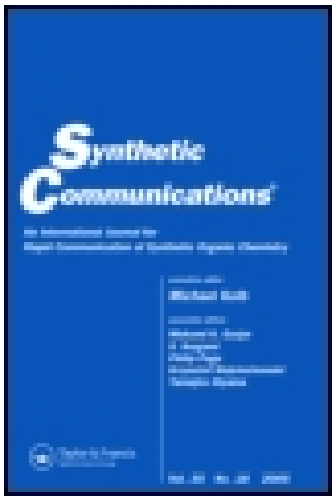

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Copper Catalyzed Synthesis of Valuable Heterocyclic Compounds Using a Tandem Oxidation Process Approach

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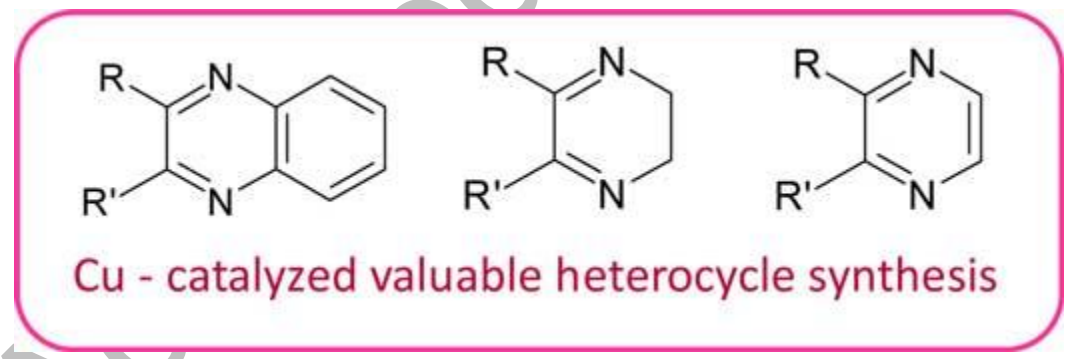
Abstract

The synthesis of quinoxalines via the tandem oxidation process using a copper acetate monohydrate/TEMPO oxidative system has been described. Using this approach, a series of quinoxaline derivatives were formed in high yields and short reaction times under microwave irradiation. The oxidative system was also extended to the selective synthesis of dihydropyrazines and pyrazines.



KEYWORDS: tandem oxidation process; quinoxalines; copper; microwave

INTRODUCTION

The tandem oxidation process (TOP) has developed into an innovative addition to synthetic organic chemistry as it is characterized by high yields and short reaction times.[1] This procedure consists of mixing an alcohol, nucleophile and oxidant in a one pot process, in which the alcohol is oxidized to the aldehyde which is immediately trapped by the nucleophile, leading to a variety of synthetically useful compounds.[2] The quinoxaline moiety is synonymous with TOP and continues to garner interest from synthetic chemists the world over due to its activity against pancreatic cancer[3] and malaria cell lines[4] as well as displaying exciting luminescence[5] and photoinduced DNA cleaving applications[6] to name but a few. The most common oxidative method to access these quinoxaline compounds, using the TOP, is through the use of transition metal catalysts such as manganese,[7] iron,[8] ruthenium,[9] palladium,[10] mercury[11] and titanium.[12] However, these methods suffer from cost, time and in some cases practicality limitations as elaborate metal catalysts are prepared using long and tedious procedures. As an example, our previous work using a titanium dioxide mediated system produced the desired quinoxalines in excellent yields although a stoichiometric quantity of metal catalyst was required.[12] Thus, we set our sights on developing a simple, transition metal based quinoxaline synthesis using the tandem oxidation process.

RESULTS AND DISCUSSION

We were particularly interested in a copper based system as previous research, towards the synthesis of quinoxalines, using this metal was carried out using highly specialized equipment with long reaction times although good yields were observed.[13] Recently, Kan

and co-workers, in their manuscript on the synthesis of indolizines, reported the use copper acetate monohydrate as a cheap and efficient oxidant.[14] They vehemently argue the merits of copper acetate monohydrate as an oxidant based on its price and ease of handling. In addition, Stahl and co-worker have reviewed the use of copper catalysts in combination with 2,2,6,6,-tetramethyl-piperidine-1-oxyl radical (TEMPO) for the selective oxidation of alcohols to their carbonyl derivatives in excellent yields.[15] However, an analysis of this review revealed that these systems used intricate copper complexes and required the addition of specific ligands and additives. Thus, we set about assembling a copper acetate monohydrate/TEMPO oxidative system under aerobic conditions by monitoring the test reaction between 2-hydroxyacetophenone and *o*-phenylenediamine. The results of this investigation into determining the optimum reaction conditions for the copper catalyzed quinoxaline synthesis are summarized in Table 1.

The copper acetate monohydrate/TEMPO system was initially evaluated using conventional heating and ultrasonic irradiation and, in both cases, satisfactory yields were observed (**Table 1, entries i – ii**). In an effort to improve the yields and decrease the reaction times, the remaining set of test reactions were conducted under microwave irradiation. The best result was observed using DMF as a solvent which produced the desired quinoxaline in an excellent isolated yield of 94% (**Table 1, entry v**) and the omission of either copper acetate monohydrate or TEMPO resulted in the formation of only trace amounts of product (**Table 1, entries vi – vii**). The exclusion of copper acetate monohydrate and TEMPO resulted in no product formation and only the starting

materials were detected (**Table 1, entry viii**). With the optimized procedure in hand, we explored the scope and limitations of the copper acetate monohydrate/TEMPO system using a diverse range of alcohols and nucleophiles (**Table 2**).

The second substrate that was analyzed was the aliphatic keto alcohol whose successor, the aliphatic keto aldehyde is especially difficult to isolate due to its "hyper-reactivity".[7] Under our copper acetate monohydrate/TEMPO conditions, the desired quinoxaline was isolated in a satisfactory yield of 63% (**Table 2, entry ii**) which was lower than expected. The decrease in yield was presumably due to the volatility of the intermediate keto-aldehyde at the elevated temperatures[10] and this was confirmed as an excellent yield of 88% was observed when the reaction was conducted at room temperature. The copper acetate monohydrate/TEMPO system was effective on a variety of alcohols and nucleophiles (**Table 2, entries iii – viii**) although a decrease in yield was observed in the case of bulkier substrates (**Table 2, entries vi – vii**).

Next, we turned our attention towards the synthesis of 2,3-diphenylpyrazine as it has been shown to display promising activity against a variety of cancer cell lines.[16] A retrosynthetic study revealed that the precursor to the pyrazine was the dihydropyrazine which was derived from benzil and ethylenediamine. Benzil, as expected, could be derived from benzoin using our copper acetate monohydrate/TEMPO system (**Scheme 1**). The retrosynthetic analysis revealed an interesting point as two valuable heterocyclic compounds were part of this synthetic approach (namely the dihydropyrazine *and* pyrazine). Dihydropyrazines and pyrazines are important moieties as they have found

applications such as pollinator sex pheromones,[17] antiviral applications[18] as well as alarm pheromones in ponerine ants.[19]

Previous research within the TOP mediated pyrazine synthesis has been divided into two main oxidative systems. The first system, commencing from the alcohol would result directly in the pyrazine being formed without the dihydropyrazine being detected and the second system, commencing from the alcohol, would result in the dihydropyrazine which would *then* require the addition of reagents to effect the aromatization. For example, Shinde and co-workers have reported a TOP mediated synthesis of pyrazines directly from the alcohol[20] (no dihydropyrazine in final mixture) while Taylor and co-workers have reported a TOP mediated pyrazine synthesis from the alcohol which initially formed the dihydropyrazine which subsequently aromatized when concentrated base/MeOH was added.[7] To the best of our knowledge, there has not been a TOP oxidative system devised which will selectively form the dihydropyrazine or the pyrazine (without the addition of further reagents) and, with this in mind, we set about the synthesis of the potential cancer antagonist, 2,3-diphenylpyrazine.

As the diphenylpyrazine compound was formed in excellent yield (**Table 2, entry viii**), we sought to effectively aromatize the ring. Firstly, the reaction time was simply doubled to determine if under prolonged microwave irradiation the desired pyrazine would form. However, even after 30 additional minutes of microwave irradiation the 2,3-diphenlpyrazine was not detected (**Table 3, entry ii**) and thus, we began to determine possible reagents to effectively aromatize the ring. In this case, elemental sulfur was

chosen to aromatize the ring as it is cheap, easy to handle and non-toxic.[21] Once again we carried out the coupling of benzoin and ethylenediamine in the presence of copper acetate monohydrate and TEMPO in DMF under microwave irradiation for 30 minutes, and to the crude mixture was added elemental sulfur and the mixture was irradiated for an additional 30 minutes. Under these conditions, the desired pyrazine was isolated in an excellent yield of 88% as well as minute amounts of the dihydropyrazine (**Table 3, entry iii**). Finally, a one pot synthesis of the pyrazine compound was verified by mixing benzoin, ethylenediamine, copper acetate monohydrate/TEMPO and elemental sulfur in DMF under microwave irradiation for 30 minutes and, to our delight, only the pyrazine derivative was isolated (**Table 3, entry iv**). Thus, by the addition (or exclusion) of elemental sulfur, two valuable heterocycles can be exclusively formed and in high yield in a one pot synthesis.

EXPERIMENTAL

General Procedure For The Synthesis Of Quinoxalines

Alcohol (0.5 mmol), diamine (0.5 mmol), copper acetate monohydrate (0.05 mmol) and TEMPO (0.05 mmol) in 2ml DMF was irradiated under open vessel microwave (150 W) conditions for 30 minutes at 110^{o}C. The cooled mixture was diluted with water and extracted with dichloromethane, to produce the crude product, which was subsequently purified using radial chromatography to afford the desired quinoxalines.

CONCLUSION

In conclusion, we have reported the one pot synthesis of quinoxalines using a copper acetate monohydrate/TEMPO system. The developed oxidative system is simple and produces the desired products in high yields in short reaction times. The copper acetate monohydrate/TEMPO system was further extended to the synthesis of 2,3-diphenylpyrazine, a known cancer antagonist and the dihyropyrazine and pyrazine derivatives can be formed exclusively and in high yield through the addition or exclusion of elemental sulfur. Further studies are underway to expand the scope of this methodology to other coupling reactions and will be reported in due course.

SUPPLEMENTAL MATERIAL

Supplemental data for this article can be accessed on the publisher's website.

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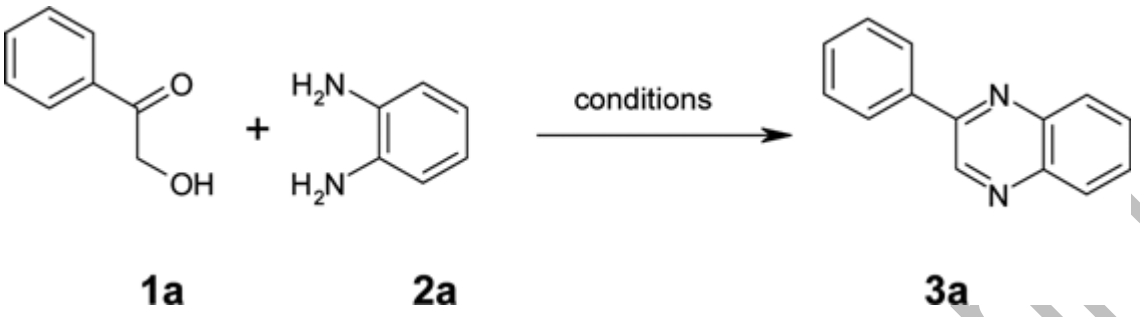
Table 1: Optimization study towards the synthesis of quinoxalines[a]

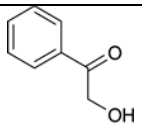
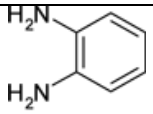
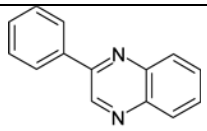
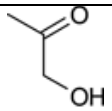
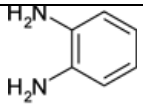
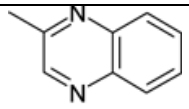
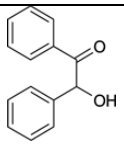
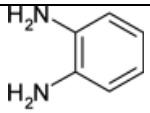
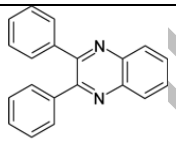
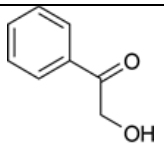
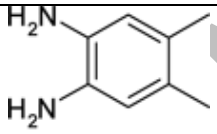
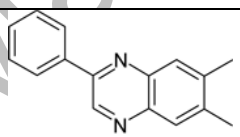
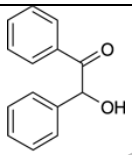
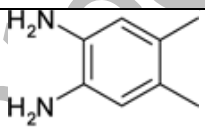
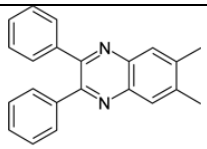
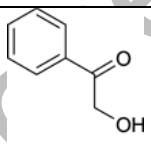
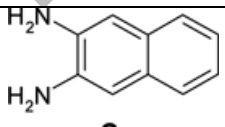
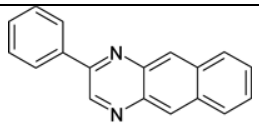
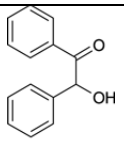
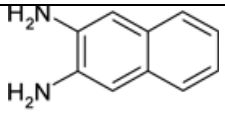
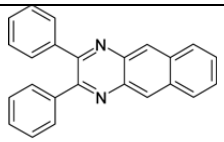


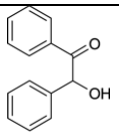
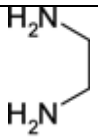
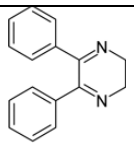
1a **2a** **3a**

Entry	Metal	Additive	Solvent	Condition	Yield[b]
i	$Cu(OAc)_2 \cdot H_2O$	TEMPO	Toluene	CH[c]	77
ii	$Cu(OAc)_2 \cdot H_2O$	TEMPO	Toluene	US[d]	62
iii	$Cu(OAc)_2 \cdot H_2O$	TEMPO	Toluene	mw	30
iv	$Cu(OAc)_2 \cdot H_2O$	TEMPO	Water	mw	38
v	**$Cu(OAc)_2 \cdot H_2O$**	**TEMPO**	**DMF**	**mw**	**94[e]**
vi	$Cu(OAc)_2 \cdot H_2O$	–	DMF	mw	trace
vii	–	TEMPO	DMF	mw	trace
viii	–	–	DMF	mw	0

[a]Alcohol (0.5 mmol), diamine (0.5 mmol), $Cu(OAc)_2.H_2O$ (0.05 mmol) and TEMPO (0.05 mmol) under open vessel conditions using microwave irradiation. [b] Yields estimated using ^{1}H NMR spectroscopy. [C] CH = conventional heating, reflux for 12h. [d] US = ultrasound irradiation for 12 h. [e] Isolated yield.

Table 2. Evaluation of the copper acetate monohydrate/TEMPO system using a range of keto-alcohols and diamines[a]

Entry	Alcohol	Nucleophile	Quinoxalines	Yield[b] (%)
i	 1a	 2a	 3a	94
ii	 1b	 2a	 3b	63[c]
iii	 1c	 2a	 3c	91
iv	 1a	 2b	 3d	96
v	 1c	 2b	 3e	85
vi	 1a	 2c	 3f	69
vii	 1c	 2c	 3g	59

viii	 1c	 2d	 3h	92

[a]Alcohol (0.5 mmol), diamine (0.5 mmol), $Cu(OAc)_2.H_2O$ (0.05 mmol), TEMPO (0.05 mmol) in 2 ml DMF under open vessel conditions using microwave irradiation. [b] Isolated yield. [c] the observed yield may be due to the volatility of the intermediate aldehyde at elevated temperatures, under room temperature, 88% was obtained. See supporting information for a detailed experimental.

Table 3: Synthesis of a dihydropyrazine and pyrazine using a copper acetate monohydrate/TEMPO TOP approach[a]

1c 2d 3h 3i

Entry	Additive	Time (min)	Yield (%)[b]	
			3h	3i
i	–	30	92	nd[c]
ii	–	60	89	nd[c]
iii[c]	sulfur	60	7	88
iv	sulfur	30	nd	94

[a] Alcohol (0.5 mmol), diamine (0.5 mmol), copper acetate monohydrate (0.05 mmol), TEMPO (0.05 mmol) in 2ml DMF under microwave irradiation. [b] Isolated yield. [c] Not detected. See supporting information for a detailed experimental.

Scheme 1. Retrosynthetic study towards 2,3-diphenyl pyrazine showing two valuable heterocycles