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SIMPLE, SELECTIVE, AND PRACTICAL SYNTHESIS OF 2-SUBSTITUTED 4(3*H*)-QUINAZOLINONES BY Yb(OTf)$_3$-CATALYZED CONDENSATION OF 2-AMINOBENZAMIDE WITH CARBOXAMIDES

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Abstract – A simple, selective, and practical synthetic method of 4(3*H*)-quinazolinones is realized by Yb(OTf)$_3$-catalyzed condensation of 2-aminobenzamide with carboxamides. As the reaction proceeds, NH_3 and H_2O were formed as byproducts; however, Yb(OTf)$_3$ can operate as an efficient Lewis acid catalyst without deactivation.

4(3*H*)-Quinazolinones belong to one of the most important classes of fused heterocyclic compounds with a wide range of biological activities;[1] *e.g.*, protein tyrosine kinase inhibitor,[2] cholecystokinin inhibitor,[3] antimalarial,[4] antibacterial,[5] antifungal,[6] antiviral,[7] anti-HIV,[8] anticancer,[9] antiinflammatory,[10] antiallergy,[11] anticonvulsant,[12] antihypertensive,[13] and antidiabetic.[14] In addition, the 4(3*H*)-quinazolinone nucleus is also the key component of chromophoric,[15] thermochromic,[16] and fluorescent materials.[17]

Typically, 4(3*H*)-quinazolinones were prepared on the basis of the Niementowski synthesis[18] by condensation of anthranilic acid with carbonyl compounds and amines, proceeding via an 2-amidobenz-amide intermediate.[19] Nevertheless, this method suffers from multi-step and tedious procedures, costly

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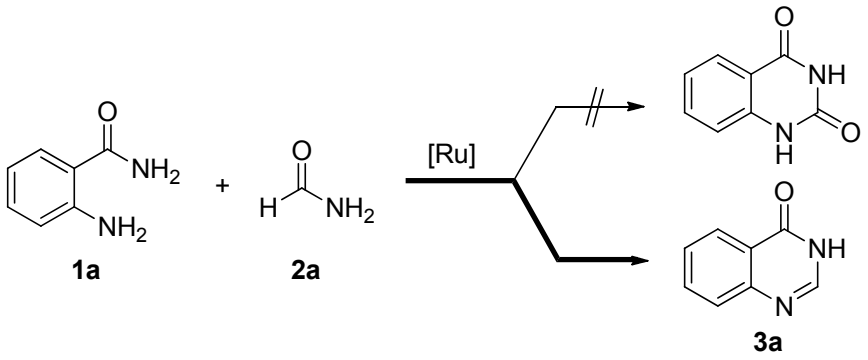
Dedicated with respect to Professor Isao Kuwajima on the occasion of his 77th birthday

reagents, and often low yields. To overcome these problems, several new methods for synthesis of 4(3*H*)-quinazolinones have recently been developed, using acids and/or oxidants such as PFPAT,[20] $NaHSO_3$,[21] DDQ/DMF,[22] I_2,[23] TBAB,[24] and using metal catalysts such as CuI,[25] CuBr,[26] PAPAT-$CuCl_2$,[27] $FeCl_3 \cdot 6H_2O$,[28] and $Ga(OTf)_3$[29] [OTf = trifluoromethanesulfonate] as well as solid catalysts.[30] Wang and coworkers have reported a pioneering study on $Yb(OTf)_3$-catalyzed one-pot synthesis of 4(3*H*)-quinazolinones by condensation of anthranilic acid, anilines, and orthoesters (or formic acid, HCO_2H) without solvents; however, only 3-substituted 4(3*H*)-quinazolinones were obtained by this reaction.[31] In addition, Liu,[32a] Bakavoli,[32b] and Wang[32c] have independently developed the microwave-assisted Niementowski reaction, and palladium-catalyzed carbonylative synthesis of 4(3*H*)-quinazolinones has also been reported.[33]

We have developed a novel method for synthesis of symmetrically substituted ureas by ruthenium-catalyzed condensation reaction of 2 equivalents of aromatic amines with formamide.[34] We have attempted to use this ruthenium-catalyzed reaction to construct *N*-heterocyclic compounds,[35] and the reaction of 2-aminobenzamide **1a** with formamide **2a** was examined, which has two possibilities to give quinazoline-2,4(1*H*,3*H*)-dione (the upper reaction in Scheme 1) and to give 4(3*H*)-quinazolinone (**3a**, the lower reaction in Scheme 1). After many trials, we have found that this reaction offers a simple, selective, and practical method for catalytic synthesis of 4(3*H*)-quinazolinones.



Scheme 1. Reaction of 2-aminobenzamide **1a** with formamide **2a** in the presence of ruthenium catalysts

First, the reaction of 2-aminobenzamide **1a** with formamide **2a** was carried out in the presence of a catalytic amount of $RuCl_2(PPh_3)_3$ in mesitylene under reflux (bath temp. 165 ^oC) for 6 h to give 4(3*H*)-quinazolinone **3a** in 24% yield (Table 1). The catalytic activities of several zero- and divalent ruthenium complexes were examined, and $[(\eta^6\text{-}C_6H_6)RuCl_2]_2$ and $RuCl_3 \cdot 3H_2O$ bearing chloro-ligands showed the high catalytic activity, while the concomitant use of basic phosphine ligands, such as P(*cyclo*-$C_6H_{11})_3$ and P^nBu_3, drastically decreased the catalytic activity of $RuCl_3 \cdot 3H_2O$.

Accordingly, we consider that ruthenium chlorides may work as a Lewis acid catalyst in the present reaction, and the catalytic activities of the representative Lewis acids were examined. As can be readily

seen from Table 2, anhydrous $AlCl_3$, $FeCl_3$, and $Yb(OTf)_3$ as well as $NiBr_2$ hydrate showed the excellent catalytic activitiy to give 4(3*H*)-quinazolinone **3a** in quantitative yield. However, $YbCl_3 \cdot 6H_2O$ and $Yb(OAc)_3 \cdot 4H_2O$ showed the moderate catalytic activity to give **3a** in 66% and 35% yield, respectively. Naturally abundant $FeCl_3$ and water-stable $Yb(OTf)_3$[36] were the strong candidate of the catalyst for the present reaction; however, the catalytic activity of $FeCl_3$ decreased, drastically, below 140 °C, while $Yb(OTf)_3$ showed high catalytic activity above 100 °C.

Table 1. Catalytic activity of several ruthenium complexes for the synthesis of **3a** from **1a** and **2a**[a]

entry	Ru catalyst	ligand	yield of **3a** (%)[b]
1	——	——	0
2	——	PPh_3	0
3	$Ru_2(PPh_3)_3$	——	24
4	Ru(η^4-cod)(η^6-cot)	——	0
5	$RuH_2(PPh_3)_4$	——	0
6	$[(\eta^6\text{-}C_6H_6)RuCl_2]_2$	——	83
7	$[RuCl_2(CO)_3]_2$	——	43
8	$RuCl_3 \cdot 3H_2O$	——	85
9	$RuCl_3 \cdot 3H_2O$	P(*cyclo*-$C_6H_{11})_3$	38
10	$RuCl_3 \cdot 3H_2O$	P^{n}Bu$_3$	38

[a] **1a** (4.0 mmol), **2a** (6.0 mmol), Ru catalyst (0.20 mmol as a Ru atom) in mesitylene (5.0 mL) at 165 °C (bath temp.) for 6 h under an Ar atmosphere. [b] Dtermined by GLC.

Table 2. Catalytic activity of several Lewis acids for the synthesis of **3a** from **1a** and **2a**[a]

entry	Lewis acid	yield of **3a** (%)[b]
1	$AlCl_3$	>99
2	$AlCl_3 \cdot 6H_2O$	72
3	$FeCl_3$	>99
4	$CoCl_2$	86
5	$NiBr_2 \cdot xH_2O$	>99
6	$RhCl_3$	66
7	$PdCl_2$	30
8	$SnCl_2$	89
9	^{n}Bu$_3$SnCl	5
10	$CeCl_3$	90
11	$EuCl_3$	77
12	$YbCl_3 \cdot 6H_2O$	66
13	$Yb(OAc)_3 \cdot 4H_2O$	35
14	$Yb(OTf)_3$	>99

[a] **1a** (4.0 mmol), **2a** (6.0 mmol), Lewis acid (0.20 mmol) in mesitylene (5.0 mL) at 165 °C (bath temp.) for 6 h under an Ar atmosphere. [b] Dtermined by GLC.

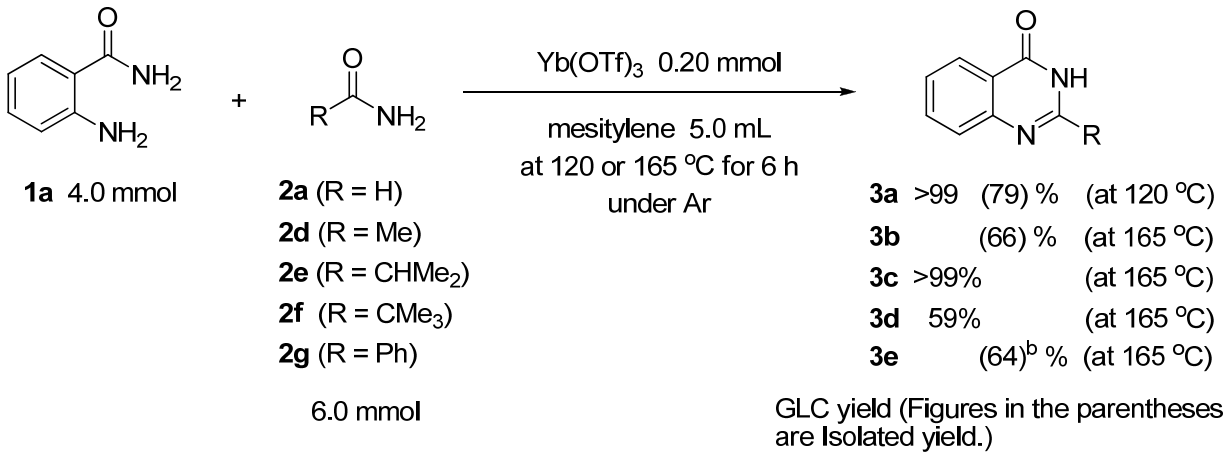
Then, catalytic activities of several metal triflates were examined, and the results were summarized in Table 3. Among metal triflates examined, $Yb(OTf)_3$ showed the highest catalytic activity, and 0.050 mmol (1.25 mol%) $Yb(OTf)_3$ was at least required for the success of the present reaction. Mesitylene is the most suitable solvent for the present reaction, while the yield of **3a** decreased, drastically, in diglyme (**3a**, 11%) and *N*-methylpiperidine (**3a**, 11%), due to their strong coordination ability through oxygen and nitrogen atoms to coordinatively unsaturated and catalytically active cationic ytterbium center (*vide infra*).

Formamide **2a** is the most effective C1 source in the construction of 4(3*H*)-quinazolinone **3a**, while methyl formate **2b** or paraformaldehyde, $(CH_2O)_n$ **2c**, instead of formamide **2a**, gave **3a** in 39% and 12% yield, respectively, even under reflux in mesitylene (bath temp. 165 °C). Besides formamide **2a**, carboxamides, such as acetamide **2d**, 2-methylpropanamide **2e**, pivalamide **2f**, and benzamide **2g**, can be used in the present reaction to give 2-methyl-, 2-isopropyl-, 2-(*tert*-butyl)-, and 2-phenyl-4(3*H*)-quinozolinone (**3b-e**) in good to high yields (Scheme 2).[37]

Table 3. Catalytic activity of several metal triflates for the synthesis of **3a** from **1a** and **2a**[a]

entry	metal triflate	yield of **3a** (%)[b]
1	LiOTf	7
2	CuOTf·benzene	27
3	$Cu(OTf)_2$	31
4	$Zn(OTf)_2$	76
5	$Fe(OTf)_2$	58
6	$Ni(OTf)_2$	59
7	$Sc(OTf)_3$	80
8	$Sm(OTf)_3$	62
9	$Yb(OTf)_3$	>99

[a] **1a** (4.0 mmol), **2a** (6.0 mmol), metal triflate (0.20 mmol) in mesitylene (5.0 mL) at 120 °C for 6 h under an Ar atmosphere. [b] Dtermined by GLC.



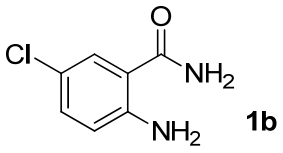
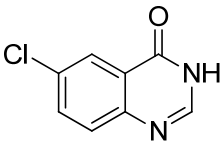
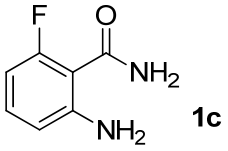
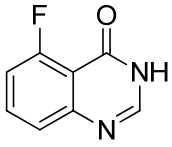
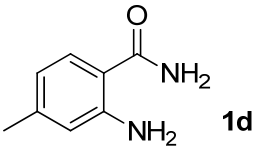
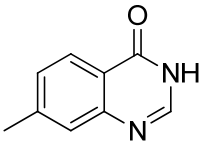
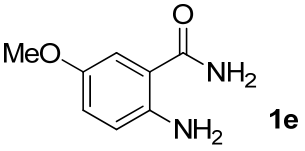
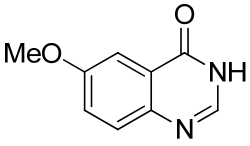
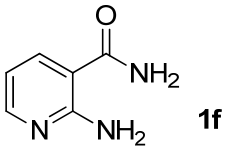
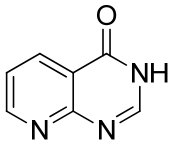
Scheme 2. $Yb(OTf)_3$-Catalyzed synthesis of 4(3*H*)-quinazolinones **3** from 2-aminobenzamide **1a** and carboxamides **2**

Condensation of several 2-aminobenzamides (**1b-e**) with formamide (**2a**) proceeded, smoothly, by $Yb(OTf)_3$ catalyst to give the corresponding 4(3*H*)-quinazolinones (**3f-i**) in moderate to high isolated yields (Table 4).[40] In addition, the related 2-aminonicotinamide (**1f**) also reacted with **2a** under the present catalytic reaction conditions to give pyrido[2,3-*d*]pyrimidin-4(3*H*)-one (**3j**) in an isolated yield of 55%.

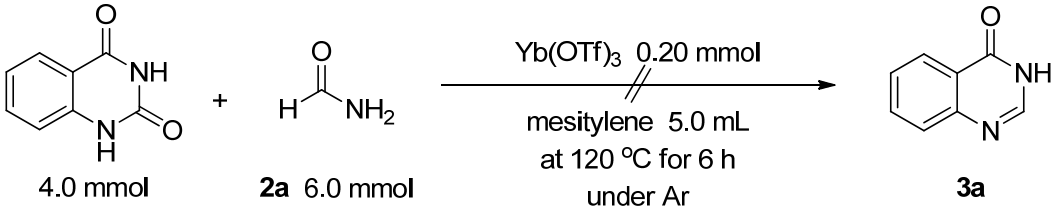
To investigate the mechanism, quinazoline-2,4(1*H*,3*H*)-dione was treated with a catalytic amount of $Yb(OTf)_3$ in mesitylene at 120 °C for 6 h under an argon atmosphere in the presence or absence of formamide **2a**. In both reactions, no **3a** was obtained at all (Scheme 3). Thus, the mechanism through the reduction of a carbonyl group in quinazolin-2,4(1*H*,3*H*)-dione was ruled out, completely.

Considering the results obtained above, the most plausible mechanism is illustrated in Scheme 4. We believe that the dissociation of a triflate anion (OTf^-) from $Yb(OTf)_3$ first occurred to generate catalytically active $Yb(OTf)_2^+$, which immediately coordinates to a carbonyl oxygen in carboxamide. Subsequent nucleophilic attack of an amino group in 2-aminobenzamide to the activated carbonyl carbon in carboxamide proceeded to give an amidine intermediate and $Yb(OTf)_2(OH)$, followed by dissociation of OH^- to regenerate $Yb(OTf)_2^+$. $Yb(OTf)_2^+$ again coordinates to a carbonyl oxygen in benzamide to promote the intramolecular nucleophilic attack of an amino group to the activated carbonyl carbon. Isomerization of the intermediate, followed by elimination of NH_3 give 4(3*H*)-quinazolinone and $Yb(OTf)_2^+$.

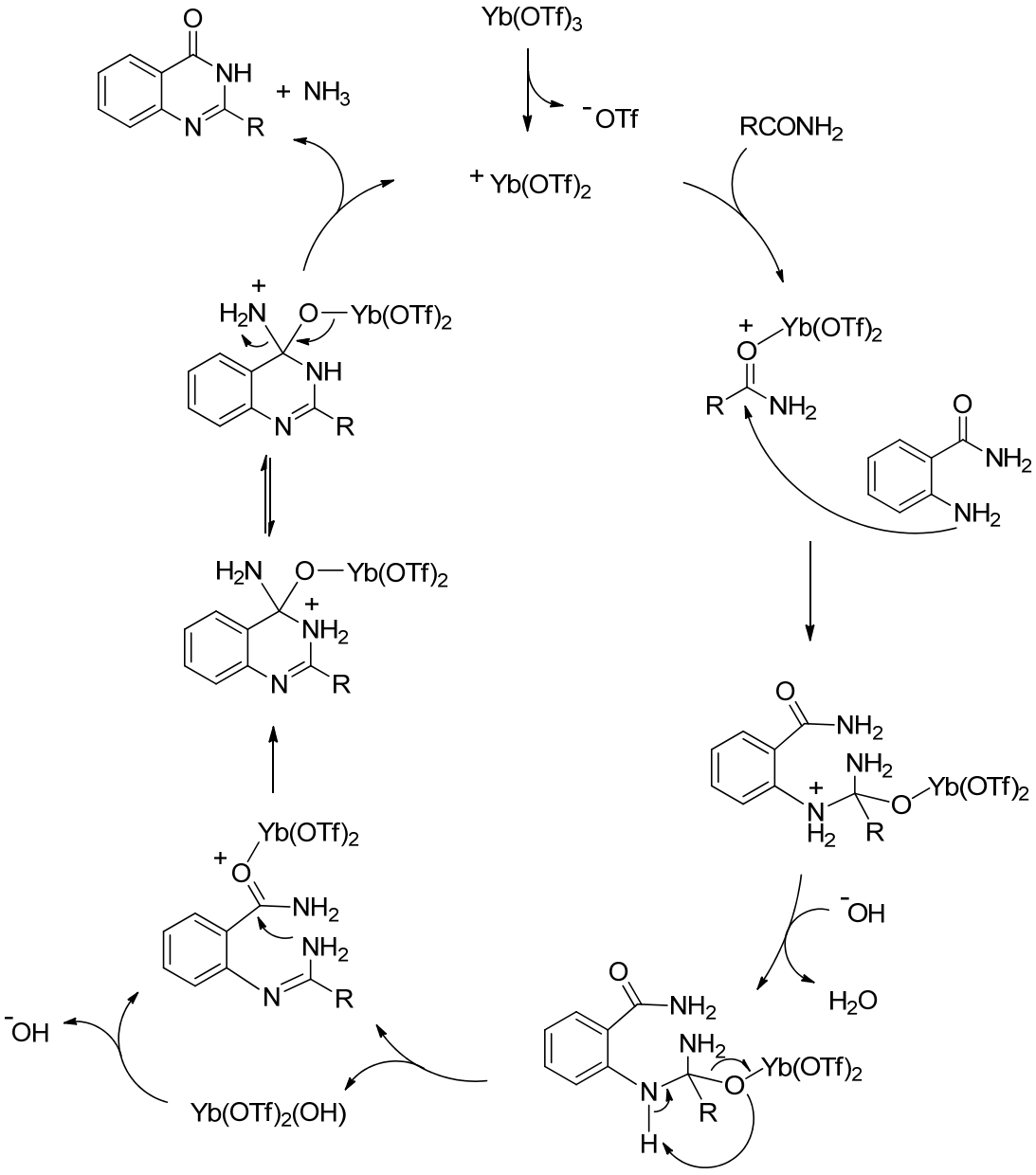
Table 4. Synthesis of 4(3*H*)-quinazolinones **3f-j** by $Yb(OTf)_3$-catalyzed condensation of 2-aminobenzamides **1b-e** and the related **1f** with formamide **2a**[a]

entry	2-aminobenzamides **1**	isolated yield of 4(3*H*)-quinazolinone **3** (%)
1	 **1b**	 **3f**, 67
2	 **1c**	 **3g**, 55
3	 **1d**	 **3h**, 76
4	 **1e**	 **3i**, 58
5	 **1f**	 **3j**, 55

[a] **1** (4.0 mmol), $HCONH_2$ **2a** (6.0 mmol), $Yb(OTf)_3$ (0.20 mmol) in mesitylene (5.0 mL) at 165 °C (bath temp.) for 6 h under an Ar atmosphere.



Scheme 3. Reaction of quinazoline-2,4(1*H*,3*H*)-dione with formamide **2a** in the presence of $Yb(OTf)_3$ catalyst



Scheme 4. The most plausible mechanism

In conclusion, we developed one-pot and environmentally benign synthesis of 2-substituted 4(3*H*)-quinazolinones by $Yb(OTf)_3$-catalyzed condensation of 2-aminobenzamides with carboxamides. Surprisingly, $Yb(OTf)_3$ can operate as an efficient Lewis acid catalyst without deactivation even in the presence of byproducts, NH_3 and H_2O. Accordingly, application of $Yb(OTf)_3$ catalyst to construct other valuable nitrogen-heterocycles is highly expected, and the study is in progress in our laboratory.

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37. A mixture of 2-aminobenzamide (**1**, 4.0 mmol), carboxamide (**2**, 6.0 mmol), $Yb(OTf)_3$ (0.20 mmol, 5.0 mol%), and mesitylene (5.0 mL) was placed in a 20-mL Pyrex flask equipped with a magnetic stirring bar and a reflux condenser under a flow of argon. The reaction was carried out at 120-165 ^{o}C (bath temp.) for 6 h with stirring. Then, the reaction mixture was cooled to room temperature, and analyzed by GLC, GC-MS (EI), and LC-MS (ESI). After evaporation of mesitylene under vacuum, the products (**3**) were isolated by recrystallization from MeOH/hexane and/or medium pressure column chromatography on silica gel (eluent: EtOAc/hexane = 50/50 ~ EtOAc 100%. For **3j**, eluent: MeOH/$CHCl_3$ = 50/50). ^{1}H NMR spectra were recorded at 400 MHz, and ^{13}C NMR spectra were recorded at 100 MHz in DMSO-d_6. The analytical and spectral data of **3a-e**,[38] **3f**,[39] **3g**,[40] **3h**,[41] and **3j**,[42] were consistent with those reported previously. The product, **3i**, was characterized below.[43]
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43. **3i**: a white solid. IR (KBr) cm^{-1}: 3127, 1698; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 12.16 (1H, br s), 8.00 (1H, s), 7.61 (1H, d, J = 8.98 Hz), 7.49 (1H, d, J = 2.86 Hz), 7.42 (1H, dd, J = 8.98 and 2.86 Hz), 3.86 (3H, s); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 160.4, 157.7, 143.2, 142.8, 128.7, 123.7, 123.4, 105.8, 55.6; MS (ESI): 177.0726 $(M+H)^{+}$.