol), 2-amino-5-chlorobenzophene (1 mmol), and ammonium acetate (5 mmol) in the presence of different amounts of HFIP under reflux conditions. We found 0.5 mL to be the optimum volume. When we conducted the reaction at room temperature, we found that it took 6 h for completion and afforded a 66% yield. We carried out the reaction at different temperatures and found that the best results were obtained at 55 °C. We



Scheme 2 Proposed mechanism for synthesis of guinazoline

did the reaction in the presence of different solvents instead of HFIP (HFIP used only as a catalyst); the results were not satisfactory and products were obtained in low yields. So, when we used HFIP both as the catalyst and solvent, we observed the best results. Also, we performed the reaction in the presence of TFE and observed limited satisfactory results in contrast to using HFIP. We believe this occurred because HFIP is a stronger acid than TFE. Under the optimized reaction conditions, the scope of this one-pot protocol was investigated by using different aldehydes as shown in Table 1. A variety of substituted aldehydes (ortho, meta and para) possessing a wide range of electron-donating and electron-withdrawing functional groups such as methoxy, methyl, hydroxy, bromo, chloro, nitro, and fluoro afforded the corresponding products in excellent yields. Heteroaromatic aldehyde such as pyridine 3-carbaldehyde produced the desired product in an excellent yield (Table 1, entry 12).

A possible mechanism for the synthesis of quinazolines using HFIP as an acid catalyst is shown in Scheme 2. In this process, HFIP with H^+ could activate the C=O groups and play a remarkable role in increasing the electrophilic character [40, 43]. This mechanism can be confirmed by our observations that TFE did not give comparable results. Based on pKa values [64], HFIP is a stronger acid than TFE and this is probably the reason why HFIP acts as an acid and gave the better results.

Conclusion

A new protocol for the synthesis of quinazoline derivatives has been developed wherein HFIP is used both as the solvent and catalyst. The protocol is operationally simple and furnishes quinazoline derivatives in very good yields.

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