An iodobenzene-catalysed domino route toward quinoxaline derivatives from simple ketones and *o*-phenylenediamines in one pot

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An iodobenzene-catalysed domino route to quinoxalines from ketones and *o*-phenylenediamines in one pot has been developed. This transformation consisted of the generation of Koser's generation, α-tosyloxylation of ketones, nucleophilic substitution and intramolecular dehydration with *o*-phenylenediamines, and dehydrogenation.

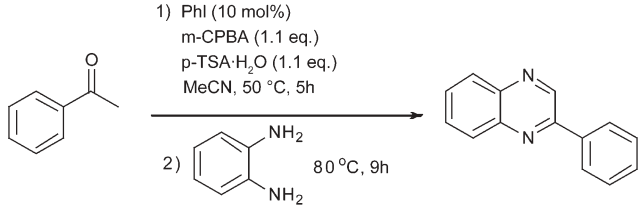
Keywords: iodobenzene, quinoxaline, ketones, *o*-phenylenediamines, tosyloxylation

Quinoxaline derivatives represent an important class of heterocyclic compounds because of their bioactivities,[1] pharmaceutical applications,[2] and physical properties.[3–4] Traditionally, this type of heterocycle was synthesised by the coupling of 1,2-diamine with prefunctionalised ketones, such as α-hydroxyketones,[5] α-halo-β-ketoesters,[6] α-halo-ketones,[7] and 1,2-dicarbonyl compound.[8–11] Several domino routes in one pot from simple ketones have also been developed to obviate the prefunctionalisation of ketones, thus simplifying the operation.[12,13] Recently, we developed a new domino protocol for the synthesis of quinoxalines from simple ketones which employs [Hydroxy(tosyloxy)iodo]benzene (HTIB) mediated α-tosyloxylation of simple ketones (Scheme 1).[14] However, it has been reported that the α-tosyloxylation of simple ketones can be achieved in a more environmentally friendly and economical manner by using iodobenzene as catalyst in the presence of *m*-CPBA and p-toluenesulfonic acid (Scheme 1).[15–17] Encouraged by our previous work, we envisioned that this methodology might also be applied to the synthesis of quinoxalines. Herein, we report the realisation of this goal leading to a convenient HTIB-free method for the construction of quinoxalines (Scheme 1).

Results and discussion

Our initial work focused on the reaction of acetophenone (**1a**) with *o*-diaminobenzene (**2a**) (Table 1). When the reaction was performed in one stage with 10 mol% of iodobenzene, 1.1 equiv. of m-CPBA and 1.1 equiv. of p-toluenesulfonic acid in acetonitrile, none of the desired product (**3a**) was obtained (Table 1, entry 1). We then tested the two-stage reactions in one pot. In the first stage, iodobenzene-catalysed α-tosyloxylation of acetophenone (**1a**) with *m*-CPBA and p-toluenesulfonic acid was carried out at 50 °C for 5 h. Then the *o*-diaminobenzene was added and the mixture was stirred for another 9 h. The desired product was isolated in 46% yield (Table 1, entry 2). Increasing the reaction temperature of the second stage to 80 °C gave the desired product **3a** in 80% yield (Table 1, entry 3). In control reactions without iodobenzene as the catalyst (Table 1, entry 4) or without m-CPBA as the oxidant (Table 1, entry 5), none of the target product was obtained.

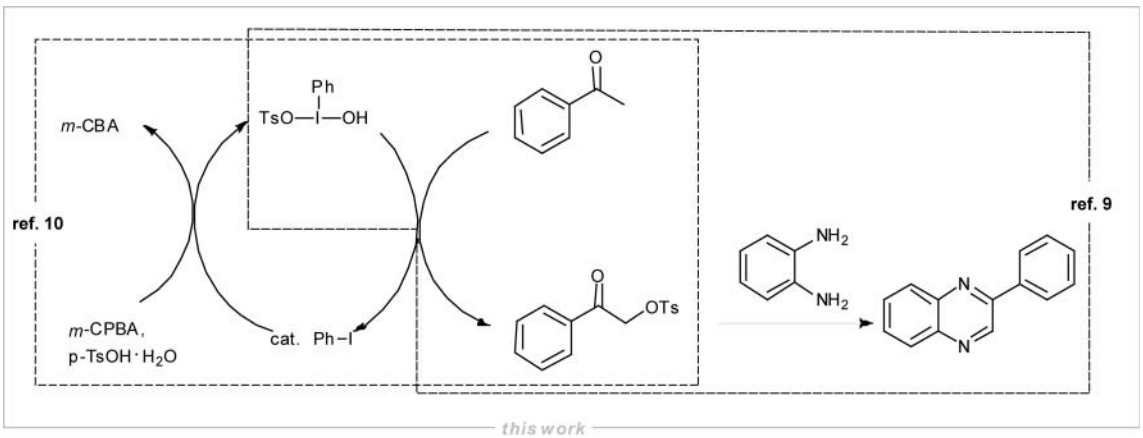
Table 1 Optimisation of the reaction conditions[a]



1a 2a 3a

Entry	Variation from the "standard conditions"	Yield/%[b]
1	One-stage reaction at 50 or 80 °C	0
2	Two-stage reaction at 50 °C	46
3	**Standard conditions**	**80**
4	No iodobenzene	0
5	No m-CPBA	0
6	Oxone® instead of m-CPBA	23

[a] Standard reaction conditions: the first stage: **1a** (0.5 mmol), iodobenzene (10 mol %), m-CPBA (0.55 mmol), p-toluenesulfonic acid (0.55 mmol), MeCN (3 mL), 50 °C, 5 h; the second stage: **2a** (0.6 mmol), 80 °C, 9h.
[b] Isolated yield.



Scheme 1 Proposed domino route toward quinoxalines.

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The yield decreased when *m*-CPBA was replaced to Oxone® (Table 1, entry 6).

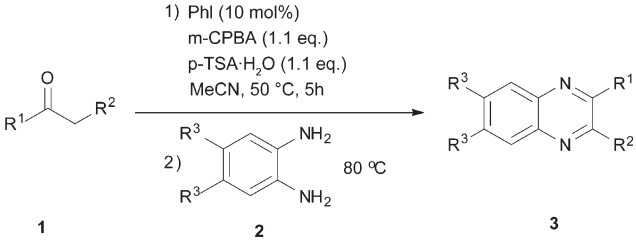
To define the scope of the oxidative coupling reaction, we applied this process to a series of acetophenones (Table 2, entries 1–9). A variety of functional groups, including methyl, methoxy, halo and naphthyl were tolerated under the optimised conditions. Heteroarenes, such as 2-acetylfuran, 2-acetylthiophene, and 2-acetylpyridine also underwent the coupling to give the corresponding quinoxalines **3l**–**n** in moderate yields (entries 10–12). We were pleased to see that under our optimized reaction conditions, the reaction of α-substituted acetophenones, such as 2-phenylacetophenone, propiophenone and ethyl benzoylacetate proceeded smoothly to afford the desired quinoxalines **3i**–**k** (entries 13–15). Preliminary results have shown that an aliphatic ketone, such as 3-pentanone also worked for this reaction (entry 16). Finally, the reaction was examined with 4,5-diCl and 4,5-diMe substituted *o*-diaminobenzene, which were treated with acetophenone under the standard reaction conditions. The reaction worked smoothly, leading to the formation of the corresponding quinoxalines **3q** and **3r** in 44% and 70% yields, respectively (entries 17 and 18).

In conclusion, we have developed a facile and economical one-pot procedure for the synthesis of quinoxalines through iodobenzene-catalysed oxidative coupling of ketones and o-phenylenediamines in the presence of m-chloroperbenzoic acid and p-toluenesulfonic acid. Compared with previous reports, this novel protocol is distinguished by the freedom from stoichiometric amounts of hypervalent iodine compounds.

Experimental

All reagents and solvents were purchased from commercial suppliers and were used without purification. Melting points were measured on a Büchi B-545. ^{1}H NMR spectra were obtained on a Bruker AVANCE III 500 (500 MHz) instrument in $CDCl_3$ using tetramethylsilane (TMS) as the internal standard. Chemical shifts (δ) are reported in ppm and coupling constants *J* are given in Hz.

Table 2 Synthesis of substituted quinoxaline[a]



Entry	R^1	R^2	R^3	Time/h[b]	Product	Yield/%[c]
1	Ph	H	H	9	**3a**	80
2	p-MeC_6H_4	H	H	8	**3b**	58
3	o-MeC_6H_4	H	H	10	**3c**	40
4	p-ClC_6H_4	H	H	6	**3d**	48
5	o-ClC_6H_4	H	H	7	**3e**	42
6	p-$MeOC_6H_4$	H	H	10	**3f**	36
7	p-FC_6H_4	H	H	10	**3g**	29
8	p-BrC_6H_4	H	H	7	**3h**	85
9	1-naphthyl	H	H	6	**3p**	47
10	2-furanyl	H	H	6	**3l**	53
11	2-thiophenyl	H	H	7	**3m**	65
12	2-pyridinyl	H	H	7	**3n**	57
13	Ph	Ph	H	11	**3i**	21
14	Ph	Me	H	9	**3j**	57
15	Ph	COOEt	H	8	**3k**	38
16	Et	Et	H	10	**3o**	32
17	Ph	H	Me	9	**3q**	44
18	Ph	H	Cl	9	**3r**	70

[a]Standard reaction conditions: the first stage: **1** (0.5 mmol), iodobenzene (10 mol %), m-CPBA (0.55 mmol), p-toluenesulfonic acid (0.55 mmol), MeCN (3 mL), 50 °C, 5 h; the second stage: **2** (0.6 mmol), 80 °C.
[b]Reaction time of the second stage.
[c]Isolated yield.

Synthesis of quinoxalines **3a–r***; general procedure*

A mixture of ketones **1** (0.5 mmol), iodobenzene (10.2 mg, 0.05 mmol), *p*-TsOH·H_2O (104.7mg, 0.55 mmol), and *m*-CPBA (75% purity, 128.7 mg, 0.55 mmol) in MeCN (3 mL) was stirred at 50 °C for 5 h. Then o-phenylenediamines **2** (0.6 mmol) was added and stirred at 80 °C until the intermediate for the first step disappeared. After the reaction, the solvent was removed under reduced pressure, and the residue was purified by chromatography on silica gel (100–200 mesh) using petroleum ether/EtOAc (15/1, v/v) as the eluent to give products **3**. The structures and yields of the products are given in Table 2. All compounds **3** are known.

2-Phenylquinoxaline (**3a**): Yellow solid, m.p. 73–74 °C (lit.[7] 74–76 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.21 (s, 1H), 8.10–8.07 (m, 2H), 8.06–8.00 (m, 2H), 7.68–7.61 (m, 2H), 7.41–7.39 (m, 3H).

2-p-Tolylquinoxaline (**3b**): Pale yellow solid, m.p. 88–90 °C (lit.[7] 90–91 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.32 (s, 1H), 8.16–8.10 (m, 4H), 7.79–7.71 (m, 2H), 7.38 (d, *J* = 8.0 Hz, 2H), 2.46 (s, 3H).

2-o-Tolylquinoxaline (**3c**): Yellow solid, m.p. 88–89 °C (lit.[5] 91–92 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.02 (s, 1H), 8.18–8.14 (m, 2H), 7.83–7.78 (m, 2H), 7.56 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.43–7.36 (m, 3H), 2.48 (s, 3H).

2-(4-Chlorophenyl)quinoxaline (**3d**): White solid, m.p. 129–130 °C (lit.[7] 127–128 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.31 (s, 1H), 8.18–8.13 (m, 4H), 7.83–7.75(m, 2H), 7.55 (d, *J* = 8.6 Hz, 2H).

2-(2-Chlorophenyl)quinoxaline (**3e**): White solid, m.p. 88–89 °C (lit.[7] 86–88 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.23 (s, 1H), 8.20–8.17 (m, 2H), 7.82 (dd, *J* = 6.4, 3.4 Hz, 2H), 7.76–7.73 (m, 1H), 7.58–7.55 (m, 1H), 7.48–7.45 (m, 2H).

2-(4-Methoxyphenyl)quinoxaline (**3f**): White solid, m.p. 98–99 °C (lit.[7] 100–101 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.30 (s, 1H), 8.20–8.17 (m, 2H), 8.14–8.09 (m, 2H), 7.79–7.75 (m, 1H), 7.72–7.70 (m, 1H), 7.10–7.07 (m, 2H), 3.91 (s, 3H).

2-(4-Fluorophenyl) quinoxaline (**3g**): Yellow solid, m.p. 119–121 °C (lit.[7] 120–122 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.30 (s, 1H), 8.24–8.18 (m, 2H), 8.15–8.12 (m, 2H), 7.81–7.74 (m, 2H), 7.28–7.23 (m, 2H).

2-(4-Bromophenyl)quinoxaline (**3h**): White solid, m.p. 132–135 °C (lit.[7] 136–139 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.30 (s, 1H), 8.17–8.12 (m, 2H), 8.10 (d, *J* = 8.6 Hz, 2H), 7.82–7.76 (m, 2H), 7.72–7.69 (m, 2H).

2,3-Diphenylquinoxaline (**3i**): White solid, m.p. 128–129 °C (lit.[18] 129–130 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21–8.17 (m, 2H), 7.80–7.76 (m, 2H), 7.55–7.50 (m, 4H), 7.39–7.32 (m, 6H).

2-Methyl-3-phenylquinoxaline (**3j**): White solid, m.p. 53–55 °C (lit.[13] 55–57 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14–8.10 (m, 1H), 8.10–8.05 (m, 1H), 7.74 (m, 2H), 7.68–7.65 (m, 2H), 7.56–7.49 (m, 3H), 2.80 (s, 3H).

Ethyl 3-phenylquinoxaline-2-carboxylate (**3k**): White solid, m.p. 45–47 °C (lit.[19] 46–48 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24–8.18 (m, 2H), 7.88–7.81 (m, 2H), 7.76–7.73 (m, 2H), 7.55–7.49 (m, 3H), 4.34 (q, *J* = 7.1 Hz, 2H), 1.18 (t, *J* = 7.1 Hz, 3H).

2-(Furan-2-yl)quinoxaline (**3l**): Pale red solid, m.p. 96–97 °C (lit.[5] 97–98 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.27 (s, 1H), 8.13–8.07 (m, 2H), 7.79–7.75 (m, 1H), 7.74–7.70 (m, 2H), 7.34 (dd, *J* = 3.5, 0.6 Hz, 1H), 6.65 (dd, *J* = 3.5, 1.7 Hz, 1H).

2-(Thiophen-2-yl)quinoxaline (**3m**):[12] Pale yellow solid, m.p. 113–114 °C (lit. 110–112 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.25 (s, 1H), 8.09–8.06 (m, 2H), 7.87 (dd, *J* = 3.7, 0.9 Hz, 1H), 7.77–7.74 (m, 1H), 7.72–7.68 (m, 1H), 7.55 (dd, *J* = 5.0, 0.9 Hz, 1H), 7.21 (dd, *J* = 5.0, 3.7 Hz, 1H).

2-(Pyridin-2-yl)quinoxaline (**3n**): Pink solid, m.p. 110–112 °C (lit.[12] 110–111 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.98 (s, 1H), 8.80 (d, *J* = 3.8 Hz, 1H), 8.61 (d, *J* = 7.9 Hz, 1H), 8.17 (dd, *J* = 6.5, 3.0 Hz, 2H), 7.94–7.91 (m, 1H), 7.83–7.77 (m, 2H), 7.43 (dd, *J* = 6.9, 5.0 Hz, 1H).

2-Ethyl-3-methylquinoxaline (**3o**): White solid, m.p. 58–59 °C (lit.[19] 55 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04–7.96 (m, 2H), 7.69–7.65 (m, 2H), 3.04 (q, *J* = 7.5 Hz, 2H), 2.77 (s, 3H), 1.42 (t, *J* = 7.5 Hz, 3H).

2-(Naphthalen-2-yl)quinoxaline (**3p**): Brown solid, m.p. 137–139 °C (lit.[5] 140–142 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.17 (s, 1H),

8.25–8.20 (m, 2H), 8.17 (d, *J* = 8.1 Hz, 1H), 8.01 (d, *J* = 8.2 Hz, 1H), 7.99–7.94 (m, 1H), 7.87–7.81 (m, 2H), 7.78 (dd, *J* = 7.0, 1.0 Hz, 1H), 7.64 (dd, *J* = 8.1, 7.2 Hz, 1H), 7.58–7.51 (m, 2H).

6,7-Dimethyl-2-phenylquinoxaline (**3q**): White solid, m.p. 126–127 °C (lit.[7] 127–129 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.21 (s, 1H), 8.15 (d, *J* = 7.1 Hz, 2H), 7.89 (s, 1H), 7.84 (s, 1H), 7.57–7.48 (m, 3H), 2.49 (s, 6H).

6,7-Dichloro-2-phenylquinoxaline (**3r**): Yellow solid, m.p. 154–156 °C (lit.[7] 153–156 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.32 (s, 1H), 8.28 (s, 1H), 8.24 (s, 1H), 8.19 (dd, *J* = 8.0, 1.6 Hz, 2H), 7.60–7.56 (m, 3H).

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