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$Zr(HSO_4)_4$: An Efficient Catalyst for the Synthesis of 3-(2'- Benzothiazolyl)-2, 3-dihydroquinazolin- 4(1*H*)-ones

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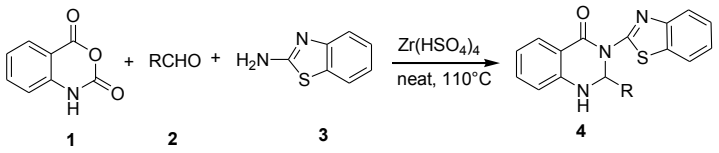
Abstract: A simple and efficient synthesis of 3-(2'-benzothiazolyl)-2,3-dihydro quinazolin-4(1*H*)- ones has been accomplished by the one-pot condensation of isatoic anhydride, aldehyde and 2-aminobenzothiazole under solvent-free conditions in the presence of $Zr(HSO_4)_4$.

Keywords: Aldehydes, 2,3-Dihydroquinazolin-4(1*H*)-ones, $Zr(HSO_4)_4$, Heterocycles, Solvent-free.

Introduction

2,3-Dihydroquinazolinones are an important class of bioactive compounds that are prescribed as plant growth regulators and as anticancer drugs[1]. In addition, these compounds are also key intermediates for the synthesis of quinazolin-4(3*H*)-ones. Benzothiazoles are used for the development of pharmaceutical agents of various applications. Compounds with the motif show a wide range of pharmacological activities, such as anti-tumour[2], anticonvulsant[3], antibacterial[4] calcium-inhibiting[5] and topoisomerase II inhibitory[6]. The formation of 3-(2'-benzothiazolyl)-2,3- dihydroquinazolin-4(1*H*)-ones is generally accomplished by condensation reaction of isatoic anhydride, aldehyde and 2-aminobenzothiazole in the presence of [bmim]Br[7], $Al_5(P_3O_{10})_3$[8] or under thermal solvent-free conditions[9]. However, most of these procedures have signicant drawbacks such as long reaction times, low yields, expensive reagents *etc*. Thus, there is still need of a simple and general for the one-pot synthesis of 3-(2'-benzothiazolyl)-2,3-dihydroquinazolin-4(1*H*)-ones. In recent years, metal hydrogen sulfates have been used as an efficient reagent in organic chemistry[10]. A broad range of reactions including deprotection, oxidation, C-C, C-N and C-O bond formation and cleavage took place in the presence of these reagents under mild and heterogeneous conditions. In addition, stability, cheapness, ability to produce highly efficient products in a short time and in many cases reusability is among other important advantages of these reagents. Herein, we report a rapid and convenient procedure for the preparation of 3-(2'-benzothiazolyl)-2,3- dihydroquinazolin-4(1*H*)-ones using a catalytic amount of $Zr(HSO_4)_4$ under solvent-free conditions (Scheme 1).



Scheme 1

Experimental

IR spectra were determined on FTS-40 infrared spectrometer; NMR spectra were recorded on Bruker AV-400 spectrometer at room temperature using TMS as an internal standard, coupling constants (*J*) were measured in Hz; Elemental analysis were performed by a Vario-III elemental analyzer; Melting points were determined on a XT-4 binocular microscope and were uncorrected; Commercially available reagents were used throughout without further purification unless otherwise stated.

General Procedure for the Preparation of 4

A mixture of the isatoic anhydride (1mmol), aldehyde (1 mmol) 2-aminobenzothiazole (1 mmol), and $Zr(HSO_4)_4$ (0.02 mmol) was stirred at 110 ºC for the appropriate time according to Table 2. Completion of the reaction was indicated by TLC. The reaction was cooled to room temperature, water was added and the mixture stirred for 5 min. The solid obtained was removed by filtration and recrystallized from acetonitril. All products were characterized by comparison of their physical data and ^{1}H and ^{13}C NMR data with those of authentic samples.

Spectral data of new product

3-(2′-Benzothiazolyl)-2,3-dihydro-2-(3-chlorophenyl)-quinazolin-4(1H)-one (4g).

IR (KBr) *v*: 3372, 1652, 1599, 1498, 1420, 1362, 1209; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 8.10 (d, 1H, J = 4.4 Hz. NH), 7.99 (d, 1H, J = 7.6 Hz. CH), 7.93 (d, 1H, J = 7.6 Hz. CH), 7.72-7.66 (m, 3H, CH), 7.48-7.10 (m, 6H, CH), 6.92-6.88 (m, 2H); Anal. calcd for $C_{21}H_{14}ClN_3OS$: C 64.36, H 3.60, N 10.72, S 8.18%; found: C 64.50, H 3.42, N 10.60, S 8.02%

Results and Discussion

In an initial endeavor, isatoic anhydride, benzaldehyde and 2-aminobenzothiazole were stirred at 120 °C under solvent-free conditions. After 5 h, only 15% of the expected product 3-(2′-benzothiazolyl)-2,3-dihydro-2- (phenyl)-quinazolin-4(1*H*)-one was obtained. To improve the yield and optimize the reaction conditions, the same reaction was carried out in the presence of a variety of catalysts under similar conditions, it was found that when the reaction occurred using catalysts such as I_2, $ZnCl_2$, H_2SO_4, HCl and $NaHSO_3$ it resulted in poor yields. However, catalysts such as *p*-TsOH, $NaHSO_4$, $Fe(HSO_4)_3$ could push the reaction forward with moderate yields. A significant improvement was observed and the yield of 3-(2′-benzothiazolyl)-2,3-dihydro-2- (phenyl)-quinazolin-4(1*H*)-one was increased to 90% in the presence of 2 mol % $Zr(HSO_4)_4$ (Table 1). Then we tried to optimize the amount of catalyst and the reaction temperature for this reaction. As could be seen on Table 1, the reaction using 2 mol % $Zr(HSO_4)_4$ at 110 °C proceeded in highest yield.

Table 1. Synthesis of 3-(2′-benzothiazolyl)-2,3-dihydro-2-(phenyl)-quinazolin-4(1*H*)-one under various conditions[a].

Entry	Catalyst	Temperature /°C	Time /h	Yield /%[b]
1	-	120	5	15
2	I_2, 2 mol%	120	3	43
3	$ZnCl_2$, 2 mol%	120	3	50
4	H_2SO_4, 2 mol%	120	4	49
5	HCl, 2 mol%	120	4	42
6	$NaHSO_3$, 2 mol%	120	4	35
7	*p*-TsOH, 2 mol%	120	1	81
8	$NaHSO_4$, 2 mol%	120	1	80
9	$Fe(HSO_4)_3$, 2 mol%	120	0.5	82
10	$Zr(HSO_4)_4$, 0.5 mol%	120	1	57
11	$Zr(HSO_4)_4$, 1 mol%	120	1	69
12	$Zr(HSO_4)_4$, 1.5 mol%	120	0.5	88
13	$Zr(HSO_4)_4$, 2 mol%	25	5	0
14	$Zr(HSO_4)_4$, 2 mol%	50	5	0
15	$Zr(HSO_4)_4$, 2 mol%	90	2	69
16	$Zr(HSO_4)_4$, 2 mol%	100	1	87
17	$Zr(HSO_4)_4$, 2 mol%	110	0.5	93
18	$Zr(HSO_4)_4$, 2 mol%	120	0.5	92
19	$Zr(HSO_4)_4$, 2 mol%	130	0.5	90
20	$Zr(HSO_4)_4$, 3 mol%	100	0.5	80
21	$Zr(HSO_4)_4$, 3 mol%	110	0.5	89
22	$Zr(HSO_4)_4$, 4 mol%	110	0.5	91
23	$Zr(HSO_4)_4$, 5 mol%	110	0.5	93

[a]*Reaction conditions: isatoic anhydride (1 mmol); benzaldehyde (1 mmol); 2-aminobenzothiazole (1 mmol); neat.* [b] *Isolated yield.*

Encouraged by this result, in order to build the generality of the reaction, our attention moved to the reactions of other aldehydes, and the results are summarized in Table 2. As expected, this reaction proceeded smoothly and the desired products were obtained in good to excellent yields. A series of aldehydes with either electron- donating or electron-withdrawing groups attaching to aromatic ring were investigated. The substitution groups on the aromatic ring had no obvious effect on the yield. When aromatic aldehydes were replaced by with aliphatic aldehyde, the corresponding products were obtained with high yields as well (Table 2, entries 10 and 11).

Table 2. Preparation of 3-(2'-benzothiazolyl)-2,3-dihydroquinazolin-4(1*H*)-ones[a].

Entry	R	Time/ h	Products[b]	Yield/ %[b]	m.p. (lit.)/ °C
1	C_6H_5	0.5	**4a**	90	232-234 (233-236)[7]
2	4-Cl-C_6H_4	0.5	**4b**	88	192-193 (198-200)[8]
3	4-Me-C_6H_4	0.5	**4c**	92	197-199 (198-199)[7]
4	4-MeO-C_6H_4	0.5	**4d**	91	182-184 (179-183)[8]
5	4-NO_2-C_6H_4	1	**4e**	87	242-245 (245-246)[7]
6	3-NO_2-C_6H_4	1	**4f**	88	250-255 251-253)[7]
7	3-Cl-C_6H_4	0.5	**4g**	86	160-162
8	2-Me-C_6H_4	0.5	**4h**	88	199-201 (198-201)[8]
9	2-MeO-C_6H_4	0.5	**4i**	89	222-225 (225-230)[8]
10	CH_3	1	**4j**	81	219-221 (215-222)[7]
11	C_6H_{13}	1	**4k**	80	149-152 (148-151)[7]

[a]*Reaction conditions: isatoic anhydride (1 mmol); aldehyde (1 mmol); 2-amino benzothiazole (1 mmol); $Zr(HSO_4)_4$ (0.02 mmol); 110 °C; neat.* [b]*Isolated yield.*

To show merit of the present work in comparison with reported results in the literature, we compared results of $Zr(HSO_4)_4$ with [bmim]Br, $Al_5(P_3O_{10})_3$ as catalysts in the reaction of

isatoic anhydride, benzaldehyde and 2-aminobenzothiazole. As shown in Table 3, $Zr(HSO_4)_4$ can act as high efficiency catalyst with fast time and high yields of the obtained products.

Table 3. $Zr(HSO_4)_4$-catalyzed synthesis of 3-(2′-benzothiazolyl)-2,3-dihydro-2-(phenyl)-quinazolin-4(1*H*)-one in comparison with other literatures.

Entry	Catalyst and conditions	Time/ min	Yield/ %	Ref.
1	[bmim]Br (136 mol%); neat; 130 ^oC	30	93	7
2	$Al_5(P_3O_{10})_3$ (16 mol%); neat; 100 ^oC	20	85	8
3	neat; 130 ^oC	132	66	9
4	$Zr(HSO_4)_4$ (2 mol%); neat; 110 ^oC	30	93	The work

Conclusion

In conclusion, we have developed an efficient one-pot procedure for the synthesis structurally diverse libraries of 3-(2'-benzothiazolyl)-2,3-dihydroquinazolin-4(1*H*)- ones by a three component condensation of isatoic anhydride, aldehydes, and 2-aminobenzothiazole in the presence of $Zr(HSO_4)_4$. The procedure is applicable to a wide range of aromatic aldehydes, and the products are obtained in high yields.

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