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Three-component tandem reactions of (2-arylsulfanyl-3-aryl-2-oxiranyl)(aryl)methanones and *o*-phenylenediamine: formation of quinoxalines

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Abstract—A series of new quinoxalines has been obtained from a one pot, three-component reaction of (2-arylsulfanyl-3-aryl-2-oxiranyl)(aryl)methanones with *o*-phenylenediamine in the presence of a catalytic amount of acetic acid. This reaction presumably involves a tandem oxirane aminolysis–cyclisation–elimination–air oxidation–condensation sequence.

One-pot tandem reactions[1] by virtue of their convergence, elegance, economy of cost, labour and time and ease of execution are powerful for the rapid construction of diverse organic molecules. These reactions fall under the fold of green chemistry,[2] as they obviate the isolation and purification of intermediates leading to diminished pollution of the environment.

In continuation of our research programme on the synthesis of novel organic molecules employing tandem reactions,[3] it was planned to synthesise a series of hitherto unreported 2,4-diaryl-3-(arylsulfanyl)-1*H*-1,5-benzodiazepines **6** (Scheme 1) from the tandem reactions of (2-arylsulfanyl-3-aryl-2-oxiranyl)(aryl)methanones **2** with *o*-phenylenediamine **3**, as benzodiazepines are of paramount biological importance[4] and reports on benzodiazepines bearing sulfur functionality are scarce. Interestingly, this reaction, in the presence of a catalytic amount of acetic acid, led to the formation of new quinoxalines **4** and the results are presented in this Letter. Incidentally, it is pertinent to note that quinoxaline is also an important pharmacophore which displays a wide range of biological activities such as anticancer,[5] antifolic,[6] human dihydrofoliate reductase,[7] antibacterial,[8] antiprotozoal,[8] antiviral[9] and antiproliferative.[10]

In the present work, the starting materials for the synthesis of quinoxalines, namely, (2-arylsulfanyl-3-aryl-2-oxiranyl)(aryl)methanones **2** were obtained by the reaction of 1,3-diaryl-2-(arylsulfanyl)-2-propen-1-ones **1** with alkaline hydrogen peroxide in ethanol in excellent yields (95–98%) at room temperature (Scheme 1).[11] Previously, only one oxirane of type **2** had been prepared by Kroehnke et al.[12] from the same reaction in acetone–methanol mixture in a lower yield (87%) and longer reaction time. The yields and melting points of (2-arylsulfanyl-3-aryl-2-oxiranyl)(aryl)methanones **2** prepared are given in Table 1. The structures of **2** were deduced from NMR spectroscopic data. The 1,3-diaryl-2-(arylsulfanyl)-2-propen-1-ones **1**, in turn, were synthesized in 70–75% yields by the condensation of substituted benzaldehydes with 1-aryl-2-(arylsulfanyl)-1-ethanones using piperidinium acetate as catalyst.[12]

The reactions of (2-arylsulfanyl-3-aryl-2-oxiranyl)-(aryl)methanones **2** with *o*-phenylenediamine in a molar ratio of 1:1 in the presence of a catalytic amount of acetic acid in ethanol failed to furnish the expected benzodiazepine **6** even in traces. Instead, this reaction led to the formation of *N*-[aryl(3-aryl-2-quinoxalinyl)methylidene]-1,2-benzenediamines **4** (Table 2). These reactions, as expected, did not go to completion as **4** requires a 1:2 stoichiometry of the reactants and hence unreacted **2** was present in the reaction mixture. Consequently, subsequent reactions were performed with a 1:2 molar ratio of **2** and **3** which led to products **4** in a pure state after column chromatography as viscous liquids in good

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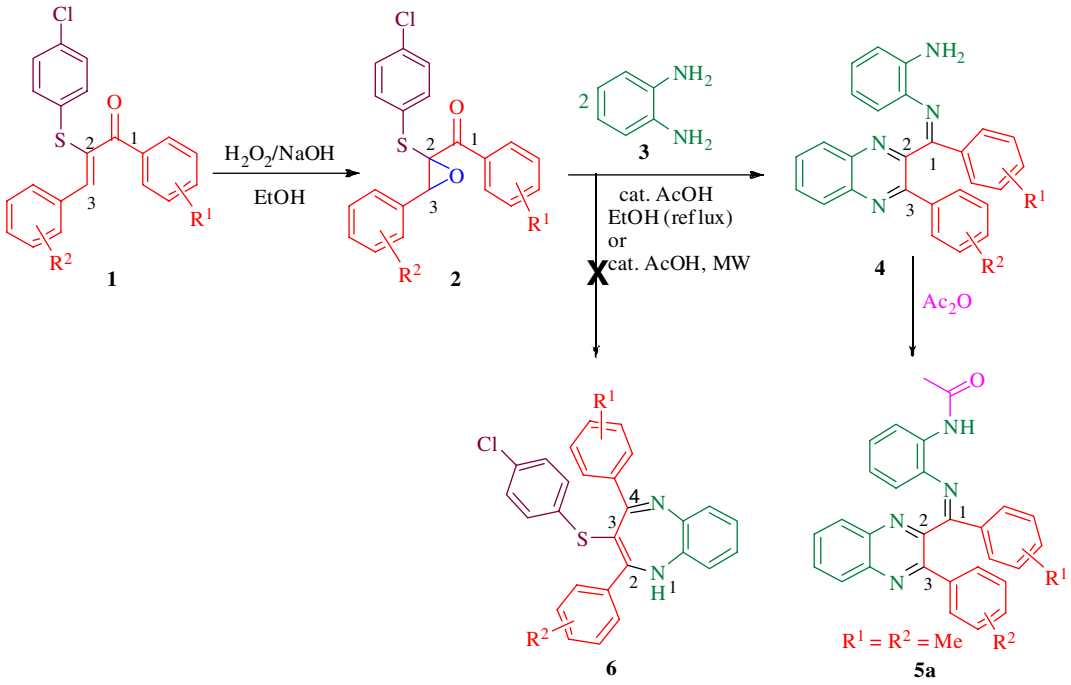


Scheme 1. Synthesis of quinoxalines.

Table 1. Physical data of oxiranes **2**

2	R^1	R^2	Yield (%)	Mp (°C)
a	*p*-Me	*p*-Me	96	88–90
b	H	*p*-Cl	95	79–81
c	H	*p*-Me	95	81–83
d	*p*-Me	H	97	78–80
e	*p*-Me	*p*-Cl	95	87–89
f	H	H	97	73–75
g	*p*-Cl	H	98	91–93
h	*p*-Cl	*p*-Cl	95	90–92
i	*p*-Cl	*p*-Me	95	85–87

Table 2. Physical data of quinoxalines[a] **4**

4	R^1	R^2	Yield[b] (%)	
			Reflux	MW
a	*p*-Me	*p*-Me	57	67
b	H	*p*-Cl	57	65
c	H	*p*-Me	60	66
d	*p*-Me	H	61	68
e	*p*-Me	*p*-Cl	60	67
f	H	H	58	68
g	*p*-Cl	H	60	70
h	*p*-Cl	*p*-Cl	56	66
i	*p*-Cl	*p*-Me	55	67

[a] All the products are viscous liquids.
[b] After purification by column chromatography.

yields (55–61%), considering the number of steps involved.[13] Presumably, the aromatic stability of **4** provides the impetus for the tandem transformation.

The structures of **4** were deduced from the ^1H and ^{13}C NMR spectroscopic data. As all the quinoxalines were viscous liquids, quinoxaline **4a** was converted into its solid acetyl derivative **5a**[14] and its structure deduced from an X-ray crystallographic study of a single crystal (Fig. 1), which, in turn, confirmed the structure of **4a** as well.

Quinoxalines **4** presumably arise from tandem reactions and the mechanism (Scheme 2) envisages an acid catalysed oxirane aminolysis–cyclisation–elimination–air oxidation–condensation sequence. The elimination of benzenethiol from **8**, requiring the phenylthio group to function as a nucleofuge, can probably be ascribed to the stabilising conjugative interactions shown in **9** as well as catalysis by acid (Scheme 2). That this reaction gives quinoxalines **4** even when a 1:1 molar ratio of **2**

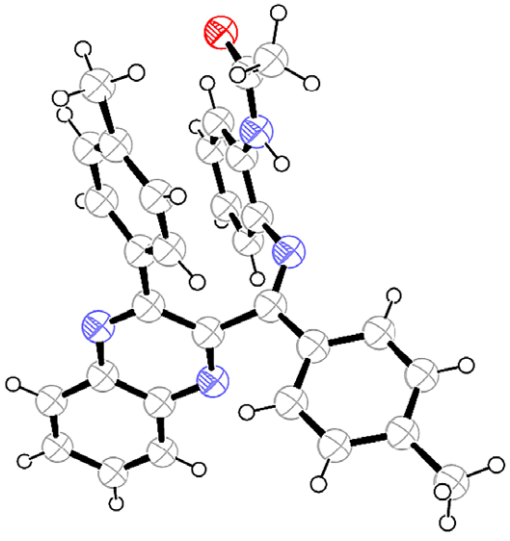
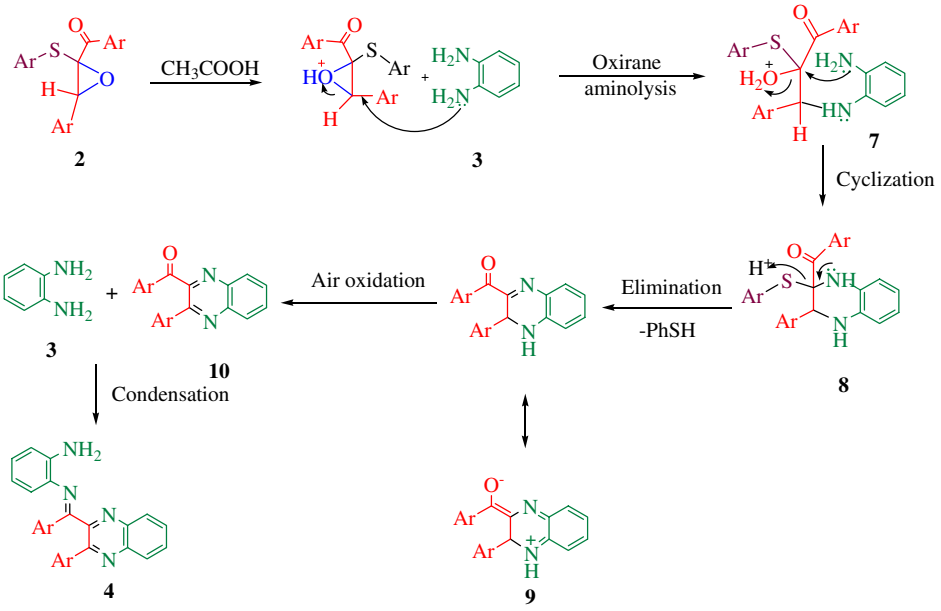


Figure 1. X-ray structure of **5a**.



Scheme 2. Mechanism for formation of quinoxalines via tandem reactions.

and **3** was employed shows that quinoxaline **10** is probably very reactive towards further condensation with *o*-phenylenediamine to afford imine **4**. This is probably due to the protonation of the carbonyl oxygen and/or nitrogen(s) of quinoxaline **10** by acetic acid, which could enhance the electrophilicity of the carbonyl functionality expediting the last step in the sequence.

Reaction between **2** and **3** under solvent-free microwave irradiation in the presence of a catalytic amount of acetic acid also furnished **4** in slightly higher yields of 65–70% compared to the thermal reaction in ethanol.[13]

To the best of the knowledge of the authors, this is the first synthesis of quinoxalines from the direct reaction of epoxyketones with *o*-phenylenediamine. Previously, syntheses of quinoxalines have been reported from epoxyketones by converting (i) the latter to 1,2-diones by treatment with either alcoholic sodium hydroxide or boron trifluoride, and (ii) reacting the resulting 1,2-diones with *o*-phenylenediamine or its dihydrochloride.[15]

The present work describes a facile, acid catalysed, one-pot three-component tandem protocol for the synthesis of novel quinoxalines from readily accessible oxiranes.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.01.106.

References and notes

1. (a) Posner, G. H. *Chem. Rev.* **1986**, *86*, 831; (b) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131; (c) Bunce, R. A. *Tetrahedron* **1995**, *48*, 13103; (d) Ho, T. L. *Tandem Organic Reactions*; John Wiley & Sons: New York, 1992.
2. Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*; Oxford University Press: New York, 2000.
3. (a) Alex Raja, V. P.; Perumal, S. *Tetrahedron* **2006**, *62*, 4892; (b) Savitha Devi, N.; Perumal, S. *Tetrahedron* **2006**, *62*, 5931; (c) Srinivasan, M.; Perumal, S. *Tetrahedron* **2006**, *62*, 7726; (d) Indumathi, S.; Ranjith Kumar, R.; Perumal, S. *Tetrahedron* **2007**, *63*, 1411; (e) Srinivasan, M.; Perumal, S. *Tetrahedron*, in press.
4. (a) Evans, B. E.; Rittle, K. E.; Bock, M. G.; DiPardo, R. M.; Freidinger, R. M.; Whitter, W. L.; Lundell, G. F.; Veber, D. F.; Anderson, P. S.; Chang, R. S. L.; Lotti, V. J.; Cerino, D. J.; Chen, T. B.; Kling, P. J.; Kunkel, K. A.; Springer, J. P.; Hirshfield, J. *J. Med. Chem.* **1988**, *31*, 2235; (b) Kariakomi, M.; Watanabe, S.; Kimura, Y.; Uyehara, T. *Tetrahedron Lett.* **2002**, *43*, 1495.
5. Stratford, I. J.; Stephens, M. A.; Naylor, M. A.; Fielden, E. M.; Adams, G. E. *Br. J. Cancer* **1992**, *65*, 17.
6. Loriga, M.; Fiore, M.; Sanna, P.; Paglietti, G. *Farmaco* **1997**, *50*, 289.
7. Loriga, M.; Piras, S.; Paglietti, G.; Costi, M. P.; Venturelli, A. *Farmaco* **2003**, *58*, 51.
8. Hannon, M.; Rodger, A.; Mann, N. H. Patent No. WO 2005033119, 2005; *Chem. Abstr.* **2005**, *142*, 402929h.
9. Carona, P.; Vitale, G.; Loriga, M.; Paglietti, G.; Colla, P. L.; Collu, G.; Sanna, G.; Loddo, R. *Eur. J. Med. Chem.* **2006**, *41*, 1102.

10. Alleca, S.; Corona, P.; Loriga, M.; Paglietti, G.; Loddo, R.; Mascia, V.; Busonera, B.; Colla, P. L. *Farmaco* **2003**, *58*, 639.
11. *Experimental procedure*: Synthesis of [2-[(4-chlorophenyl)sulfanyl]-3-(4-methyl-phenyl)-2-oxiranyl](4-methylphenyl)methanone (**2a**). In a typical reaction, hydrogen peroxide (1.6 mL, 30%) was added in one lot to a stirred solution of 2-[(4-chlorophenyl)sulfanyl]-1,3-bis(4-methylphenyl)-2-propen-1-one (**1a**) (0.76 g, 2 mmol) in ethanol (6 mL), followed by dropwise addition of sodium hydroxide solution (2 mL, 10%). After completion of the reaction (1 h), the product was washed with water to afford a colourless solid (0.76 g, in 96% yield), which was recrystallised from alcohol. Compound **2a**: white solid, mp 88–90 °C. Anal. Calcd for $C_{23}H_{19}ClO_2S$: C, 69.95; H, 4.85. Found: C, 70.07; H, 4.77; IR (KBr) ν 3020, 1650, 1210 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.42 (s, 6H), 4.39 (s, 1H), 7.16–7.84 (m, 12H); δ_C (75 MHz, $CDCl_3$) 21.4, 21.8, 62.3, 75.0, 127.3, 127.9, 128.8, 129.0, 129.2, 129.5, 131.2, 134.6, 134.8, 139.2, 144.8, 190.4.
12. Kroehnke, F.; Ahrenholz, G. W.; Gross, K. F. *J. Prakt. Chem.* **1960**, *11*, 256.
13. *Experimental procedure*: Synthesis of *N*-{(4-methylphenyl)[3-(4-methylphenyl)-2-quinoxalinyl]methylidene}-1,2-benzenediamine (**4a**): 1. *Conventional method*. A mixture of [2-[(4-chlorophenyl)sulfanyl]-3-(4-methylphenyl)-2-oxiranyl](4-methyl-phenyl)methanone (**2a**) (0.39 g, 1 mmol), *o*-phenylenediamine (**3**) (0.22 g, 2 mmol) and a catalytic amount of acetic acid (0.02 mL) was refluxed in ethanol (1 mL) for 30 min. After completion (TLC), the reaction mixture was poured into water, extracted with dichloromethane, the organic layer separated and the solvent removed and the residue purified by flash column chromatography on silica gel employing petroleum ether–ethyl acetate [19:1 (v/v)] as eluent to give the desired product as a viscous liquid (0.24 g, 57% yield).
2. *Under microwave irradiation*. In a glass tube, [2-[(4-chlorophenyl)sulfanyl]-3-(4-methylphenyl)-2-oxiranyl](4-methylphenyl)methanone (**2a**) (0.39 g, 1 mmol), *o*-phenylenediamine (**3**) (0.22 g, 2 mmol) and a catalytic amount of acetic acid (0.09 mL) were thoroughly mixed and the open glass tube was kept in a silica bath in a microwave oven (IFB, model-Electron, 1000 W capacity, microwave frequency of 2450 MHz) and irradiated for 5 min periods for 40 min at power level 4 in a total scale of 5. After each irradiation, the reaction mixture was cooled to room temperature and thoroughly mixed. The maximum temperature of the silica bath, measured immediately after irradiation by stirring the silica bath with the thermometer, was found to be 78 °C. After completion of the reaction (TLC), the product was obtained in a pure state as described under thermal conditions (0.28 g, 67% yield). Compound **4a**: viscous liquid. Anal. Calcd for $C_{29}H_{24}N_4$: C, 81.28; H, 5.65; N, 13.07. Found: C, 81.18; H, 5.72; N, 13.15; IR (KBr) ν 3320, 1590 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.25 (s, 3H), 2.35 (s, 3H), 2.96 (s, 2H), 5.69 (d, $J = 7.8$ Hz, 1H), 6.01 (t, $J = 7.5$ Hz, 1H), 6.28 (d, $J = 7.8$ Hz, 1H), 6.59 (t, $J = 7.5$ Hz, 1H), 6.95–8.11 (m, 12H); δ_C (75 MHz, $CDCl_3$) 21.8, 22.0, 115.6, 117.7, 120.9, 126.2, 129.1, 129.2, 129.5, 129.7, 129.8, 130.3, 131.2, 135.1, 135.7, 136.3, 139.9, 140.5, 141.3, 141.9, 142.0, 152.2, 153.7, 163.7.
14. *Experimental procedure for the synthesis of N-[2-[(4-methylphenyl)[3-(4-methylphenyl)-2-quinoxalinyl]methylidene]-aminophenyl]acetamide* (**5a**). Compound **4a** (0.09 g, 0.21 mmol) dissolved in acetic anhydride (3 mL) was stirred at room temperature for 5.5 h. Then the reaction mixture was poured into water (100 mL), stirred for 4 h and extracted with dichloromethane. The organic layer was washed repeatedly with water, dried over anhydrous sodium sulfate and the solvent removed. The resulting colourless solid was recrystallised from alcohol (0.094 g, 95% yield; mp 121–122 ° C). Compound **5a**: pale yellow crystal. Anal. Calcd for $C_{31}H_{26}N_4O$: C, 79.12; H, 5.57; N, 11.91. Found: C, 78.98; H, 5.68; N, 12.03, IR (KBr) ν 3365, 1690 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.82 (s, 1H), 1.92 (s, 3H), 2.35 (s, 3H), 2.50 (s, 3H), 5.81 (d, $J = 7.2$ Hz, 1H), 6.40 (t, $J = 7.5$ Hz, 1H), 6.89 (t, $J = 7.8$ Hz, 1H), 8.11 (d, $J = 7.5$ Hz, 1H), 7.00–8.21 (m, 12H). δ_C (75 MHz, $CDCl_3$) 21.8, 22.1, 25.2, 119.2, 120.3, 122.6, 126.3, 128.8, 129.4, 129.7, 129.8, 129.9, 130.1, 130.6, 131.5, 132.9, 134.7, 136.0, 136.8, 140.3, 140.4, 142.0, 142.8, 151.4, 153.7, 165.8, 167.4. Crystallographic data (excluding structure factors) for **5a** in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 628360. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].
15. (a) House, H. O.; Reif, D. J. *J. Am. Chem. Soc.* **1955**, *77*, 6525; (b) House, H. O. *J. Am. Chem. Soc.* **1954**, *76*, 1235.