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GREEN SYNTHESIS OF QUINOXALINE AND SUBSTITUTED QUINOXALINES

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ABSTRACT

One pot green synthesis for quinoxaline and substituted quinoxalines has been developed using environmental friendly technique of microwave assisted synthesis. The quinoxaline itself **(3g)** and numerous other substituted qunoxalines **(3a-3f)** have been synthesized by using the condensation reaction of o-phenylenediamine and glyoxal, ethylene glycol, oxalic acid, glycolic acid, chloroacetic acid, benzil and benzoin, respectively. These have been synthesized in microwave after irradiation for 60 seconds at 160 watts. The granular solids obtained were crystallized from ethanol, while quinoxaline itself was purified by distillation. All the quinoxalines, barring **(3a)** and **(3f)**, all other have been converted into their monoacetyl and monobenzoyl derivatives by treating them with acetic anhydride and benzoyl chloride in 1 : 1 proportion, respectively. The structural determination of different quinoxalines and their derivatives were established on the basis of elemental analysis and spectral data including IR, PMR and Mass spectra.

Key words: Green synthesis, Quinoxalines, Microwaves.

INTRODUCTION

Quinoxaline derivatives are important members of heterocyclic compound that are widely applied in many fields, as curatorial intermediates, bactericides and insecticides[1]. Although rarely described in the nature, synthetic quinoxaline ring is a part of number of antibiotics which are known to inhibit the growth of Gram-positive bacteria and are also active agents various transplantable tumors[2-4]. Due to their wide range of applications, these compounds have received a great deal of attention in connection with their synthesis.

Several kinds of synthetic routes towards quinoxalines have been developed, including the condensation of o-phenylenediamine with a 1,2-diketones[5-14]. Bi-catalyzed oxidative coupling of epoxides with ene-1,2-diamines[15], heteroannulation of nitroketene

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N,S-arylimino-acetals with $POCl_3$[16], cyclisation of α-arylimino oximes of α-dicarbonyl compounds[17] and formation of α- hydroxyl ketones via a tandem oxidation process using Pd $(OAC)_2$ or $RuCl_2$-$(PPh_3)_3$TEMPO[18,19] as well as MnO_2[20-35]. It is worth nothing that the methods that have been established for the preparation of quinoxaline derivatives are associated with one or more of following draw backs (i) unsatisfactory yields, (ii) long reaction time, (iii) harsh reaction condition and (iv) occurrence of several side products. Thus, it seems highly desirable to find a more efficient and milder protocol for synthesis of quinoxalines.

As a part of our research interest towards the development of efficient and environmentally benign synthetic methodologies using eco-friendly conditions[9], We report here the synthesis of quinoxalines from o-phenylenediamine with glyoxal and other related compounds.

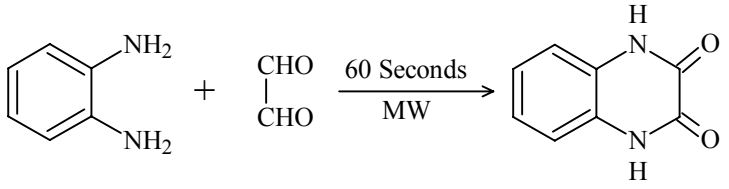
EXPERIMENTAL

Melting points were determined in open capillary tube and are uncorrected.^{1}H NMR spectra ($CDCl_3$) were recorded on Bruker Advance II 400 NMR spectrophotometer using TMS as internal standard. IR spectra were recorded on Perkin-Elmer-1800 FTIR spectrophotometer in the frequency range 4000-450 cm^{-1} in Nujol mull and as KBr pellets. Mass spectra were recorded on a LC-MS Q-Tof Micro, Amino Acid analyzer (Shimadzu). Chemicals were of AR grade.

General procedure for the preparation of Quinoxaline (3g)

A mixture of o- phenylenediamine (0.01 mole) and glyoxal (0.01 mole) was taken in a glass beaker. The beaker was covered with watch glass and irradiated with microwave irradiation by keeping in microwave oven for 60 seconds at 160 watts. After completion of reaction, beaker was cooled when the liquid product obtained. It was purified by simple distillation and the boiling point was tallied with known literature value.

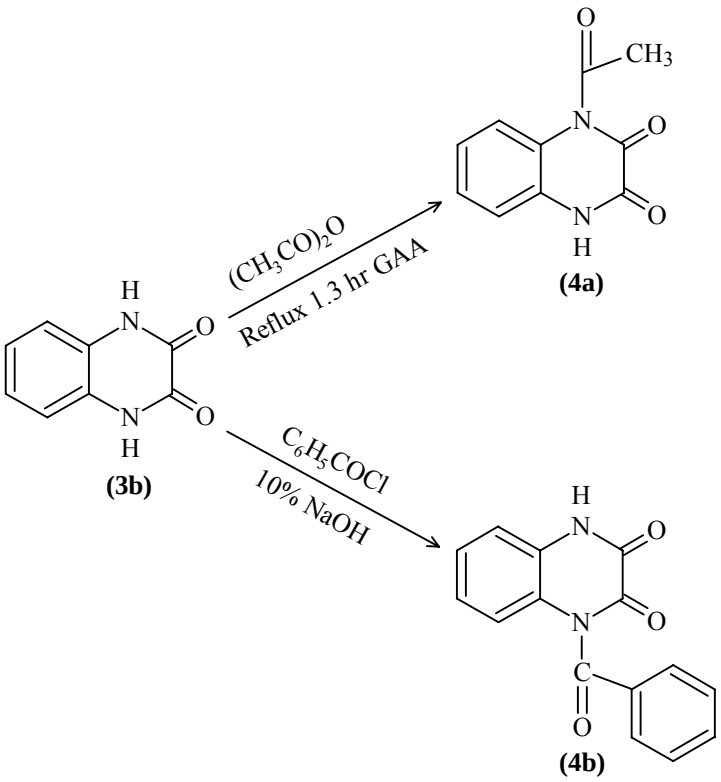
Reaction Scheme



(1) **(2g)** **(3g)**

Scheme 1

Where: (2a) = Ethylene glycol, **(2b)** = Oxalic acid, **(2c)** = Glycolic acid, **(2d)** = Chloroacetic acid, **(2e)** = Benzoin, **(2f)** = Benzil and **(2g)** = Glyoxal.



Scheme 2

General procedure for the preparation of quinoxaline derivatives (3b-3g)

Similar procedure was adapted for the preparation of quinoxaline derivatives involving condensation of o- phenylenediamine with other reactants as indicated in Table 1.

Spectral interpretation of (3a) and (3b)

The IR of **(3a)** showed absorption at *v* NH (3364.4 cm^{-1}), *v* Ar-H (3186.8 cm^{-1}) and *v* C=C (1631.6 cm^{-1}).

The ^{1}H NMR spectrum of **(3a)** showed absorption peaks at δ 6.7 (4H), δ 3.3 (4H); The mass spectrum of the compound showed molecular ion peak at (m/z) : 134 (M^{+})

The IR of **(3b)** showed absorption at *v* NH (3343.2 cm^{-1}) and *v* C=O (1679.1 cm^{-1}).

The ^1H NMR spectrum of **(3b)** showed absorption peaks at δ 6.66 (2H), δ 6.9 (2H), δ 7.23 (2H); the mass spectrum of the compound showed molecular ion peak at (m/z): 162 (M^+).

Table 1: Reaction of o-phenylenediamine (1) with -

Entry	Reactant (2)	Time of irradiation (seconds)	Yield (%)[a]	M.P. ^oC (Lit)	N[b] Found (Calculated)
a	$(CH_2\text{-}OH)_2$ **(2a)**	60	75%	98^oC	20.69 (20.88)
b	$(COOH)_2$ **(2b)**	60	97%	Above 300^oC (~390^oC)[10]	17.15 (17.28)
c	HOOC-CH-OH **(2c)**	60	84.45%	80^oC	18.82 (18.91)
d	HOOC-CH_2-Cl **(2d)**	60	97.29%	240^oC	18.75 (18.91)
e	Ph-CO-CH-OH-Ph **(2e)**	60	90%	127^oC (128-129^oC)[5,7,12,37]	9.60 (9.92)
f	Ph-CO-CH-OH-Ph **(2f)**	60	89%	130^oC (128-129^oC)[5,12]	9.55 (9.85)
g	OHC-CHO **(2g)**	60	92%	(B.P.) 190^oC	21.30 (21.50)

[a] Yields of the isolated product.

[b]All the compounds gave satisfactory value of C,H analysis.

RESULTS AND DISCUSSION

In order to solve the problem in quinoxaline synthesis, a relatively more versatile yet simplified procedure was perceived. Our arguments have been that microwave heating would lead to an instantaneous condensation to afford quinoxaline and its derivatives with the use of any solvent or catalyst. The strategy worked well affording the desired product in respectable yields (Table 1). The present reaction have been relatively faster, as anticipated, compared to those in conventional solution phase synthesis. It is necessary to mention that in all cases, the conversion was never 100 %. Small amounts of starting material were

recovered after each reaction. To prepare the quinoxaline derivatives, different reactants were reacted with o- phenylenediamine and the results are displayed in Table 1.

Compound **(3a-3f)** were purified by crystallization from ethanol while **(3g)** was purified by distillation. These quinoxalines have been converted into their acetyl and benzoyl derivatives by treating them with acetic anhydride and benzyol chloride, respectively.

CONCLUSION

In conclusion, We have developed a simple methodology for the preparation of quinoxalines from o-phenylenediamine and glyoxal and related compounds. The advantages of this method are extremely mild reaction conditions, short reaction time, high yield, simple experimental technique and compliance with the green chemistry protocols.

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REFERENCES

1. M. G. Monoley, Nat. Prod. Rep., **19**, 597 (2002).
2. C. Bailly, S. Echepare, F. Gago and M. Waring, Anti-cancer Drug Des., **14**, 291 (1999).
3. A. Dell, D. H .Williams, H. R. Morris, G. A. Smith, J. Feeney and G. C. K. Roberts, J. Am. Chem. Soc., **97**, 2497 (1975).
4. S. Sato, O. Shiratori and K. Katagiri, J. Antibiot., **20**, 270 (1967).
5. M. M. Heravi, K. Bakhtiari, M. H. Tehrani, N. M. Javadi and H. A. Oskooie, ARKIVOC, **XVI**, 16 (2006).
6. H. R. Darabi, S. Mohandessi, K. Aghapoor and F. Mohsenzadeh, Catal. Commun., 389 (2007).
7. M. Heravi, S. Taheri, K. Bakhtiari and H. A. Oskooie, Catal. Commun., 211 (2007).
8. S. V. More, M. N. V. Sastry and C. F. Yao, Green Chem., 91 (2006).

9. Z. Zhao, D. D. Wisnoski, S. E. Wolkenberg, W. H. Leister, Y. Wang and C. W. Lindsley, Tetrahedron Lett., **45**, 4873 (2004).

10. R. S. Bhosale, S. R. Sarda, S. S. Ardhapure, W. N. Jadhav, S. R. Bhusare and R. P. Pawar, Tetrahedron Lett., **46**, 7183 (2005).

11. S. V. More, M. N. V. Sastry, C. C. Wang and C. F. Yao, Tetrahedron Lett., **46**, 6345 (2005).

12. M. M. Heravi, K. Bakhtiari, F. F. Bamoharram and M. H. Tehrani, Monatsh. Chem., **138**, 465 (2007).

13. H. A. Oskooie, M. M. Heravi, K. Bakhtiari and S. Taheri, Monatsh. Chem., **138**, 875 (2007).

14. S. Antoniotti and E. Donach, Tetrahedron Lett., **43**, 3971 (2002).

15. C. Venkatesh, B. Singh, P. K. Mohata and H. Junjappa IIa H Org. Lett., **7**, 2169 (2005).

16. N. P. Xekoukoulotakis and M. C. P. Hadjiantonious, Maroulis, Tetrahedron Lett., **41**, 10299 (2000).

17. R. S. Robinson and R. J. K. Taylor, Synlett., 1003 (2005).

18. S. A. Raw, C. D. Wilfred and R. J. K. Taylor, Org. Biomol. Chem., **2**,788 (2004).

19. S. A. Raw, C. D. Wilfred and R. J. K. Taylor, Chem. Commun., 2286 (2003).

20. A. Khalafi-Nezhad, A. Zare, A. Parhami, A. Hasaninejad and A. R. Moosavi Zare, J. Iran. Chem.Soc., **5**, S40 (2008).

21. A. Khalafi-Nezhad, A. Parhami, A. Zare and A. R. Moosavi Zare, J. Iran Chem. Soc., **5**, 413 (2008).

22. A. Zare, A. Hasaninejad, A. R. Moosavi Zare, A. Khalafi-Nezhad and A. Parhami, J. Iran.Chem. Soc., **5**, 617 (2008).

23. G. H. Imanzadeh, A. Zare, A. Khalafi-Nezhad, A. Hasaninejad, A. R. Moosavi Zare and A. Parhami J. Iran Chem. Soc., **4**, 467 (2007).

24. A. Khalafi-Nezhad, A. Zare, A. Parhami, M. N. Soltani Rad and G. R. Nejabat, J. Iran Chem. Soc., **4**, 271 (2007).

25. G. H. Imanzadeh, A. Khalafi-Nezhad, A. Zare, A. Hasaninejad, A. R. Moosavi Zare and A. Parhami, J. Iran Chem. Soc., **4**, 229 (2007).

26. A. Zare, A. Hasaninejad, A. Khalafi-Nezhad, A. Parhami and A. R. Moosavi Zare, J. Iran Chem. Soc., **5**, 100 (2008).

27. A. Hasaninejad, A. Zare, H. Sharghi, M. Shekouhy, R. Khalifeh, A. Salimi Beni and A. R. Moosavi Zare, Can. J. Chem., **85**, 416 (2007).

28. A. Hasaninejad and A. Zare, J. Sulfur Chem., **28**, 357 (2007).

29. A. Hasaninejad and H. Sharghi, Phosphorus, Sulfur, and Silicon, **182**, 873 (2007).

30. A. Zare, A. Hasaninejad, A. Khalafi-Nezhad, A. R. Moosavi Zare, A. Parhami and G. R. Nejabat, ARKIVOC, **i**, 58 (2007).

31. A. Zare, A. Hasaninejad, A. R. Moosavi Zare, A. Parhami, H. Sharghi and A. Khalafi-Nezhad, Can. J. Chem., **85**, 438 (2007).

32. A. Zare, A. Hasaninejad, A. Khalafi-Nezhad, A. R. Moosavi Zare and A. Parhami, ARKIVOC, **xiii**, 105(2007).

33. A. Khalafi-Nezhad, A. Parhami, M. N. Soltani Rad, M. A. Zolfigol and A. Zare, Tetrahedron Lett., **48**, 5219 (2007).

34. A. Hasaninejad, A. Zare, H. Sharghi, K. Niknam and Shekouhy, ARKIVOC, **XIV**, 39 (2007).

35. A. Khalafi-Nezhad, A. Zare, A. Parhami , M. N. Soltani Rad and G. R. Nejabat, Phosphorus, Sulfur, and Silicon, **182**, 657 (2007).

36. Harjyoti Thakuria and Gopal Das, J. Chem. Sci., **118**, 425 (2006).

37. S. A. Kotharkar and D. B. Shinde, J. Iran Chem. Soc., **3**, 267 (2006).

38. A. Hasaninejad, A. Zare, M. R. Mohammadizadeh and Z. Karami, J. Iran Chem. Soc., **6**, 153 (2009).

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