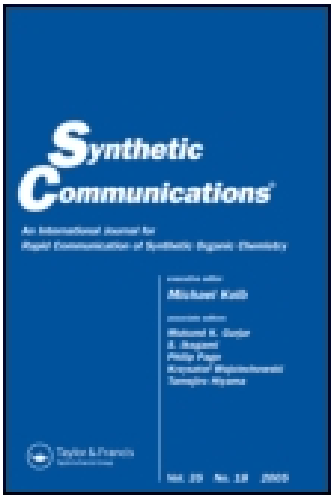

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Facile and Efficient Oxidation of Quinazolines into Quinazolin-4(3H)-ones by Peracetic Acid

Jian-Wen Jin [a], Lin Zhang [a], Guang-Rong Meng [a], Jian-Hua Zhu [b] & Qian Zhang [a]

[a] Department of Medicinal Chemistry, School of Pharmacy, Fudan University, Shanghai, China

[b] Key Laboratory of Smart Drug Delivery, Ministry of Education, Fudan University, Shanghai, China

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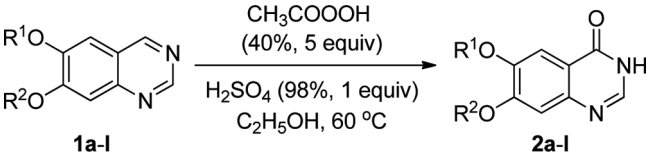
FACILE AND EFFICIENT OXIDATION OF QUINAZOLINES INTO QUINAZOLIN-4(3*H*)-ONES BY PERACETIC ACID

Jian-Wen Jin,[1] Lin Zhang,[1] Guang-Rong Meng,[1] Jian-Hua Zhu,[2] and Qian Zhang[1]

[1]*Department of Medicinal Chemistry, School of Pharmacy, Fudan University, Shanghai, China*
[2]*Key Laboratory of Smart Drug Delivery, Ministry of Education, Fudan University, Shanghai, China*

GRAPHICAL ABSTRACT



Abstract *A new approach to synthesize quinazoline-4(3*H*)-ones was achieved by oxidation of quinazolines using peracetic acid, which possesses some advantages of economic reagents, simplified operation, high efficiency, and environmental friendliness. Application of this method allowed us to synthesize a series of quinazolin-4(3*H*)-ones with different substituents at 6 and 7 positions in good to excellent yields, including the key intermediates of tyrosine kinase inhibitors such as PD153035, Erlotinib, and Gefitinib.*

[Supplementary materials are available for this article. Go to the publisher's online edition of Synthetic Communications® *for the following free supplemental resource(s): Full experimental and spectral details.]*

Keywords 4-Anilinoquinazolines; oxidation; peracetic acid; quinazolin-4(3*H*)-ones

INTRODUCTION

Quinazoline-4(3*H*)-one is one of the most important heterocycles that can be found in a number of active pharmaceutical ingredients with a wide spectrum of bioactivities. Some examples include afloqualone (sedative and muscle relaxant),[1] methaqualone (sedative hypnotics),[2] halofuginone (coccidiostat in veterinary medicine),[3] and diproqualone (anti-inflammatory agent).[4] In particular, quinazoline-4(3*H*)-ones are the key intermediates for synthesizing 4-anilinoquinazolines, a class of compounds with strong inhibitory activity on receptor tyrosine kinases (RTKs),

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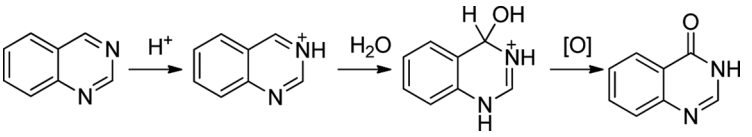
Address correspondence to Qian Zhang, Department of Medicinal Chemistry, School of Pharmacy, Fudan University, Shanghai 201203, China. E-mail: zhangqian511@shmu.edu.cn



Scheme 1. Proposed mechanism for quinazoline oxidation.

especially EGFR and VEGFR. Up to now, several 4-anilinoquinazolines including gefitinib,[5] erlotinib,[6] lapatinib,[7] vandetanib,[8] and afatinib[9] have been approved by the U.S. Food and Drug Administration and achieved significant clinical benefit for non-small-cell lung cancer (NSCLC) patients.

The most common synthetic procedure for the preparation of quinazolin-4(3*H*)-ones used in the literature involved the condensation of anthranilic acid or its derivatives with formamidine.[10] Beyond that, there were a few studies focusing on the oxidation of quinazoline by introducing a hydroxyl-group at 4-position on account of the anomalous behavior of quinazoline. Under acidic conditions, one molecule of water attacks the carbon at the 4-position of quinazolin-3-ium to form a nonaromatic cation, which can then be oxidized by H_2O_2/CrO_3,[11] Co diacetylacetonate,[12] or quinaldine 4-oxidase[13] to afford the 4-oxo partial structure, that is, quinazolin-4(3*H*)-one (Scheme 1). However, these oxidation reactions have not been widely used because of poor yield, toxic reagents, or the narrow application scope of the oxidant.

Recently, Marzaro and coworkers developed a method to prepare quinazolin-4(3*H*)-one using ceric ammonium nitrate (CAN) as oxidant in good yields, along with a concise strategy in synthesizing quinazoline ring via ethyl phenylcarbamate.[14,15] However, CAN is relatively expensive and not suitable for pharmaceutical manufacturing because of the low threshold of residual tolerance in active pharmaceutical gradients.

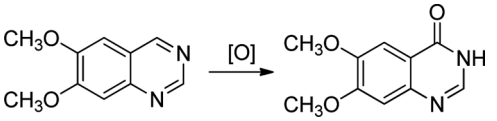
Herein we report another efficient method, employing peracetic acid to oxidize qunazolines into quinazolin-4(3*H*)-ones with a moderate or relatively good yield. The oxidant is more economical and environmentally friendly, and the processing is simple and nonlaborious.

RESULTS AND DISCUSSION

Initially, 6,7-dimethoxylquinazoline (**1a**) was selected as the reference compound. To avoid the metal-catalyzed reagent, H_2O_2 was used as oxidant at first. As listed in Table 1, when the solvent was H_2O or diluted H_2SO_4 (20%), no oxidation product could be detected from the reaction (entries 1 and 2). When the solvent was changed to H_2O/AcOH or EtOH/AcOH, the reaction afforded a small quantity of the desired compound in 15% and 10% yields, respectively (entries 3 and 4). Although the reactions had a poor yield, it suggested that the solvent AcOH should play an essential role in the oxidation of **1a**. We hypothesized that the solvent AcOH, when stirred with H_2O_2, could be converted into AcOOH, which acts as an oxidant in the reaction.

Therefore, we tested the possiblity of using peracetic acid (40%) as an oxidant for the reaction, and H_2SO_4 (1 equiv, 98%) was added as an acidic catalyst. The

Table 1. Optimization of the oxidation conditions for 6,7-dimethoxylquinazolin-4(3*H*)-one (**2a**)



1a **2a**

Entry	Oxidant (equiv)	Solvent	Temp. (°C)	Time (h)	Yield (%)[a]
1	H_2O_2 (5–10)	H_2O	50	24	0
2	H_2O_2 (5–10)	H_2O/H_2SO_4	50	24	0
3	H_2O_2 (5)	H_2O/AcOH	rt	48	15
4	H_2O_2 (5)	C_2H_5OH/AcOH	rt	48	10
5	CH_3COOOH (5)	CH_3COCH_3/H_2SO_4	55	24	0
6	CH_3COOOH (5)	CH_3CN/H_2SO_4	80	24	12
7	CH_3COOOH (5)	THF/H_2SO_4	65	4	45
8	CH_3COOOH (5)	CH_3OH/H_2SO_4	60	4	82
9	CH_3COOOH (5)	C_2H_5OH/H_2SO_4	60	4	83

[a]Isolated yield.

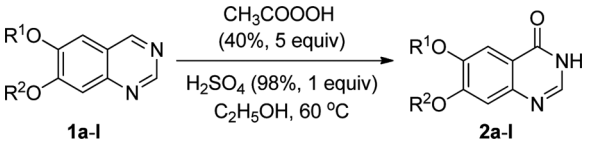
production yield of the reactions varied dramatically because of the solubility of **1a** in different reaction solvents. The mixture of **1a** (100 mg, 0.52 mmol), peracetic acid (40%, 0.5 mL, 2.60 mmol), and H_2SO_4 (98%, 0.03 mL, 0.56 mmol) in 20 mL of acetone or acetonitrile was refluxed for 24 h to afford the product with only 0% and 12% yields, respectively (entries 5 and 6). The yield could be improved moderately to 45% in tetrahydrofuran (THF) (entry 7), and **2a** was obtained with significant good yield (82–83%) in CH_3OH or in CH_3CH_2OH after the reaction was stirred at 60 °C for 4 h (entries 8 and 9). The structure of **2a** was consistent with the spectra and the published chemical and physical data.[14]

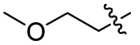
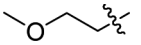
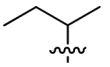
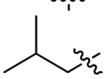
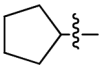
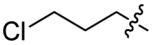
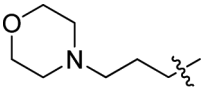
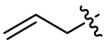
Subsequently, we conducted the oxidation of a series of quinazoline derivatives with hydroxyl or alkoxy at 6 and 7 positions under the optimized conditions (Table 2). All quinazolines were smoothly oxidized to give the desired quinazoline-4(3*H*)-ones in good to excellent yields. The quantitative yields were almost achieved as the substrates possessing hydroxyl group at either C6 or C7 position owing to its strong electron-donation activity (entries 5 and 6). It must be pointed out that this oxidant system is selective for quinazoline ring oxidation and has no effect on hydroxyl or any other unsaturated bonds (entries 5, 6, and 12). Additionally, the oxidation of unsubstituted quinazoline was similar to that of 6,7-dialkyl substrates, providing quinazolin-4(3*H*)-one (**2m**) in 94% under the same condition with stirring over 3 h.

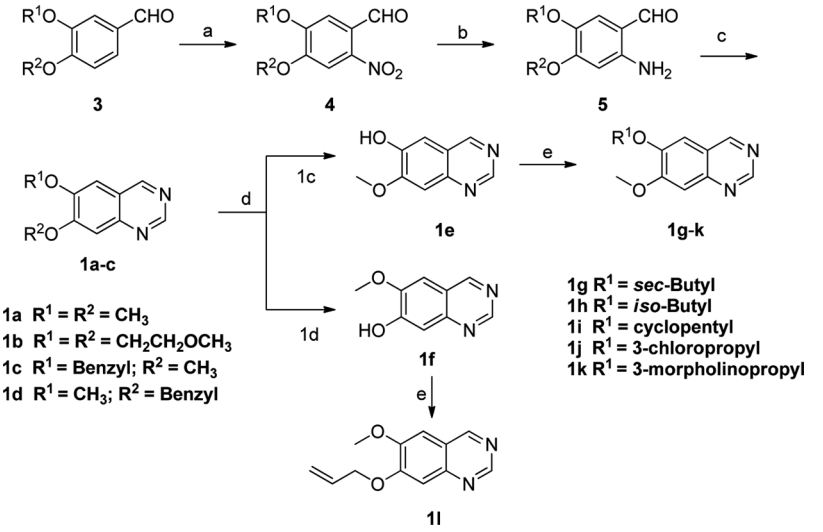
Compounds **2a, 2b**, and **2k** are the synthons of PD153035, erlotinib, and gefitinib respectively. These compounds could be converted to their target 4-anilinoquinazolines via chlorination by $POCl_3$ and a followed condensation step with corresponding substituted anilines according to the reported synthetic methods.[16]

Quinazoline was purchased from a commercial source and the substituted quinazolines (**1a–l**) mentioned in Tables 1 and 2 were prepared by the procedure shown in Scheme 2. The nitration of 3,4-dialkoxylbenzaldehydes (**3**) with 75% HNO_3

Table 2. Oxidation of quinazoline derivatives into quinazolin-4(3*H*)-ones



Entry	R^1	R^2	Product	Time (h)	Isolated yield (%)
1	CH_3	CH_3	**2a**	4	83
2			**2b**	4	93
3	Bn	CH_3	**2c**	10	88
4	CH_3	Bn	**2d**	3	95
5	CH_3	H	**2e**	12	96
6	H	CH_3	**2f**	12	98
7		CH_3	**2g**	6	90
8		CH_3	**2h**	8	89
9		CH_3	**2i**	8	76
10		CH_3	**2j**	8	85
11		CH_3	**2k**	12	85
12	CH_3		**2l**	4	90



Scheme 2. Synthetic route for quinazolines (**1a–l**). Reagents and conditions: (a) 75% HNO_3, 71–92%; (b) Fe/HCl, C_2H_5OH, 67–84%; (c) formamidine acetate, C_2H_5OH, reflux, 82–90%; (d) H_2, Pd-C, 91–99%; and (e) RBr, K_2CO_3, DMF, 40–99%.

afforded **4**, which were then reduced by Fe/HCl to produce *ortho*-aminobenzaldehydes (**5**). Quinazoline rings were constructed through the cyclization of **5** with formamidine acetate to afford **1a–c** in good yields. The debenzylation of **1c** and **1d** produced 6-hydroxy-7-methoxyquinazoline (**1e**) and 7-hydroxy-6-methoxyquinazoline (**1f**). Compounds **1g–k** and **1l** were finally obtained by etherification of the hydroxy group of **1e** or **1f** with corresponding alkyl bromines.

CONCLUSION

In summary, we reported a novel method for the oxidation of quinazolines to quinazoline-4(3*H*)-ones under metal-free conditions. The method works well for a number of quinazoline substrates with advantages of economic reagents, excellent selectivity, good efficiency, and environmental friendliness. This method has the potential to be widely used in the preparation of quinazoline derivatives not only for quick SAR studies but also for pharmaceutical manufacturing.

EXPERIMENTAL

All chemicals and solvents were purchased from commercial sources and were used without further purification unless otherwise noted. Column chromatography (CC) was carried out on silica gel (300–400 mesh, Qindao Ocean Chemical Company, China), and thin-layer chromatography (TLC) analyses were carried out on silica gel GF254 glass plates (2.5 cm × 10 cm with 250-μm layer, Qindao Ocean Chemical Company, China). Melting points of compounds were measured on a SGW X-4 melting-point apparatus and uncorrected. Nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker-DPX (400-MHz) spectrometer. Electrospray ionization–mass spectrometry (ESI-MS) spectra were recorded on a Agilent G1946D mass spectrometer. High-resolution mass spectra (HRMS) were obtained by using a Bruker Daltonics APEXIII 7.0 TESLA FTMS spectrometer (HRESI-MS).

General Procedure for Oxidation of Quinazolines into Quinazoline-4(*3H*)-ones (2a as Example)

To a solution of 6,7-dimethoxyquinazoline **1a** (200.0 mg, 1.05 mmol) in ethanol (20 mL) were added 40% peracetic acid (1.0 mL, 5.26 mmol) and 0.01 mL sulfuric acid (1.8 mmol). After the reaction was stirred at 60 °C for 4–12 h (see Table 2) and then cooled to room temperature, excess sodium bisulfite (541.8 mg, 5.26 mmol) was added to get rid of the peroxide. The solid was filtered off after stirring for 20 min, and the filtrate was concentrated under reduced pressure to give the crude product, which was washed by ethanol and petroleum ether to give **2a** as a light yellow solid (179.7 mg, 83%), mp > 300 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 12.19 (br s, 1H, -NH), 7.96 (s, 1H, 2-H), 7.41 (s, 1H, 8-H), 7.11 (s, 1H, 5-H), 3.88 (s, 3H, $-OCH_3$), 3.84 (s, 3H, $-OCH_3$). ESI-MS: m/z (%) = 207 (100) [MH^+]. ESI-HRMS: m/z calcd. For $C_{10}H_{11}N_2O_3$ [MH^+]: 207.07642; found: 207.07613.

Supplementary Information

Full experimental detail, characterization data, and copies of ^{1}H and MS (ESI) spectra can be found via the Supplementary Content section of this article's Web page.

ACKNOWLEDGMENTS

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