A facile and rapid access towards the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones

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PII: S0040-4039(13)01390-7
DOI: http://dx.doi.org/10.1016/j.tetlet.2013.08.037
Reference: TETL 43399

To appear in: *Tetrahedron Letters*

Received Date: 2 June 2013
Revised Date: 7 August 2013
Accepted Date: 9 August 2013

Please cite this article as: Labade, V.B., Shinde, P.V., Shingare, M.S., A facile and rapid access towards the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones, *Tetrahedron Letters* (2013), doi: http://dx.doi.org/10.1016/j.tetlet.2013.08.037

A facile and rapid access towards the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones

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Abstract: An efficient synthetic route for 2,3-dihydroquinazolin-4(1*H*)-ones using 2-morpholinoethanesulfonic acid as a potential and new organocatalyst is described. The developed synthetic protocol represents novel and very simple route for the preparation of 2,3-dihydroquinazolin-4(1*H*)-one derivatives. In addition, microwave irradiation technique is successfully implemented for carrying out the reactions in shorter reaction times.

Keywords: 2-Morpholinoethanesulfonic Acid, 2,3-Dihydroquinazolin-4(1*H*)-ones, Organocatalyst, Microwave irradiations, Aqueous medium.

Quinazoline represents a significant heterocyclic core of many organic molecules endowed with diverse biological activities.[1] Various quinazolin-4-ones, quinazolin-2,4-diones and their derivatives are well known to possess an array of physiological activities. 2,3-Dihydroquinazolinones exhibit a wide range of biological activities, such as antitumor, antibiotic, antidefibrillatory, antipyretic, analgesic, diuretic, antihistamine, antidepressant, and vasodilating behavior.[2] Furthermore, quinazolinone skeleton is frequently found in various natural products. Some examples include the anticancer compound trimetrexate, the sedative methaqualone, the alpha adrenergic receptor antagonist such as doxazosin and the antihypertensive agent ketanserin. Quinazolinones have also been reported as potent chemotherapeutic agents in the treatment of tuberculosis.[3,4] In particular, 2,3-dihydroquinazolin-4(1*H*)-ones are owned with antihyperlipidemic,[5] antiviral,[6] anti-parkinsonism,[7] antimicrobial,[8] anti-inflammatory,[9] bronchodilator[10] and antihypertensive[11] activities. As a consequence of these biodynamic and pharmacological properties 2,3-dihydroquinazolin-4(1*H*)-ones have been very attractive targets in synthetic chemistry in recent years.

Development of novel synthetic methodologies to facilitate preparation of the desired molecule is an intense area of research. In this regard, efforts have been made constantly to introduce new methodologies that are efficient and more compatible with the environment.

In the recent years, there has been a growing demand for the development of more sustainable chemistry, particularly in the synthesis of value added materials, in order to minimize the great amounts of waste and consecutive treatment.[12] In performing the majority of organic transformations, thermal activation plays a crucial role in making the reaction homogeneous and allowing molecular interactions to be more efficient. One of the key principles of green chemistry is the elimination of excessive and wasteful heating during chemical operations or the replacement of conventional thermal equipments such as oil bath, heating mantle, etc. by non- conventional sources like microwave irradiations.[13]

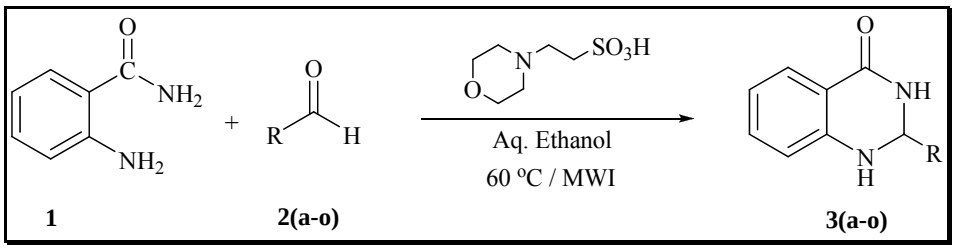
A variety of methods have been developed for the synthesis of quinazolinone scaffolds with their own merits and demerits.[14,15] Of these, the condensation of 2-aminobenzamide with aldehydes or ketones is one of the simplest and direct methods for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones. Number of acid catalysts, such as *p*-TSA/$NaHSO_3$,[16a] $TiCl_4$/Zn,[16b] $CuCl_2$,[16c] ionic liquid-water,[16d] TFA,[16e] ammonium chloride[16f] and chiral phosphoric acids[17] have been utilized to accomplish this transformation. Moreover,

very recently heteropolyacid ($H_3PW_{12}O_{40}$),[18a] silica-bonded *N*-propylsulfamic acid[18b] and cellulose-SO_3H[18c] have been reported to catalyze this reaction. Many of the reported synthetic protocols are associated with the use of expensive reagents, extended reaction times, high reaction temperatures, and also involve tedious work-up procedures.

Considering the above discussed significance of 2,3-dihydroquinazolin-4(1*H*)-ones, and in continuation of our endeavor towards the development of ecofriendly synthetic protocols for heterocyclic compounds, it was thought worthwhile to develop a novel, simple, greener, and expeditious synthetic route for obtaining 2,3-dihydroquinazolin-4(1*H*)-one derivatives.

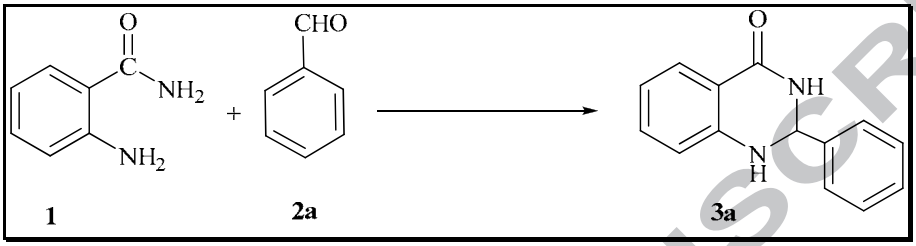
As literature reveals that the quinazolinone derivatives are best synthesized in the presence of catalysts bearing sulphonic acid functionality, our efforts were directed for finding out sulphonic acid based organocatalysts, which should be water soluble, mild in nature and resists pH change during reaction, i.e. it should act as catalyst as well as buffer. In this endeavor, 2-(*N*-morpholino)ethanesulfonic acid perfectly stood out as mild acid catalyst meeting most of the abovementioned requirements. 2-(*N*-morpholino)ethanesulfonic acid, well known as MES is commonly used as a buffering agent in biology and biochemistry. It has pH 2.5-4.0 (1% sol. at 25 °C) and its useful pH range is 5.5-6.7 with pK_a value of 6.2 at 20 °C. MES is highly soluble in water and thermally stable organic molecule (higher melting point -approx. 300 °C).

As per the literature and to the best of our knowledge, till date there are no reports on the use of MES as a catalyst for carrying out any organic transformation. In view of unique properties of MES and its ability to act as acidic organocatalyst, herein we wish to disclose MES as a potential organocatalyst for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones (Scheme 1). The developed synthetic protocol represents novel and very simple route for the preparation of 2,3-dihydroquinazolin-4(1*H*)-one derivatives. In addition, microwave irradiation technique is successfully implemented for carrying out the reactions in shorter reaction times.



Scheme 1. Synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones.

In search of the best experimental reaction conditions for the preparation of 2,3-dihydroquinazolin-4(1*H*)-ones, reaction of 2-amino benzamide **1** and benzaldehyde **2a** was selected as a model reaction (Scheme 2). During the initial study, various acid catalysts bearing sulphonated functionalities were screened, owing to their widespread catalytic applications in organic synthesis. For this purpose, sulphamic acid, sulphanilic acid, zinc sulphate and 2-morpholinoethanesulfonic acid were screened.



Scheme 2. Standard model reaction.

During optimization studies, all the aforementioned catalysts were examined using ethanol as solvent at reflux temperature. When sulphamic acid and zinc sulphate were used as catalyst, reaction rate was very slow and product was obtained in lower yield (Table 1, entries 1-2). While sulphanilic acid afforded the desired compound in acceptable yield, the time required for the completion of the reaction was much longer (Table 1, entry 3). In comparison, 2-morpholinoethanesulfonic acid (MES) proved as an excellent catalyst furnishing the product in excellent yield (Table 1, entry 4) and therefore, it was chosen as a catalyst of choice for further optimization studies.

For evaluation of the effect of solvents on model reaction, various solvents such as toluene, 1,4-dioxane, acetonitrile, methanol and aqueous ethanol (50%) were tested at their respective reflux temperatures (Table 1, entries 5-10). Among the solvents tested, aqueous ethanol was superior over the other solvents in terms of both product yield and reaction time (Table 1, entry 10).

In further attempts, to reduce the reaction time and increase the product yield, model reaction was tested at different temperatures like RT, 45 ºC, 60 ºC, 80 ºC and reflux condition. Surprisingly, increase in product yield was observed along with decrease in the reaction temperature up to 60 ºC (Table 2, entries 1-5).

To establish the appropriate amount of the catalyst, we investigated the model reaction using varied concentrations of 2-morpholinoethanesulfonic acid such as 5, 10, 15, 20 and 25 mol%. In this study, formation of the product was observed in 65%, 93%, 91% and

83% yield, respectively. This indicated that 10 mol% of 2-morpholinoethanesulfonic acid is sufficient to carry out the reaction smoothly.

Table 1. Screening of the catalysts and solvents[a]

Entry	Catalyst	Solvent	Time (h)	Yield[b] (%)
1	Sulphamic acid	Ethanol	8	42
2[c]	Zinc sulphate	Ethanol	8	49
3	Sulphanilic acid	Ethanol	6	63
4	MES	Ethanol	4	78
5	MES	Toluene	4	39
6	MES	1,4-Dioxane	4	26
7	MES	Acetonitrile	4	48
8	MES	Methanol	4	63
9	MES	Water	4	67
10	MES	Aq. ethanol (50%)	2.5	84

[a]*Reaction conditions*: **1** (1 mmol), **2a** (1 mmol), catalyst (20 mol%) and solvent (10 mL) at reflux temperature; [b]Isolated yields.

Reasons behind the excellent catalytic reactivity of 2-morpholinoethanesulfonic acid may be due to - (i) presence of sulphonic acid functionality which plays the role of acid catalyst thereby enhancing the electrophilicity of carbonyl carbon of aldehydes; (ii) MES being buffering agent and it may be minimizing the formation of the side products, caused by polymerization of the aldehydes, under the mild buffered conditions; (iii) organic nature of 2-morpholinoethanesulfonic acid and its good solubility in aqueous ethanol. Thus it forms homogeneous solution with reacting species and enhances the rate of reaction by shifting equilibrium of the reaction towards product giving excellent yield in shorter reaction times.

In further set of experiments, model reaction was performed using non-classical activation energy source, i.e. microwave irradiations. In this experiment, model reaction was found to proceed effectively within very short reaction time delivering the desired product in excellent yield. Inspired by this, it was decided to synthesize number of derivatives following developed reaction conditions by classical as well as non-classical method.

Table 2. Screening of temperature and catalyst concentration[a]

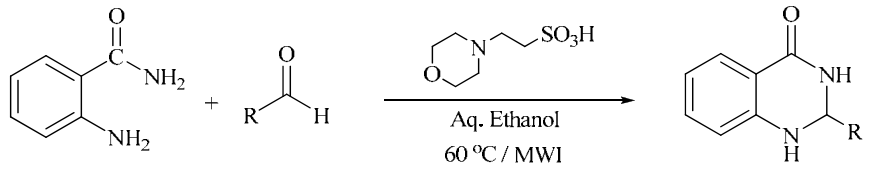
Entry	Temperature (°C)	Catalyst Conc. (mol%)	Yield[b] (%)
1	RT	20	30
2[c]	45	20	63
3	60	20	88
4	80	20	87
5	Reflux	20	84
6	60	5	65
7	60	10	93
8	60	15	91
9	60	25	83

[a]*Reaction conditions*: **1** (1 mmol), **2a** (1 mmol) and MES in Aq. ethanol (50%) (10 mL) for 2.5 h; [b]Isolated yields.

To further establish the scope of optimized reaction conditions and in order to generalize the synthetic procedure,[19] variety of electronically divergent aromatic aldehydes were treated with 2-amino benzamide under conventional and microwave irradiation method. The presence of electron-withdrawing and electron-releasing groups on the aromatic rings does not affect yield of the product. More importantly, various hetero aryl aldehydes were observed to be well tolerated under optimized conditions furnishing the product in good yields. All the results are compiled in Table 3. Formation of the desired product was confirmed with the help of ^{1}H NMR, ^{13}C NMR and mass spectroscopic data.[20]

In summary, we have developed an exceedingly simple and novel synthetic protocol for 2,3-dihydroquinazolin-4(1*H*)-one derivatives. To the best our knowledge, application of 2-morpholinoethanesulfonic acid is reported for the first time to carry out any organic transformation under conventional as well as non-conventional method. Remarkable advantages of this synthetic strategy over the others are (i) higher product yields, (ii) utilization of microwave irradiations, (iii) decreased reaction times, (iv) simplified work-up procedure, and (v) most importantly introduction of newer organic catalyst, which may act as a key catalyst for achieving various organic transformations.

Table 3. Synthesis of *2,3-dihydroquinazolin-4(1H)-one derivatives* ***3(a-o)***[a]



1 **2(a-o)** **3(a-o)**

Entry	Compound	R	Time (min)	Yield[a] (%)	M.P.[c] (C)
			A/B	A/B	
1	**3a**	Ph	150/10	93/95	224-226
2	**3b**	2-OH-Ph	150/8	93/95	220-221
3	**3c**	2-NO_2-Ph	120/5	88/89	191-192
4	**3d**	3-NO_2-Ph	150/5	85/88	192-194
5	**3e**	4-NO_2-Ph	120/5	91/93	200-201
6	**3f**	2-OMe-Ph	120/8	96/95	166-168
7	**3g**	2-Cl-Ph	120/8	86/94	202-204
8	**3h**	4-$N(Me)_2$-Ph	90/6	92/94	208-210
9	**3i**	4-OH-Ph	120/8	89/86	>300
10	**3j**	4-Me-Ph	180/15	91/93	232-233
11	**3k**	4-OMe-Ph	120/5	93/96	177-178
12	**3l**	4-Cl-Ph	180/12	89/92	197-198
13	**3m**	3,4-OMe-Ph	180/12	86/88	211-213
14	**3n**	4-OH-3-OMe-Ph	120/10	88/90	227-228
15	**3o**	Furfuryl	180/20	81/83	166-167

[a]*Reaction conditions*: **1** (1 mmol), **2** (1 mmol) and 2-morpholinoethanesulfonic acid (10 mol%) in 50% aq. ethanol (10 mL); [b]Isolated Yields; [c]Melting points matches with literature values; **A**=Conventional method and **B**=MWI method.

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19. *General experimental procedure for the synthesis of 2-(aryl)-2,3-dihydroquinazolin-4(1H)-ones* ***3(a-o)***

Conventional method: A mixture of 2-amino benzamide **1** (1 mmol), aldehyde **2** (1 mmol) and 2-morpholinoethanesulfonic acid (0.1 mmol) in 50% aq. ethanol (10 mL) was stirred at 60 C. Reaction progress was monitored by TLC (ethyl acetate:*n*-hexane, 1:9). After time specified in Table 3, reaction mass was allowed to cool down to room temperature. Thus obtained product was collected by simple filtration and washed with 50% aq. ethanol (10 mL) This crude product **4** was purified by crystallization using Aq. ethanol (water:ethanol, 2:8).

Microwave irradiation method: A mixture of 2-amino benzamide **1** (1 mmol), aldehyde **2** (1 mmol) and 2-morpholinoethanesulfonic acid (0.1 mmol) in 50% aq. ethanol (5 mL) was subjected to microwave irradiations (600 W). Reaction progress was monitored by TLC (ethyl acetate:*n*-hexane, 1:9). After time specified in Table 3, reaction mass was taken out and allowed to cool down to room temperature. Thus obtained product was collected by simple filtration and washed with 50% aq. ethanol (10 mL) This crude product **4** was purified by crystallization using Aq. ethanol (water:ethanol, 2:8).

20. *Spectral data for representative compound*

2-phenyl-2,3-dihydroquinazolin-4(1H)-one **(3a):** *^{1}H NMR (400 MHz, DMSO-d_6)* δ 5.75 (s, 1H), 6.65-6.90 (dt, 1H, *J* = 0.8 and 7.6 Hz, Ar-H), 6.69-6.72 (dd, 1H, *J* = 0.4 and 7.6 Hz, Ar-H), 7.08 (s, 1H, exchangeable with D_2O), 7.22-7.26 (m, 1H, Ar-H), 7.34-7.41 (m, 3H, Ar-H), 7.48-7.50 (m, 2H, Ar-H), 7.60-7.62 (dd, 1H, *J* = 1.6 and 8.0 Hz, Ar-H), 8.24 (s, 1H, exchangeable with D_2O); *^{13}C NMR (100 MHz, DMSO-d_6)* δ 66.6, 114.4, 114.9, 117.1, 126.8, 127.3, 128.3, 128.4, 133.3, 141.6, 147.8, 163.6; *Mass (ES-MS)* m/z 225.1 (M^+).

Graphical Abstract

A facile and rapid access towards the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones

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An efficient synthetic route for 2,3-dihydroquinazolin-4(1*H*)-ones using 2-morpholinoethanesulfonic acid as a potential and new organocatalyst is described. The developed synthetic protocol represents novel and very simple route for the preparation of 2,3-dihydroquinazolin-4(1H)-one derivatives. In addition, microwave irradiation technique is successfully implemented for carrying out the reactions in shorter reaction times.