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COMMUNICATION

Oxidant- and Metal-Free Synthesis of 4(3*H*)-Quinazolinones from 2-Amino-*N*-methoxybenzamides and Aldehydes via Acid-Promoted Cyclocondensation and Elimination†

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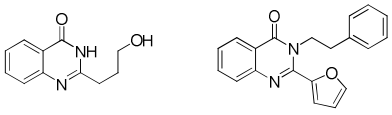
A series of biologically important 4(3*H*)-quinazolinones were readily synthesized in good to excellent yields from 2-amino-*N*-methoxybenzamides and aldehydes via a cascade reaction consisting of AcOH-promoted cyclocondensation and elimination. The current method sets itself apart from the conventional approach utilizing anthranilamide derivatives and aldehydes as building blocks, by its unique features, other than the high yields and one-pot procedure, including the absence of an oxidant, the obviation of a heavy-metal catalyst, and the formation of a non-toxic ester byproduct.

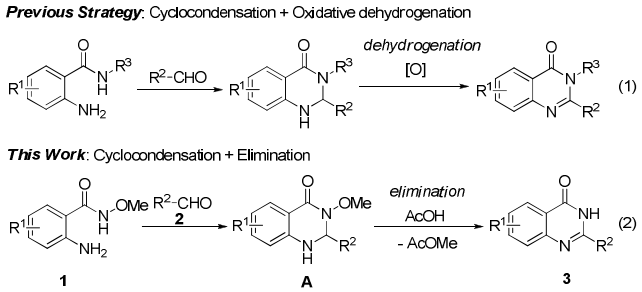
Quinazolinones are an important class of nitrogen-containing heterocycles (azaheterocycles) which exhibit a range of biological and pharmaceutical properties,[1] including but not limited to antihypertensive,[2] anticancer,[3] anti-inflammatory,[4] antimalarial[5] and antimicrobial[6] activities. In addition to their occurrence in natural products, they also frequently appear in pharmaceutical agents for their applications as potent antagonistic receptors.[7] For example, Pegamine, isolated from *Peganum harmala*, has been found to possess cytotoxic activity,[8] and NPS 53574, a new calcilytic template for blocking calcium receptor (CaR) activity, is proven to be capable of treating osteoporosis (Figure 1).[9] Both of these two biologically active compounds possess the common quinazolinone skeleton in their respective structure.



Pegamine NPS 53574

Fig. 1 Representative quinazolinones in natural products and pharmaceutical agents.

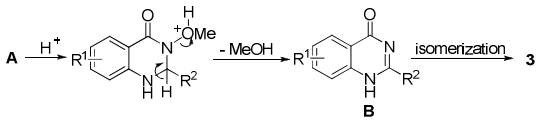
Considering the significance of this class of compounds, many efforts have been devoted to explore the methodologies for the construction of 4(3*H*)-quinazolinone skeletons. The representative methods involve cyclization of *o*-acylaminobenzamide,[10] amination of benzoxazin-4-one,[11] multicomponent reactions (MCRs) among isatoic anhydride, amine with aldehyde,[12] benzyl halide[13] or orthoester.[14] In addition, transition metal catalysts such as copper,[15] ruthenium,[16] iridium[17] and palladium[18] have also been applied to the synthesis of quinazolinones through a one-pot oxidative cyclization of primary alcohols with *o*-aminobenzamides as well as through a domino process of *N*-arylation followed by condensative cyclization. Another extensively studied strategy was a sometimes metal-free, one-pot protocol which involves a cyclocondensation of anthranilamides with aldehydes followed by a subsequent oxidant-mediated dehydrogenation process (Scheme 1, eq 1).[19] Various non-metal oxidants such as DDQ,[19a] I_2,[19f] O_2[20] as well as metal ones such as $CuCl_2$,[19c] $KMnO_4$,[19e] have been applied to realize the second oxidative step. Although this last strategy has some practical advantages and potential applications, many of the existing methods have the disadvantages such as harsh conditions, unsatisfactory yields and most seriously, the use of the stoichiometric oxidants or heavy-metal reagents. To the best of our knowledge, there are few reports, if any, describing the dehydrogenation step that does not require the participation of an oxidantor a heavy-metal catalyst.[21] In this communication, we report a novel green protocol for the synthesis of 4(3*H*)-quinazolinone compounds **3**, that is free of oxidant or catalyst and was carried out in a convenient one-pot reaction between 2-amino-*N*-methoxybenzamides **1** and various aldehydes **2**, going through an intermediate of 3-methoxy-2,3-dihydroquinazolin-4(1*H*)-one **A** (Scheme 1, eq 2). It is worthy to note that the generated MeOH was converted to a nontoxic ester as a byproduct in this approach.[22]



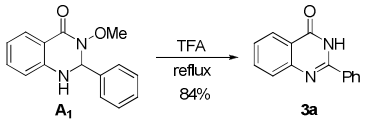
Scheme 1 Strategies of synthesis of 4(3*H*)-quinazolinones.

In our previous work,[23] we found that the reaction of 2-amino-*N*-methoxybenzamides **1** with aldehydes **2** conveniently afforded 3-methoxy-2,3-dihydroquinazolin-4(1*H*)-ones **A** in the presence of catalytic amount of TsOH. We envisaged that the treatment of

3-methoxy-2,3-dihydroquinazolin-4(1*H*)-one **A** with a suitable acid might trigger an acid-promoted demethanolization and thereafter give 4(1*H*)-quinazolinone **B**, which should quickly isomerize into 4(3*H*)-quinazolinone **3** (Scheme 2). To our pleasant surprise, we found that by heating the isolated 3-methoxy-2,3-dihydroquinazolin-4(1*H*)-one $\mathbf{A_1}$ in refluxed TFA for 55 minutes, the desired 4(3*H*)-quinazolinone **3a** was obtained in 84% yield (Scheme 3).



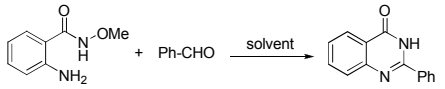
Scheme 2 Proposed route to access 4(3*H*)-quinazolinones.



Scheme 3 Conversion of $\mathbf{A_1}$ into **3a** through acid-promoted elimination of MeOH.

Considering the fact the formation of 3-methoxy-2,3-dihydroquinazolin-4(3*H*)-one **A** was also realized under acidic conditions, we next focused on designing a cascade reaction which entails developing a one-pot protocol for the synthesis of **3** from **1** and **2**. We selected 2-amino-*N*-methoxybenzamide **1a** and benzaldehyde **2a** as model substrates. To our delight, after heating the two starting materials in TFA for 1 h, the reaction afforded the desired product **3a** in 81% yield (Table 1, entry 1). Various acids were used as solvent to further screen for the more favorable reaction conditions (Table 1, entries 2-7). Judging by the yield of the desired product, acetic acid was concluded as the best solvent (Table 1, entry 7). By increasing the reaction temperature from 80 °C to 100 °C, the reaction time was cut down by half, from 3 h to 1.5 h, and the yield was slightly increased (Table 1, entry 8). However, operating the reaction at even higher temperature did not improve the product yield, although the reaction time was further shortened to 1 h (Table 1, entry 9). Study on the concentration of the reactant **1a** showed neither higher nor lower concentration was beneficial to the reaction as negative consequences such as more byproducts (therefore less desired product) or lengthened reaction time were observed, respectively (Table 1, entries 10-11).

Table 1 Optimization of reaction conditions[a]

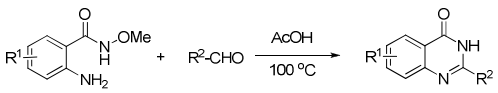


entry	solvent	T (°C)	time (h)	yield (%)[b]
1	TFA	reflux	1	81
2	PivOH	80	8	0
3	Cl_2COOH	80	1.5	70
4	T_fOH	80	12	ND
5	HCl	80	3	12
6	HCO_2H	80	12	34
7	AcOH	80	3	88
8	AcOH	100	1.5	93
9	AcOH	110	1	89
10[c]	AcOH	100	1.5	82
11[d]	AcOH	100	4	92

[a] Reaction conditions: substrate **1a** (1.0 mmol) and aldehyde **2a** (1.1 mmol) in solvent (4 mL). [b] Isolated yields. [c] The concentration of the reaction was 0.5 mol·L^{-1}, based on substrate **1a**. [d] The concentration of the reaction was 0.20 mol·L^{-1}, based on substrate **1a**.

With the optimal reaction conditions in hand, the scope and generality of this new one-pot protocol was investigated, the results of which are summarized in Table 2. By reacting 2-amino-*N*-methoxybenzamides **1b-e** with substituted aldehydes **2b-e**, bearing electron-withdrawing groups, the desired products **3b-e** were conveniently achieved in satisfactory to excellent yields (Table 2, entries 2-5) in each case. One slight exception was the reaction between **1e** and **2e**, which was completed in a much longer 4.5 h and afforded the desired product **3e** in relatively lower yield. This was obviously due to the steric hindrance brought by the *o*-substituted bulky trifluoromethyl group in aldehyde **2e** (Table 2, entry 5). The method was equally well applicable to the benzaldehydes bearing electron-rich substituent (Table 2, entries 6-8). In the case of di-substituted benzaldehydes, bearing either electron-withdrawing or electron-donating group, the desired products were obtained in even better yields (Table 2, entries 9-10). Each of the substrates, containing either an electron-deficient or electron-rich substituent on the benzene ring of 2-amino-*N*-alkoxybenzamide, was converted to the corresponding 4(3*H*)-quinazolinone products **3k-m** in good to excellent yields (Table 2, entries 11-13). Further study revealed that the aromatic aldehydes could also be replaced with aliphatic

Table 2 Synthesis of 4(3*H*)-quinazolinones via AcOH-promoted cyclocondensation and elimination[a]

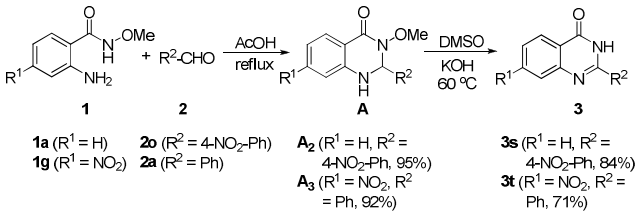


entry	1		2		product	time	yield
	R^1		R^2		3	(h)	(%)[b]
1	H	**1a**	Ph	**2a**	**3a**	1.5	93
2	H	**1a**	*p*-Br-Ph	**2b**	**3b**	1	95
3	H	**1a**	*p*-F-Ph	**2c**	**3c**	0.5	95
4	H	**1a**	*m*-Cl-Ph	**2d**	**3d**	0.3	82
5	H	**1a**	*o*-CF_3-Ph	**2e**	**3e**	4.5	81
6	H	**1a**	*p*-Me-Ph	**2f**	**3f**	1	87
7	H	**1a**	*p*-MeO-Ph	**2g**	**3g**	1	73
8	H	**1a**	*p*-OH-Ph	**2h**	**3h**	2	92
9	H	**1a**	2,6-diCl-Ph	**2i**	**3i**	2	95
10	H	**1a**	3,4-diMeO-Ph	**2j**	**3j**	1	98
11	5-Br	**1b**	Ph	**2a**	**3k**	0.3	93
12	3-Me	**1c**	Ph	**2a**	**3l**	0.5	80
13	4-MeO	**1d**	Ph	**2a**	**3m**	0.5	98
14	H	**1a**	*n*-propyl	**2k**	**3n**	1	79
15	6-Cl	**1e**	*n*-propyl	**2k**	**3o**	1	75
16[c]	4-F	**1f**	Me	**2l**	**3p**	5	95
17[c]	4-MeO	**1d**	*i*-propyl	**2m**	**3q**	3	80
18	H	**1a**	(*E*)-Ph-CH=C(Me)	**2n**	**3r**	3	82

[a] Reaction conditions: substrate **1a** (1.0 mmol) and aldehyde **2a** (1.1 mmol) in solvent (4 mL). [b] Isolated yields. [c] 3 equiv of aldehyde was used.

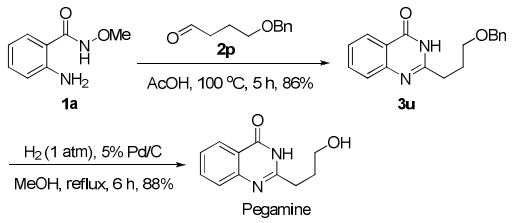
aldehydes, rendering the method applicable to the synthesis of 2-alkyl 4(3*H*)-quinazolinones **3n-q** in good to excellent yields (Table 2, entries 14-17). Furthermore, we were pleased to find that (*E*)-2-(1-phenylprop-1-en-2-yl)quinazolin-4(3*H*)-one **3r** could also be obtained in good yield, which indicated that this method was also compatible with the aldehydes bearing an α,β-unsaturated double bond (Table 2, entry 18).

Unfortunately, when 4-nitrobenzaldehyde **2o** and 2-amino-*N*-methoxy-4-nitrobenzamide **1g** were applied, the reaction only gave 3-methoxy-2-(4-nitrophenyl)-2,3-dihydroquinazolin-4(1*H*)-one $\mathbf{A_2}$ and 3-methoxy-7-nitro-2-phenyl-2,3-dihydroquinazolin-4(1*H*)-one $\mathbf{A_3}$ as the only products, rather than the expected 4(3*H*)-quinazolinones even at reflux temperature for 14 hrs. To our delightful surprise, treating the obtained compound $\mathbf{A_2}$ and $\mathbf{A_3}$ with KOH in DMSO could also trigger the elimination and finally afforded the desired 4(3*H*)-quinazolinone products **3s** and **3t** in satisfactory yields (Scheme 4).



Scheme 4 Another way to synthesize nitro-substituted 4(3*H*)-quinazolinones.

To further demonstrate the potential applications of this novel acid-promoted synthesis of 4(3*H*)-quinazolinones, we directed our efforts toward the synthesis of the naturally occurring Pegamine. The required substrate aldehyde **2p** can be easily prepared from butane-1,4-diol according to the reported procedures.[24] To our delight, subjecting **1a** and **2p** to our optimized reaction conditions afforded the 4(3*H*)-quinazolinone **3u** in a satisfactory 86% yield. After deprotecting the benzyl group of **3u** by hydrogenation over Pd/C, the desired natural product Pegamine was obtained in 88% yield.



Scheme 5 Application of the method to the synthesis of natural product Pegamine.

Conclusions

In summary, we have developed an efficient green approach which allows for rapid construction of the 4(3*H*)-quinazolinone skeleton from 2-amino-*N*-methoxybenzamides **1** and aldehydes **2** through a novel one-pot AcOH-promoted cyclocondensation and elimination process. This is a successful example of synthesizing the biologically important 4(3*H*)-quinazolinone compounds obviating the participation of either an oxidant or a heavy-metal catalyst. The method has proven to apply to a broad scope of substrates and to afford the desired 4(3*H*)-quinazolinone in satisfactory to excellent yields. The numerous attractive properties such as the oxidant-free and environmental benignancy characteristics, the one-pot protocol, and simple setup and work-up procedure, altogether promise this method many potentially useful applications in organic synthesis.

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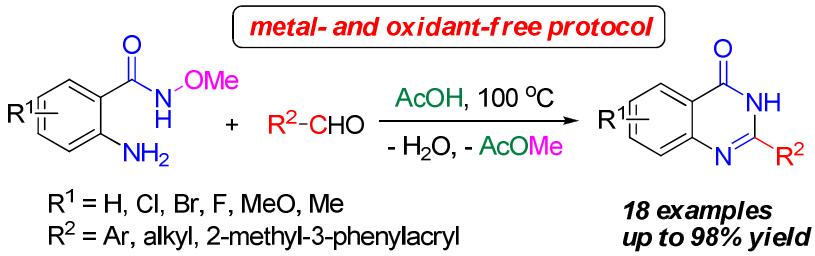
Graphical Abstract

Oxidant- and Metal-Free Synthesis of 4(3*H*)-Quinazolinones from 2-Amino-*N*-methoxybenzamides and Aldehydes via Acid-Promoted Cyclocondensation and Elimination



Abstract: A series of biologically important 4(3*H*)-quinazolinones were readily synthesized in good to excellent yields from 2-amino-*N*-methoxybenzamides and aldehydes via a cascade reaction consisting of AcOH-promoted cyclocondensation and elimination. The current method sets itself apart from the conventional approach utilizing anthranilamide derivatives and aldehydes as building blocks, by its unique features, other than the high yields and one-pot procedure, including the absence of an oxidant, the obviation of a heavy-metal catalyst, and the formation of a non-toxic ester byproduct.