Reaction of benzyl alcohols, isatoic anhydride and primary amines mediated by I_2/K_2CO_3 in water: A new and green approach for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones

Seyedeh Bahareh Azimi, Javad Azizian

PII: S0040-4039(15)30398-1
DOI: http://dx.doi.org/10.1016/j.tetlet.2015.11.090
Reference: TETL 47030

To appear in: *Tetrahedron Letters*

Received Date: 2 June 2015
Revised Date: 12 November 2015
Accepted Date: 28 November 2015

Please cite this article as: Azimi, S.B., Azizian, J., Reaction of benzyl alcohols, isatoic anhydride and primary amines mediated by I_2/K_2CO_3 in water: A new and green approach for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones, *Tetrahedron Letters* (2015), doi: http://dx.doi.org/10.1016/j.tetlet.2015.11.090

Graphical Abstract

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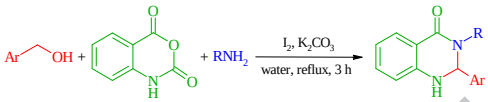

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journal homepage: www.elsevier.com

Reaction of benzyl alcohols, isatoic anhydride and primary amines mediated by I_2/K_2CO_3 in water: a new and green approach for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones

Seyedeh Bahareh Azimi, Javad Azizian*

Department of Chemistry, Science and Research Branch, Islamic Azad University, P. O. Box 19395-1775, Tehran, Iran

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Benzyl alcohols
Iodine
Oxidation
2,3-Dihydroquinazolin-4(1*H*)-ones (DHQZs)
Green chemistry

ABSTRACT

An efficient synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones proceeding *via* a three-component reaction between benzyl alcohols, isatoic anhydride and primary amines in the presence of iodine and potassium carbonate is reported. This protocol allows the straightforward preparation of the titled products using readily available benzyl alcohols instead of unstable aldehydes under mild oxidative conditions.

Green chemistry concerns the design of environmentally friendly products and chemical processes while minimizing the usage and generation of hazardous substances. Organic solvents are a key factor in environmental pollution and many are carcinogenic and toxic making reactions which do not require the use of organic solvents desirable. Water is an alternative solvent for many chemical reactions, possessing desirable properties such as ready availability, chemical stability, nontoxicity, recyclability and easy handling.[1] Moreover, in many reactions, water has been shown to significantly enhance the reaction rate in comparison to organic solvents due to hydrogen bonding, hydrophobic effect, high heat capacity, high cohesive energy density.[2]

2,3-Dihydroquinazolin-4(1*H*)-ones (DHQZs) are *N*-heterocycles that are of notable interest in medicinal chemistry and have a wide range of biological and pharmaceutical properties such as antibiotic,[3a] antiviral,[3b] antitumor,[3c,d] antihistamine,[3e] anti-inflamatory,[3f,g] cytotoxic,[3c] vasodilatory,[3h] anticonvulsant,[3i] antispermatogenic,[3d] antihypertensive,[3j] anti-osteoporosis,[3h] analgesic,[3i] and antidefibrillatory activities.[3l] Fenquizone, metolazone, evodiamine and aquamox are examples of clinically significant DHQZ medications (Figure 1).

Accordingly, several synthetic methods have been developed for the preparation of DHQZs. The most widely used approaches for the synthesis of these compounds include the condensation of anthranilamide with aldehydes or ketones or the three-component reaction between isatoic anhydride, amines and aldehydes using catalysts such as β-cyclodextrin,[4] montmorillonite K-10,[5] Amberlyst-15,[6] molecular iodine,[7] methylimidazolium tetrafluoroborate ([bmim]BF_4),[8] silica sulfuric acid,[9] 1-butyl-3-cyanuric chloride,[10] zinc(II) perfluorooctanoate [$Zn(PFO)_2$],[11] $KAl(SO_4)_2$•$12H_2O$,[12] Al/Al_2O_3 nanocatalyst,[13] $Al(H_2PO_4)_3$,[14] MCM-41-SO_3H,[15] and gallium(III) triflate.[16]

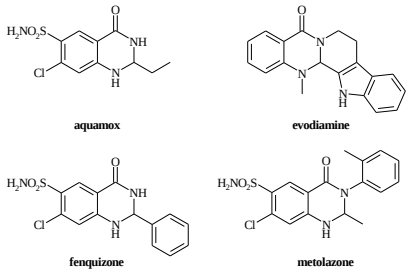


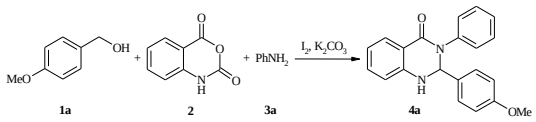
Figure 1

However, some of these procedures have noticeable disadvantages such as long reaction times, harsh reaction conditions, low yields, and use of toxic and expensive catalysts or media. In addition, in some of cases the utilized aldehydes are unstable, oxidizable, volatile or capable of hydrolysis or polymerization. Therefore, the development a novel and efficient approach for the preparation of 2,3-dihydroquinazolin-4(1*H*)-ones in which the aldehydes are generated *in situ* is desirable.

* Corresponding author. Tel./fax: +98(21)44580762.
E-mail address: j.azizian13@gmail.com (J. Azizian).

Adib and coworkers have reported a novel oxidative reaction between isatoic anhydride, amines and benzyl halides under Kornblum oxidation conditions. In this reaction the benzyl halides were oxidized to required aldehydes, however this protocol led to the synthesis of 4(3*H*)-quinazolinones.[17]

Herein, we describe a convenient and straightforward route for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones using benzyl alcohols instead of aldehydes. Thus, treatment of 4-methoxybenzyl alcohol **1a** with iodine and potassium carbonate led to 4-methoxybenzaldehyde. Subsequently, the 2-amino-*N*-phenylbenzamide which was generated from nucleophilic addition of aniline **3a** onto isatoic anhydride **2** was condensed with the *in situ* prepared aldehyde to produce **4a**.



1a 2 3a 4a

Scheme 1

Table 1. Optimization for the oxidative synthesis of **4a**

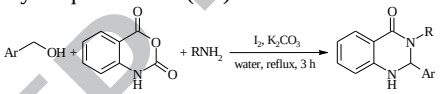
Entry	Solvent	I_2 (eq.) / K_2CO_3 (eq.)	Time (h)	Yield (%)
1	MeCN	0.2 / 1.0	10	Trace
2	MeCN	0.5 / 1.0	10	10
3	MeCN	1.0 / 1.0	10	25
4	Toluene	1.0 / 1.0	10	Trace
5	DMSO	0.5 / 1.0	10	26
6	DMSO	1.0 / 1.0	10	65
7	Dioxane	1.0 / 1.0	10	46
8	DCE	1.0 / 1.0	10	13
9	^{t}BuOH	1.0 / 1.0	10	53
10	EtOAc	1.0 / 1.0	10	48
11	Water	0.5 / 1.0	10	43
12	Water	1.0 / 1.0	3	91

The reaction was carried out at reflux in several solvents including acetonitrile, toluene, dimethyl sulfoxide, dioxane, 1,2-dichloroethane (DCE), *tert*-butanol, ethyl acetate and water using various amounts of iodine (Table 1). The maximum yield and shortest reaction time was obtained in water in the presence of equimolar iodine and potassium carbonate (entry 12). In addition to K_2CO_3, several bases such as Et_3N, DBU, pyridine, NaOH and ^{t}BuOK were also examined. Inorganic bases were shown to give better results, and K_2CO_3 was chosen due to the high yield of desired product and relatively lower cost. The reaction did not proceed cleanly in the absence of base.

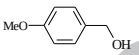
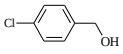
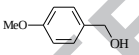
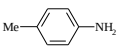
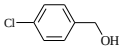
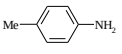
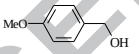
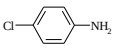
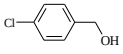
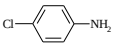
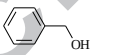
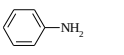
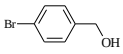
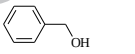
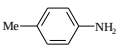
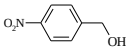
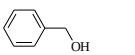
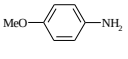
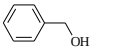
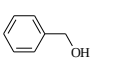
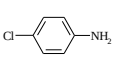
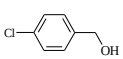
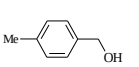
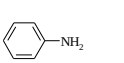
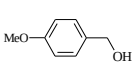
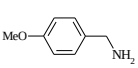
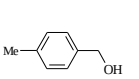
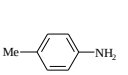
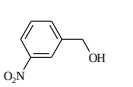
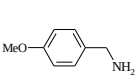
To demonstrate the generality of this strategy, various primary amines and benzyl alcohols were examined. All reactions proceeded to completion within 3 hours. ^{1}H NMR analysis of the reaction mixtures clearly indicated formation of the desired DHQZs **4a–r** in excellent yields (Table 2).

The structures were characterized by melting point determination and from ^{1}H and ^{13}C NMR spectral data.[18]

Table 2. Direct synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones **4a–r** under oxidative conditions[a]



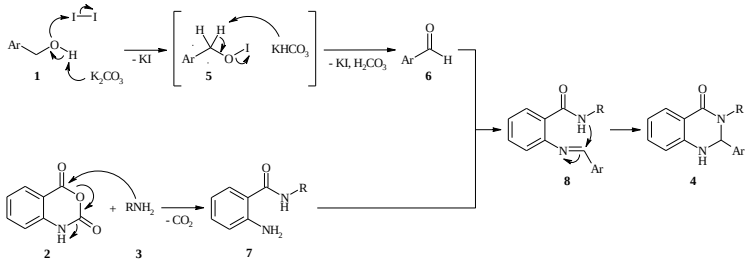
1 2 3 4

Product	Alcohol (**1**)	Amine (**3**)	Yield (%)[b]	Product	Alcohol (**1**)	Amine (**3**)	Yield (%)[b]
4a			91[19b]	**4j**			92[16]
4b			90[19b]	**4k**			93[19a]
4c			92[19b]	**4l**			93[19c]
4d			92[16]	**4m**			92[19a]
4e			92[11]	**4n**			94[11]
4f			90[11]	**4o**			93[19d]
4g			93[9]	**4p**			91[19e]
4h			91[19a]	**4q**			90[19e]
4i			93[19b]	**4r**			92[19e]

[a] Reaction conditions: 4-methoxy benzyl alcohol (1 mmol), isatoic anhydride (1 mmol), aniline (1 mmol), I_2 (1 mmol), K_2CO_3 (1 mmol), water (5 mL), reflux, 3 h. [b] Isolated yield.

Formation of 2,3-dihydroquinazolin-4(1*H*)-ones could be rationalized *via* a plausible mechanism (Scheme 2). Treatment of benzyl alcohol with iodine in the presence of K_2CO_3 leads to the formation of intermediate **5** and potassium bicarbonate. This intermediate undergoes elimination of H and I to form the corresponding aldehyde **6**. Next, the aldehyde is condensed with substituted anthranilamide **7,** generated from nucleophilic addition of amine **3** onto isatoic anhydride **2**, to give the imine intermediate **8**, which undergoes cyclization to afford the isolated 2,3-dihydroquinazolin-4(1*H*)-ones **4**. This mechanism is in agreement with achieving the best result in water, which can be explained by better polarizability of molecular iodine in water as a polar solvent. The relatively better result in DMSO (entry 6: 65%), dioxane (entry 7: 46%), *tert*-butanol (entry 9: 53%) and ethyl acetate (entry 10: 48%) in comparison with other nonpolar solvents, may also be illustrated by the term of polarizability (Table 1). In addition, the produced KI and H_2CO_3 are highly soluble in water; based on Le Châtelier's principle, this favors the

desired aldehyde **6**. However, the three-component reaction between aldehydes, amines and isatoic anhydride have been reported in various solvents.[5–16]



Scheme 2. Plausible reaction mechanism

In conclusion, we have developed a new, efficient and green approach for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones of potential synthetic and pharmacological interest using a one-pot, three-component reaction between benzyl alcohols, isatoic anhydride and primary amines. Benzyl alcohols were successfully oxidized *in situ* using an environmentally friendly and inexpensive system (I_2/K_2CO_3). Use of stable benzyl alcohols in place of aldehydes, ease of experimental procedure, relatively short reaction times and excellent yields are the main advantages of this reaction. To the best of our knowledge, this is the first report on the use of benzyl alcohols instead of aldehydes for the production of DHQZs. We believe that the success in this oxidative process could open the door to the design of diverse reactions and the generation of interesting organic compounds in mild and green oxidative media.

Acknowledgements

We wish to express our gratitude to the research council of Islamic Azad University, Tehran Science and Research Branch.

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18. **General Procedure for the Preparation of Compounds 4:** A mixture of 4-methoxybenzyl alcohol (0.138 g, 1 mmol), I_2 (0.254 g, 1 mmol), K_2CO_3 (0.138 g, 1 mmol), isatoic anhydride (0.163 g, 1 mmol) and aniline (0.093 g, 1 mmol) in water (5 mL) was stirred for 3 h at reflux. After reaction completion, the mixture was cooled to room temperature and stirred for 1 h. The resulting precipitate was filtered, washed with water (3 × 3 mL), and purified by recrystallization from ethanol to give **4a** as a white solid. *2,3-Dihydro-2-(4-methoxyphenyl)-3-phenylquinazolin-4(1H)-one* (**4a**) Yield: 0.30 g, 91%; m.p = 205–206 ºC. ^{1}H NMR (300 MHz, DMSO–d_6): δ = 3.67 (3 H, s, OCH_3), 6.22 (1 H, br s, CH), 6.71 (1 H, t, *J* = 7.7 Hz, CH), 6.76 (1 H, d, *J* = 7.9 Hz, CH), 6.84 (2 H, d, *J* = 8.5 Hz, 2 CH), 7.17 (1 H, t, *J* = 7.1 Hz, 1 CH), 7.23–7.34 (7 H, m, 7 CH), 7.55 (1 H, br s, NH), 7.73 (1 H, d, *J* = 7.9 Hz, CH). ^{13}C NMR (75 MHz, DMSO–d_6): δ = 55.0, 72.3, 113.7, 114.8, 115.3, 117.4, 126.0, 126.3, 127.9, 128.6, 128.7, 132.6, 133.7, 140.8, 146.7, 159.5, 162.3. *3-(4-Methoxybenzyl)-2,3-dihydro-2-(4-methoxyphenyl)quinazolin-4(1H)-one* (**4q**) Yield: 0.34 g, 90%; m.p = 160–161 ºC. ^{1}H NMR (300 MHz, DMSO–d_6): δ = 3.63 (1 H, d, $^2J_{HH}$ = 15.2 Hz, CH), 3.74 (3 H, s, OCH_3), 3.76 (3H, s, OCH_3), 5.42 (1 H, d, $^2J_{HH}$ = 15.2 Hz, CH), 6.18 (1 H, br s, CH), 6.63 (1 H, d, *J* = 8.0 Hz, CH), 6.87–6.92 (5 H, m, CH), 7.17 (2 H, d, *J* = 8.4 Hz, CH), 7.23 (1 H, d, *J* = 7.9 Hz, CH), 7.26 (2 H, d, *J* = 8.3 Hz, CH), 7.61 (1 H, br s, NH), 8.04 (1 H, d, *J* = 8.0 Hz, CH). ^{13}C NMR (75 MHz, DMSO–d_6): δ = 46.6, 55.4, 55.6, 71.8, 113.8, 114.3, 115.7, 118.7, 127.1, 129.0, 129.1, 129.7, 131.4, 133.6, 144.9, 157.3, 160.2, 162.5.
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