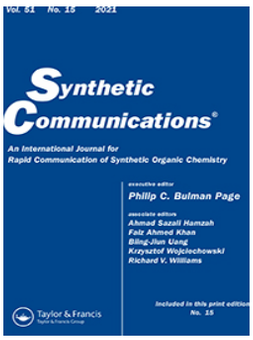

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Eco-friendly H_2O_2 oxidation of 1,2-dihydroquinazoline-3-oxides to quinazoline-3-oxides

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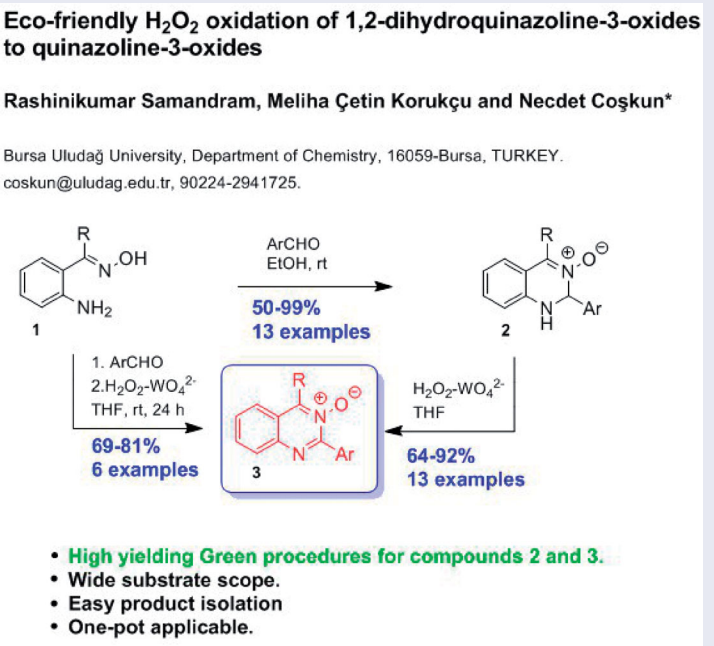
ABSTRACT

2-Aminobenzaldehyde, 1-(2-aminophenyl)ethanone, and 2-aminophenyl phenyl methanone oximes **1** were reacted with aromatic aldehydes to give the corresponding 1,2-dihydroquinazoline-3-oxides **2**. The latter were converted in high yields to a series of quinazoline-3-oxides **3** using an environmentally benign H_2O_2-tungstate oxidant system at room temperature. A high yielding one-pot procedure was also developed for the synthesis of compounds **3**.

GRAPHICAL ABSTRACT



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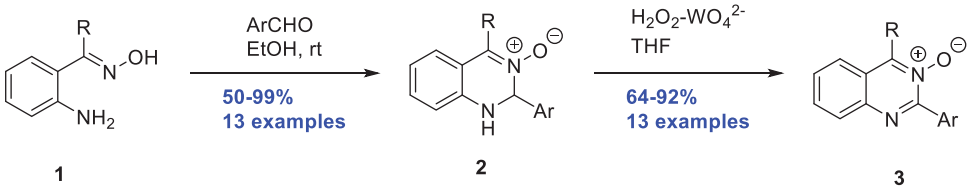
Introduction

The quinazoline ring system is an important structural unit frequently encountered in medicinal chemistry as well as in organic synthesis.[1–3] Many alkaloids containing quinazoline skeletons are known.[4–6] They constitute an important class of compounds with anticonvulsant, antibacterial, antidiabetic, and anticancer activities.[1,7–10] Many methods for the synthesis of quinazoline derivatives are known.[11–15] In an earlier study, we have reported the synthesis of quinazoline-1-ols and their ring expansion upon carbamoylation with aryl isocyanates.[16] Later on, 2-substituted-1,2,3,4-tetrahydroquinazolines were oxidized using the H_2O_2-tungstate system to give regioselectively the corresponding quinazoline-1-oxides.[17] In the same report, the photochemical and thermal behavior of the latter was discussed in detail. Afterward, a significant number of studies on the synthesis of quinazoline-3-oxides have appeared in the literature.[18–21] According to one approach,[18] 1,2-dihydroquinazoline-3-oxides were converted to 4-methyl-2-substituted quinazolines by visible light irradiation. It was assumed a light-induced water elimination from the dihydroquinazoline-3-oxide to give the corresponding quinazoline. The water elimination in the case of 4-methyl-2-(4-nitrophenyl)-1,2-dihydroquinazoline-3-oxide was reported to be unsuccessful. A series of 2,4-disubstituted quinazoline-3-oxides were synthesized by oxidation of the corresponding 1,2-dihydroquinazoline-3-oxides using activated MnO_2.[22] This novel approach is simple and convenient and provides a series of 2,4-disubstituted quinazoline-3-oxides. Hydrogen peroxide is a widely used green oxidant for many transformations.[23] Oxidations of various organic compounds with aqueous H_2O_2 in the presence of catalytic amounts of pharmacologically harmless tungstates are described in the literature.[24]

In this work, the synthesis of 1,2-dihydroquinazoline-3-oxides and their eco-friendly transformation into quinazoline-3-oxides using H_2O_2-tungstate oxidant system is reported (Scheme 1).

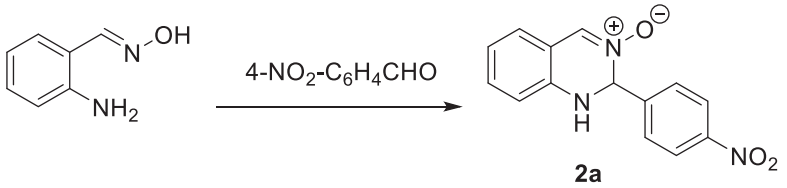
Results and discussion

As a continuation of our investigations on the reactions of cyclic nitrones like 3,4-dihydroisoquinoline-2-oxides[25] and 2,5-dihydro-1*H*-imidazole-3-oxides[26,27] and photochemical conversions of quinazoline-1-oxides[17] we needed a series of 4-unsubstituted-quinazoline-3-oxides **3a–j** to investigate their photochemical as well as thermal behaviors. To begin with, we have prepared first compounds **2a–j** from the reaction of amino oximes **1** with the corresponding aldehydes[18,28] (Scheme 1). The optimization



Scheme 1. The synthesis of 1,2-dihydroquinazoline- and quinazoline-3-oxides.

Table 1. Optimization of the reaction conditions for the synthesis of compounds **2**.



2a

Entry[a]	Solvent (cat)	Yield (%)
1	CH_2Cl_2 (AgOTf)	94
2	CH_2Cl_2	96
3	$CHCl_3$	96
4	Benzene	93
5	Toluene	94
6	MeOH/H_2O[b]	91
7	EtOH	97

[a]All reactions were performed in 20 mL of solvent using equivalent amounts of oxime 1 (1 mmol) and the corresponding aldehyde. The reaction mixtures were stirred at room temperature for 24 h. In the case of entry 1, 0.02 mol% AgOTf was used as a catalyst. [b]The solvent ratio is 1/1.

(Table 1) of the reaction conditions was conducted in the case of aminobenzaldehyde oxime and *p*-nitrobenzaldehyde.

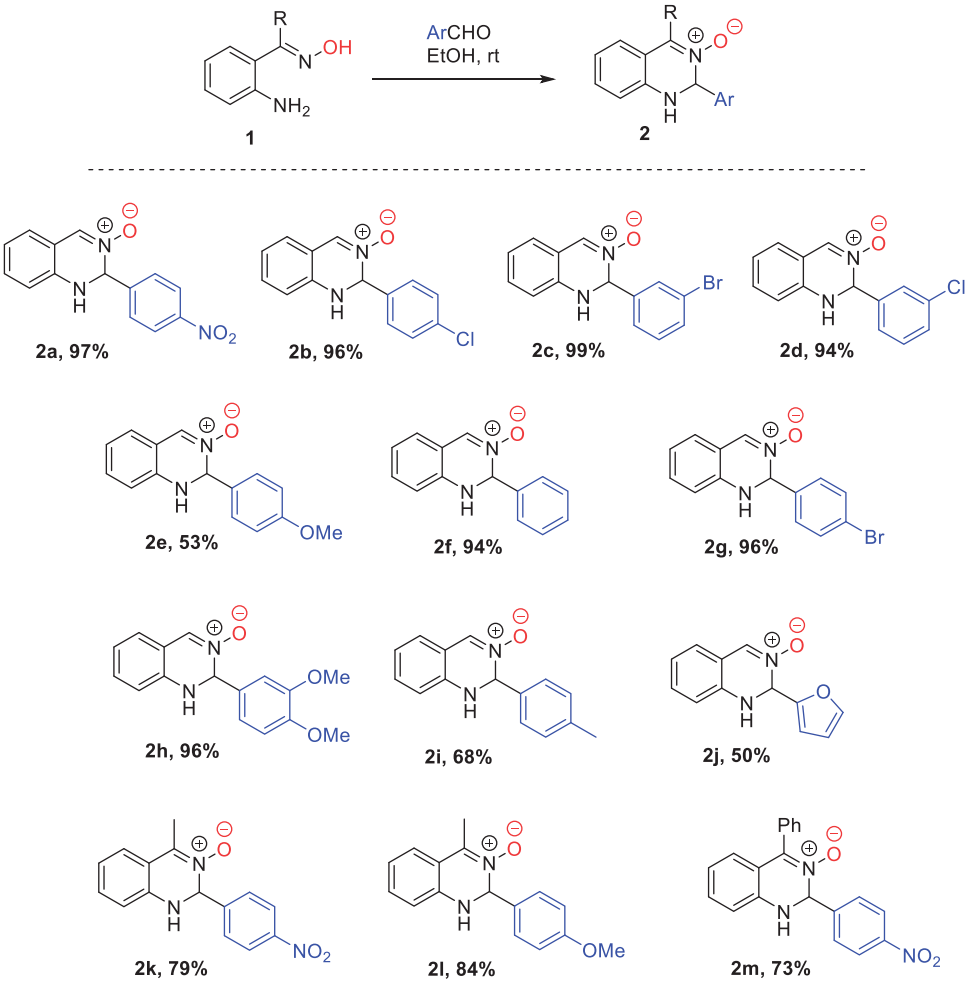
The reaction was first performed in CH_2Cl_2 at room temperature using AgOTf as a catalyst and the corresponding **2a** was obtained in 94% yield. The yield of the reaction in the same solvent was 96% when it was performed in the absence of the catalyst. Chloroform, benzene, and toluene were also good media for the conversion of **1** into **2a**. However, ethanol proved to be the best solvent for the reaction at room temperature.

Equimolar amounts of amino oxime **1** and aromatic aldehydes were dissolved in ethanol and stirred at room temperature for *ca* 24 h. In all cases, except **2f** the products are precipitating and easily isolated by filtration. The precipitates were washed several times with warm hexane then dried under vacuum. The structures and the yields of compounds **2a–m** are presented in Table 2.

Compounds **2k–l** and **3k–l** are known,[18,22] however to the best of our knowledge a method for the synthesis and characterization data for **2a–j** and **3a–j** are not available in the literature. Therefore, we propose a simple high yielding procedure for the synthesis of compounds **2a–m** and their oxidation with H_2O_2-tungstate in THF to the synthetically important quinazoline-3-oxides **3a–m**. The newly prepared compounds were characterized by spectral as well as analytical methods.

Compound **2a** was subjected to oxidation with AgOTf, MnO_2, and $KMnO_4$ (Table 3, entries 1–3) in DMSO, and the reaction product **3a** was formed only in the cases of entries 2–3 in low yields. No product formation was observed in the case of AgOTf (Table 3, entry 1). The use of MnO_2 and $KMnO_4$ without solvent did not produce the expected **3a** (Table 3, entries 4–5). The use of $KMnO_4/MnO_2$ mixtures in DMSO and DMF or without solvent produced the quinazoline-3-oxide in moderate yields (Table 3, entries 6–8). The oxidation of **2a** with the H_2O_2-Na_2WO_4 in THF-H_2O and THF provided the formation of product **3a** in high yields at room

Table 2. Structures and yields[a,b] of 1,2-dihydroquinazoline-3-oxides **2a–m**.

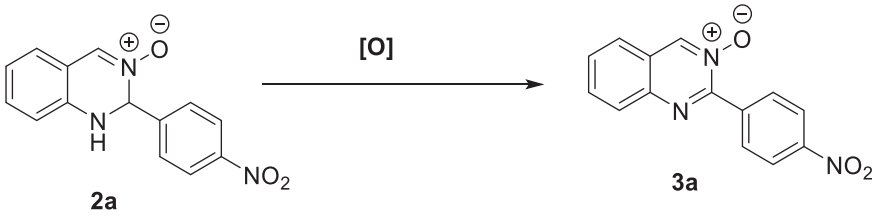


[a]Isolated yields: [b]*Reaction conditions*: amino oxime **1** and aldehyde each 1 mmol, dissolved in EtOH (20 mL) were stirred at room temperature for 24 h (for compounds **2k–m**, 47 h).

temperature (Table 3, entries 9–10). The use of dry THF proved to be the better choice as a reaction solvent.

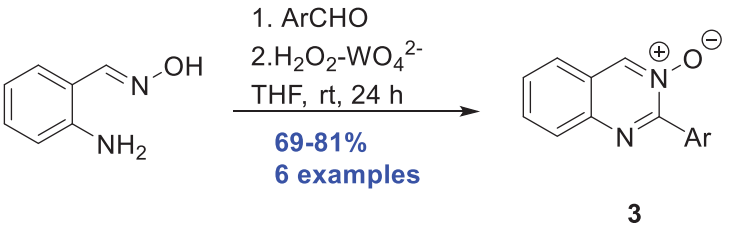
Compounds **2a–m** were subjected to oxidation under the optimized conditions to give compounds **3a–m** in good to high yields (Table 4). The structures of compounds **3** were elucidated by elemental analysis, ^{1}H and ^{13}C NMR data. 4-Methyl-2-(4-nitrophenyl)-1,2-dihydroquinazoline-3-oxide **2k** was identical with the one obtained by irradiation of **1k** in acetonitrile in the presence of $Ru(bpy)_3Cl_2$.[18] The first 4-unsubstituted quinazoline-3-oxide **3b** was obtained in our lab as a by-product from the oxidation of the corresponding tetrahydroquinazoline.[17] The physical and spectral data for **3b** obtained by oxidation of **2b** with H_2O_2-tungstate were the same as for our previously reported one.

Table 3. Optimization of the reaction conditions for the synthesis of compounds **3**.



Entry	Solvent	Oxidizing agent	Time (h)	Temp (°C)	Yield (%)[a]
1	DMSO[b]	AgOTf[c]	8	90	
2	DMSO[b]	MnO_2[c]	23	130	52
3	DMSO[b]	$KMnO_4$[c]	22	130	43
4		MnO_2[c]	8	rt	
5		$KMnO_4$[c]	5	rt	
6	DMSO[b]	$KMnO_4/MnO_2$[d]	23	100	49
7	DMF[b]	$KMnO_4/MnO_2$[d]	20	100	47
8		$KMnO_4/MnO_2$[d]	21	rt	52
9	THF/H_2O[f]	H_2O_2-Na_2WO_4[e]	24	rt	74
10	THF[b]	H_2O_2-Na_2WO_4[e]	24	rt	92

[a]Isolated yields; [b]The reactions were performed in 4 mL of solvent with 1 mmol of **2a**; [c]1 mmol of the oxidizer was used; [d]The ratio is 0.3/0.7; [e] 4/0.05; [f]4 mL (1/1).



Scheme 2. One-pot synthesis of compounds **3b,c,e–g,i**.

One-pot procedure involving the short time stirring of the amino oxime and aldehyde mixture in THF and addition of the oxidizing system provided compounds **3b,c,e–g,i** with improved overall yields (Scheme 2, Table 4).

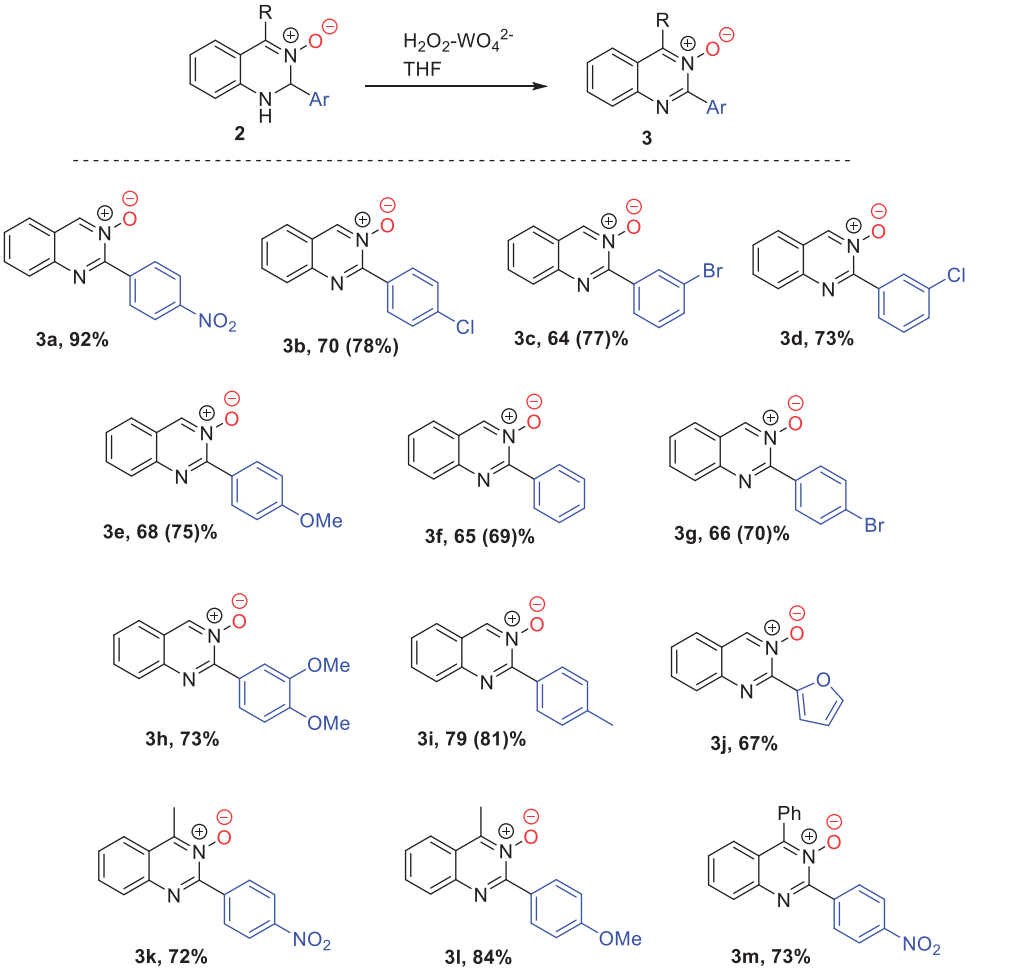
Experimental section

Materials and methods

Melting points were recorded on an Electrothermal Digital melting point apparatus. IR spectra were obtained using a JASCO FT-IR 6800 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker at 600, Jeol 500, and Agilent 400 MHz spectrometers. The elemental analyses were performed on TruSpec and EuroEA 3000 CHNS analyzers. The compounds prepared were dried in a vacuum oven at room temperature.

Column chromatography was performed by using 70–230 mesh (0.063–0.200 mm) silica gel and preparative TLC with silica gel 60 HF254 (90% <45 µm) by using technical

Table 4. Oxidation of 1,2-dihydroquinazoline-3-oxides[a,b] **2a–m** with H_2O_2-Na_2WO_4 in THF at rt.



[a]Isolated yields; The yields in the parenthesis are according to the one-pot procedure. [b]*Reaction conditions*: To the solution of compound **2** (1 mmol) in THF (4 mL), H_2O_2 (4 mmol, 35%, 0.389 g) and $Na_2WO_4.2H_2O$ (0.05 mmol, 0.017 g) were added and the mixture was stirred at room temperature (for compounds **3a–j** 20–24 h). For the compounds **3k–m** the reaction was performed at 60 °C (47 h).

grade solvents. All of the reagents used in this work were purchased from commercial suppliers and used without any further purifications.

General procedure for the preparation of compounds 2a–m

To a solution of amino oxime (1 mmol) in EtOH (20 mL) aldehyde (1 mmol) was added at room temperature and stirred for 24 h (for compounds **2k–m**, 47 h). The precipitating product was isolated by filtration through a sintered glass funnel and washed with warm hexane. In the case of **2f** the solvent was evaporated and the crude was treated with warm hexane. Recrystallization from acetonitrile provided yellow-colored crystals.

General procedure for the preparation of compounds 3a–m

To a solution of substrate **2a–m** (1 mmol) in THF (4 mL), H_2O_2 (4 mmol, 35%, 0.389 g) and $Na_2WO_4{\cdot}2H_2O$ (0.05 mmol, 0.017 g) were added and the mixture was stirred at room temperature for compounds **3a–j** (20–24 h). For the compounds **3k–m** the reaction was performed at 60 °C (47 h). After evaporation of the solvent, water was added (15 mL) and the mixture was basified with 10% NaOH. The mixture was extracted with chloroform (3 × 15 mL) and the combined extracts were dried over anhydrous Na_2SO_4, filtered. The residue after evaporation of the solvent was subjected to flash column chromatography using silica gel as an adsorbent and ethyl acetate-petroleum ether (gradually increasing the amount of ethyl acetate) as eluent mixture. The isolated products were recrystallized from acetonitrile.

One-pot procedure for the preparation of compounds 3a–m

To a solution of amino oxime **1** (1 mmol) in THF (4 mL) aldehyde (1 mmol) was added at room temperature and after an hour H_2O_2 (4 mmol, 35%, 0.389 g) and $Na_2WO_4{\cdot}2H_2O$ (0.05 mmol, 0.017 g) were added and the mixture was stirred for 24 h. The isolation procedure is the same for compounds **3** obtained according to the general procedure starting from isolated **2**.

Conclusion

Thus the developed methods provide the synthesis of 1,2-dihydroquinazoline, **2a–m** and quinazoline-3-oxides, **3a–m** in high yields at room temperature. The method for the synthesis of compound **2** involves the none photochemical, expensive metal complexes free condensation of compound **1** with the corresponding aldehydes. The ease of the product isolation, simply filtering the formed precipitate, is another advantage worth mentioning. Compounds **3** were prepared by oxidation of isolated **2** in high yields at room temperature using H_2O_2-tungstate system. Compounds **3** can also be obtained in improved overall yields and for shorter reaction times when the mixture of **1** and the aromatic aldehyde in THF is treated with the aforementioned oxidizing system.

Full experimental detail and ^{1}H and ^{13}C NMR spectra can be found via the "Supplementary Content" section of this article's webpage.'

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