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Synthesis of 2-substituted quinazolines *via* iridium catalysis†

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An iridium-catalyzed hydrogen transfer reaction was successfully applied in the synthesis of 2-substituted quinazolines in moderate yields starting from aldehydes or alcohols with 2-aminobenzylamines.

Quinazolines occur frequently in natural products and synthetic pharmaceuticals which exhibit important biological properties, such as antidiabetic, antibacterial, anticonvulsant and anticancer activities. For example, prazosin was an effective medicine as α -adrenergic blockers for the treatment of high blood pressure, panic disorder and anxiety, and lapatinib was used to treat solid tumor and breast cancer.

Syntheses of substituted quinazolines have been widely explored,⁴ and many efficient methods have been developed recently. As shown in Scheme 1, one of the synthetic methods to quinazolines utilizes condensations between aldehydes 2 and 2-aminobenzylamines 1 followed by oxidation of the aminal intermediate 3. However, stoichiometric or large excess amounts of toxic oxidants were required for this oxidation; *e.g.*, DDQ, *p*-chloranil,^{4c} NaClO^{4k} and MnO₂ ^{4l} were used. In continuation of our work in the application of hydrogen transfer catalysis in the syntheses of quinazolinones,⁵ we were interested to test if a hydrogen transfer catalyst⁶ will catalyze the oxidation of aminal 3 to 2-substituted quinazoline 4 in one-pot as shown in Scheme 1.

Firstly, 2-aminobenzylamine **1a** with benzaldehyde **2a** was selected as the model substrate to test the one-pot reaction and the results are summarized in Table 1. We discovered that without a hydrogen acceptor, only 10% product **4a** was formed using $[Cp*IrCl_2]_2$ (2.5 mol%) as the catalyst (Cp*= pentamethylcyclopentadienyl, entry 1). The major byproduct isolated was the *N*-benzylation product 5^7 as shown in Scheme 2.

This byproduct formation could have originated from hydrogen transfer⁸ to the imine intermediate **6**. Compound **5** could not be

$$\begin{array}{c|c}
 & NH_2 \\
 & 1 \\
 & R_2 \\
 & R_1 \\
 & O \\
 & 2
\end{array}$$

$$\begin{array}{c|c}
 & NH \\
 & R_2 \\
 & H \\
 & R_1
\end{array}$$

$$\begin{array}{c|c}
 & NH \\
 & R_2 \\
 & R_2
\end{array}$$

$$\begin{array}{c|c}
 & NH \\
 & R_1
\end{array}$$

Scheme 1 One-pot synthesis of quinazolines

further transformed to the product quinazoline 4a under hydrogen transfer catalysis, which accounted for the low yield of 4a in this reaction. To improve the yields of 4a, we decided to add a hydrogen acceptor to the reaction mixture. To our delight, the

Table 1 Optimization of conditions for the synthesis of quinazoline ${\bf 4a}$ between ${\bf 1a}$ and ${\bf 2a}^a$

$$NH_2$$
 + Ph O N Ph

Entry	Catalyst	Additive	Acceptor	Solvent	Yield ^b
1	[Cp*IrCl ₂] ₂	No	No	xylene	10%
2	Cp*IrCl ₂] ₂	No	styrene	xylene	66% ^c
3	$[Cp*IrCl_2]_2$	No	<i>E</i> -crotonitrile	xylene	$50\%^{c}$
4	Cp*IrCl ₂] ₂	AcOH	styrene	xylene	43%
5	[Cp*IrCl ₂] ₂	0.2 eq. KOH 0.2 eq.	styrene	xylene	54%
6	$[Cp*IrCl_2]_2$	t-BuONa	styrene	xylene	60%
7	$[\mathrm{Cp*IrCl_2}]_2$	0.2 eq. K_2CO_3 0.2 eq.	styrene	xylene	46%
8	$[Cp*IrCl_2]_2$	No	styrene	toluene	35%
9	Cp*IrCl ₂] ₂	No	styrene	DMF	50%
10	$[Cp*IrI_2]_2$	No	styrene	xylene	57%
11	RuCl ₂ (PPh ₃) ₃	KOH	styrene	xylene	26%
12	[Ru(p-cymene)Cl ₂] ₂ ^d	0.2 eq. KOH 0.2 eq.	styrene	xylene	52%

 $[^]a$ Conditions: 1a (0.5 mmol), 2a (0.5 mmol), catalyst (2.5 mol%), styrene (4.0 eq.) in refluxing temperature of the solvent listed (1 mL) under N₂, 24 h. b H-NMR yield. c Isolated yield, 12% of byproduct 5 was also isolated in entry 2. d 2.5 mol% dppf was added.

^aChemical and Analytical Development, Suzhou Novartis Pharma Technology Co. Ltd, Changshu, Jiangsu, China 215537. E-mail: jianguang.zhou@novartis.com ^bSchool of Chemical Engineering, Nanjing University of Science & Technology, Nanjing. Jiangsu. China 210094

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Scheme 2 Possible pathway to **5** from hydrogenation of imine **6** and reaction of 5 under hydrogen transfer conditions.

yields of 4a were improved to 66% with addition of styrene (entry 2) and 50% with E-crotonitrile (entry 3). Further optimizations of the reaction by using acid or base additives were also tried (entries 4 to 7), but the best yield of 60% obtained by addition of NaOtBu (entry 6) was inferior to the results of 66% without such additives in entry 2. The effects of solvents (entries 8 and 9) and catalysts (entries 10 to 12) were also examined briefly with no increase of the yield of 4a. After examining the reaction profiles, we decided to select the conditions of entry 2 (2.5 mol% [Cp*IrCl₂]₂ in refluxing xylene with addition of 4.0 eq. styrene) for our investigations of the substrate scope of the reaction.

Table 2 One-pot synthesis of quinazolines via Ir-catalyzed hydrogen transfers^a

$$\begin{array}{c|c} R_1 & \mathbf{Z} \\ \hline \\ NH_2 & \mathbf{Z} \\ NH_2 & \mathbf{A.0 \ eq. \ styrene} \\ \mathbf{1a, R=H} \\ \mathbf{1b, R=F} & \mathbf{N}_2, \ \mathbf{xylene \ reflux} \\ \end{array}$$

Entry	R_1	R_2	Yield ^b
1	Н	C_6H_5	4a 66%
2	H	$3-Cl-C_6H_4$	4b 54%
3	H	$3-Br-C_6H_4$	4c 48%
4	H	$3-NO_2-C_6H_4$	4d 58%
5	H	$3-Me-C_6H_4$	4e 54%
6	H	3 -OMe- C_6H_4	4f 51%
7	H	4 -F- C_6H_4	4g 51%
8	H	$4-Br-C_6H_4$	4h 55%
9	H	$4-NO_2-C_6H_4$	4i 57%
10	H	4 – Me – C_6H_4	4j 50%
11	H	Furyl	4k 55%
12	H	Benzyl	4l 49%
13	H	<i>n</i> -Pentanyl	4m 57%
14	F	C_6H_5	4n 56%
15	\mathbf{F}	$4-Br-C_6H_4$	4o 60%
16	F	4 –Me– C_6H_4	4p 62%
17	F	<i>n</i> -Pentanyl	4q 65%

^a Conditions: Entries 1-13: 1a (1.0 mmol), 2 (1.0 mmol), catalyst (2.5 mol%), styrene (4.0 eq.) in refluxing xylene (2 mL) under N₂, 24 h. Entries 14-17: 1b (1.0 mmol), 2 (1.0 mmol), catalyst (2.5 mol%), styrene (4.0 eq.) in refluxing xylene (2 mL) under N₂, 24 h. ^b Isolated yield.

Scheme 3 One-pot synthesis of 2-phenylquinazoline starting with benzyl alcohol.

Subsequently, a variety of substituted quinazolines were synthesized using our optimized conditions. As shown in Table 2, both aliphatic and aromatic aldehydes reacted with 2-aminobenzylamines to give the corresponding quinazolines 4 in moderate yields. Reactions between 1a and aromatic aldehydes with either electron-withdrawing or electron-donating groups (entries 2 to 10) showed that the yields were not affected significantly in the range of 48% to 58%. Furthermore, the reactions also performed well when 2-furyl aldehyde (55% yield, entry 11), 2-phenylacetaldehyde (49% yield, entry 12) and hexanal (57% yield, entry 13) were involed. Investigations of 2-(aminomethyl)-3-fluoroaniline 1b with several aldehydes again gave substituted quinazolines 4n to 4q in moderate yields (56% to 65%, entries 14 to 17).

It was our next interest to test the employment of benzyl alcohol 7 instead of benzaldehyde 2a in the synthesis of quinazoline 4a. The above described conditions using benzaldehyde did not give a satisfactory yield of 4a (only 10%) when benzylalcohol 7 was used. Some optimizations (see supporting information, ESI†) identified that the addition of base additives, such as KOH (0.2 eq.) was necessary to increase the yield of 4a to 61% (Scheme 3).

When 2-aminobenzyl alcohol 8 was used, the condensation with benzaldehydes 2a gave 2-phenyl-4H-benzo[d][1,3]oxazine 9 in 45% yield as shown in Scheme 4.9 The optimized conditions also involved the use of KOH (2 eq.) to give a better yield (see supporting information, ESI†).

Scheme 4 One-pot synthesis of 2-phenyl-4H-benzo[d][1,3] oxazine between 8 and 2a

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Conclusion

We have demonstrated a one-pot synthesis of 2-substituted quinazolines between 2-aminobenzylamines 1 and aldehydes 2 via iridium-catalyzed hydrogen transfers using styrene as a hydrogen acceptor. The use of benzyl alcohol 7 instead of benzyaldehyde also successfully gave a quinazoline product in moderate yield. Further extension for the synthesis of 4H-3,1benzoxazine was also demonstrated by the example using 2-aminobenzyl alcohol 8.

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