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Synthesis of Quinazolines from (2-Aminoaryl)methanols and Arylmethanamines Catalyzed by Rhodium Complex[1]

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Abstract—Efficient synthesis of quinazoline derivatives via rhodium-catalyzed dehydrogenation and ring-closing method was developed with moderate to high yields.

Keywords: dehydrogenation, rhodium, arylmethanamines, alcohols, quinazoline

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INTRODUCTION

Quinazoline and its derivatives are commonly occurring structural blocks of numerous natural compounds and pharmaceuticals [1–3]. Over the recent years nitrogen containing analogues of quinazoline derivatives attracted close attention due to their high biological activity [4–10]. Zhang et al. [11] developed a facile and efficient synthesis of 2-phenylquinazolines via a tandem reaction with moderate to high yields and a metal-free intramolecular oxidative decarboxylative coupling of α-amino acids, that led to a wide range of 2-substituted quinazolines [12]. Han et al. [13] reported an one-pot approach to the aerobic oxidative synthesis of 2-aryl quinazolines via benzyl C–H bond amination, using 2-aminobenz-aldehydes or 2-aminobenzoketones with arylmethanamines as starting materials. Chen et al. [14] described the first example of a copper-catalyzed cascade reaction of aldehydes and (2-aminophenyl)methanols in the presence of cerium nitrate hexahydrate and ammonium chloride leading to synthesis of 2-substituted quinazolines. Synthesis of quinazolines from 1,2-dihydroquinazoline-3-oxides was carried out under visible light mediation [15]. In most studies the starting materials scope mainly focused on aldehydes, ketones, with amine or nitriles [16–20]. Herein, we present an efficient synthesis of quinazoline derivatives via rhodium-catalyzed dehydrogenation ring-closing method (Scheme 1).

[1] The text was submitted by the authors in English.

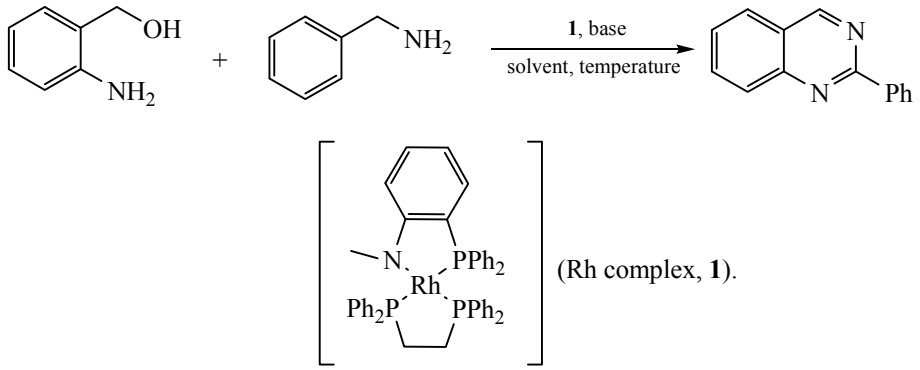
RESULTS AND DISCUSSION

Primarily we examined Rh-catalyzed dehydrogenation ring-closing reaction using (2-aminophenyl)methanol (**2a**) and benzylamine (**3a**) as a model substrate catalyzed by a highly active rhodium complex, [(P,P-dppe)(P,N-Ph_2PAr)Rh], [21]. The anticipated quinazoline **4a** was obtained in low yield (28%) (Table 1, entry 1). Following screening of reaction conditions including solvents and bases was carried out (Table 1, entries 2–8). The tests of solvents demonstrated that 1,3,5-trimethylbenzene (TMB) was the best. Screening of bases revealed that Cs_2CO_3 was superior to the others tested (Table 1, entry 13). Attempts to decrease the reaction temperature did not improve the yields.

The worked out optimal conditions made it possible to evaluate the scope and limitations of the reaction (Table 2). According to the accumulated data, various benzylamines containing electron-donating and electron-withdrawing groups could be converted to the quinazoline derivatives smoothly (Table 2, compounds **4b**–**4e**) with moderate to high yields. However, substrates with strong electron- withdrawing groups gave slightly lower yields (Table 2, compounds **4b** and **4e**). Additionally, thiophenemethylamine was also found to be a good reaction partner (Table 2, compound **4f**).

To get some insights into the reaction procedure, a test experiment was carried out. Under optimal conditions 2-aminobenzaldehyde gave the desired product with almost the same yield. Supposedly, the

Scheme 1. Synthesis of quinazoline derivatives from alcohols with arylmethanamines.



first step of the reaction was dehydrogenation of (2-aminophenyl)methanol leading to 2-aminobenzaldehyde.

EXPERIMENTAL

Chemicals used were commercially available and applied without further purification. Reactions progress was monitored by TLC (100–400 mesh silica gel plates, GF_{254}). The products were isolated by column chromatography on silica gel (200–300 mesh or 100–200 mesh) using petroleum ether (60–90°C) with ethyl acetate as the eluent. ^{1}H NMR spectra were measured on a Bruker Advance 400 in $CDCl_3$ using TMS as the internal reference.

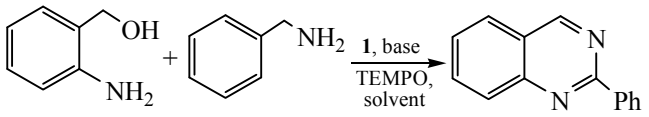
General procedyre of synthesis of 4a. To the mixture of (2-aminophenyl)methanol **2a** (0.5 mmol) with TMB (5 mL) were added phenylmethanamine **3a** (0.6 mmol) and TEMPO (0.1 mmol) at room temperature. Upon following addition of Cs_2CO_3 (2.0 mmol) the mixture was stirred for 5 min and then refluxed upon stirring for 16 h. Upon the reaction completion, the mixture was cooled down and purified by column chromatography with petroleum ether/ethyl acetate (10 : 1) eluent leading to the product **4a**.

2-Phenylquinazoline (4a). Yellowish solid, mp 97–98°C. ^{1}H NMR spectrum, δ, ppm: 7.46 m (3H), 7.55 t (J = 7.8 Hz, 1H), 7.85 t (J = 8.2 Hz, 2H), 8.03 d (J = 8.2 Hz, 1H), 8.56 d (J = 7.8 Hz, 2H), 9.41 s (1H). ^{13}C NMR spectrum, δ, ppm: 123.6, 127.1, 127.2, 128.6, 128.65, 128.67, 130.6, 134.0, 138.0, 150.8, 160.5, 161.6.

2-(3-Fluorophenyl)quinazoline (4b). Yellowish solid, mp 95–96°C. ^{1}H NMR spectrum, δ, ppm: 7.23 t (J = 7.8 Hz, 1H), 7.53 d.d (J = 14.3, 7.2 Hz, 1H), 7.66 t (J = 8.2 Hz, 1H), 7.95 t (J = 8.2 Hz, 2H), 8.11 d (J = 8.2 Hz, 1H), 8.37 d (J = 11.8 Hz, 1H), 8.46 d (J = 7.8 Hz, 1H), 9.49 s (1H). ^{13}C NMR spectrum, δ, ppm: 115.4 d (J = 22.8 Hz), 117.4 d (J = 21.8 Hz), 123.7, 124.1 d (J = 3.2 Hz), 127.1, 127.6, 128.7, 130.0 d (J = 8.2 Hz), 134.2, 140.4 d (J = 8.0 Hz), 150.6, 159.8, 160.5, 163.3 d (J = 242.8 Hz).

2-(4-(Methylthio)phenyl)quinazoline (4c). Yellow solid, mp 106–107°C. ^{1}H NMR spectrum, δ, ppm: 2.48 s (3H), 7.31 d (J = 7.8 Hz, 2H), 7.51 t (J = 7.8 Hz, 1H), 7.79–7.75 m (2H), 7.97 d (J = 7.8 Hz, 1H), 8.48 d

Table 1. Screening of reaction conditions[a]



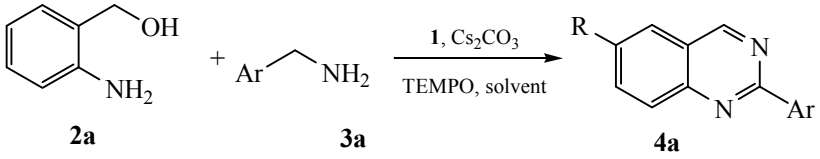
2a **3a** **4a**

Entry	Base	Solvent	Yield[b], %
1	NEt_3	Toluene	28
2	NEt_3	DMF	<5
3	NEt_3	Dioxane	<5
4	NEt_3	DCM	<5
5	NEt_3	CH_3CN	<5
6	NEt_3	Xylene	38
7	NEt_3	TMB	47
9	–	TMB	<5
10	KOH	TMB	16
11	K_2CO_3	TMB	56
12	Na_2CO_3	TMB	52
13	Cs_2CO_3	TMB	76

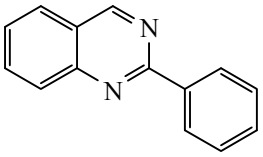
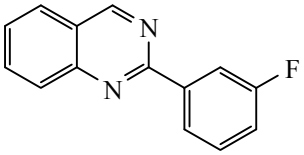
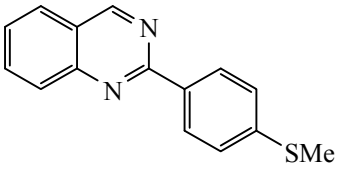
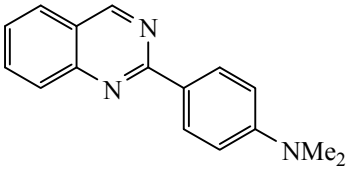
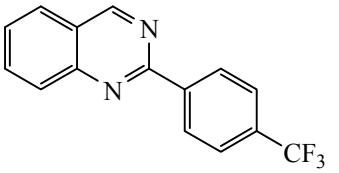
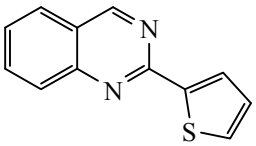
[a] Reaction conditions: **2a** (0.5 mmol), **3a** (0.6 mmol), Rh **1** (5 mol %), TEMPO (0.1 mmol), base (2.0 mmol), solvent (5 mL), 150°C or reflux, 16 h, TMB = 1,3,5-trimethylbenzene, N_2.

[b] Isolated yield.

Table 2. Substrate scope of the reaction[a,b]



2a **3a** **4a**

Comp. no.	Ar	Product	Yield[b], %
4a	C_6H_5		76
4b	3-F-C_6H_4		72
4c	4-SMe-C_6H_4		87
4d	4-NMe_2-C_6H_4		85
4e	4-CF_3-C_6H_4		63
4f	2-Thiophene		78

[a] Reaction conditions: 2 (0.5 mmol), 3 (0.6 mmol), Rh 1 (5 mol %), TEMPO (0.1 mmol), Cs_2CO_3 (2.0 mmol), TMB (5 mL), reflux, 16 h, TMB = 1,3,5-trimethylbenzene, N_2. [b] Isolated yield.

(*J* = 8.2 Hz, 2H), 9.35 s (1H). ^{13}C NMR spectrum, δ, ppm: 15.2, 123.5, 125.8, 127.10, 127.14, 128.52, 128.9, 134.1, 134.6, 142.0, 150.8, 160.4, 160.6.

***N,N*-Dimethyl-4-(quinazolin-2-yl)aniline (4d).** Yellowish solid, mp 126–127°C. ^{1}H NMR spectrum, δ, ppm: 2.95 s (6H), 6.72 d (*J* = 7.8 Hz, 2H), 7.41 t (*J* = 7.8 Hz, 1H), 7.72 t (*J* = 7.8 Hz, 2H), 7.91 d (*J* = 7.8 Hz, 1H), 8.41 d (*J* = 7.8 Hz, 2H), 9.25 s (1H). ^{13}C NMR spectrum, δ, ppm: 40.2, 111.7, 123.0, 125.7, 126.1, 127.1, 128.1,129.9, 133.8, 151.0, 152.2, 160.2, 161.5.

6-Methyl-2-(4-(trifluoromethyl)phenyl)quinazoline (4e). Yellow solid, mp 155–156°C. ^{1}H NMR spectrum, δ, ppm: 2.51 s (3H), 7.62 s (1H), 7.69 d (*J* = 8.2 Hz, 3H), 7.92 d (*J* = 7.8 Hz, 1H), 8.64 d (*J* = 8.0 Hz, 2H), 9.31 s (1H). ^{13}C NMR spectrum, δ, ppm: 21.6, 123.8, 125.4, 125.8, 128.4, 128.6, 131.7, 132.0, 136.6, 138.1, 141.4, 149.2, 158.9, 159.8.

2-(Thiophen-2-yl)quinazoline (4f). Yellow solid, mp 131–132°C. ^{1}H NMR spectrum, δ, ppm: 7.09 m (1H), 7.50–7.35 m (2H), 7.75 d (*J* = 7.8 Hz, 2H), 7.89

d (J = 8.2 Hz, 1H), 8.05(m, 1H), 9.23 s (1H). ^{13}C NMR spectrum, δ, ppm: 123.3, 127.0, 127.2, 128.19, 128.4, 129.2, 129.9, 134.3, 143.8, 150.6, 157.8, 160.5.

CONCLUSIONS

A rhodium-catalyzed synthesis of quinazoline derivatives via dehydrogenation and ring-closing reaction is developed. This method provides an easy and efficient approach to quinazoline derivatives with moderate to high yields.

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