Iridium catalysed synthesis of piperazines from diols†

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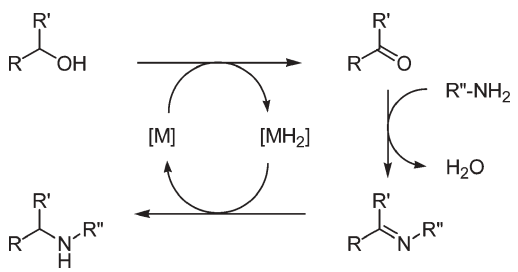
A green and atom-economical method has been developed for the synthesis of piperazines by cyclocondensation of diols and amines in aqueous media in the presence of a catalytic amount of $[Cp^*IrCl_2]_2$.

The piperazine moiety is an important pharmacophore which is found in a large number of biologically active molecules. A recent survey of more than 1000 orally administered drugs showed that about 6% of these contained a piperazine fragment.[1] The synthesis of piperazines and substituted piperazines is usually performed by reduction of the corresponding (di)ketopiperazines[2,3] or by various cyclisation reactions, *e.g.* dialkylation of amines with bis(2-chloroethyl)amine[4] or intramolecular reductive coupling of diimines.[5] However, a more environmentally friendly and atom-economical[6] method for forming a carbon–nitrogen bond is the direct condensation between an amine and an alcohol, since this transformation only produces a molecule of water as the by-product.[7] Recently, several iridium[8] and ruthenium[9] catalysts were shown to mediate the alkylation of amines with alcohols. The mechanism involves dehydrogenation of the alcohol to the corresponding aldehyde/ketone followed by imine formation and reduction to the product amine with the liberated hydrogen from the first step (Scheme 1). We envisioned that the piperazine ring system could be formed in this way by cyclocondensation of a 1,2-diol with either a primary amine or a 1,2-diamine. Herein, we report our results on the synthesis of differently substituted piperazines in the presence of the trivalent iridium complex $[Cp^*IrCl_2]_2$.

The initial studies were performed with equimolar amounts of (±)-*trans*-1,2-diaminocyclohexane and ethylene glycol by reaction in a sealed flask overnight (Scheme 2). The commercially available



Scheme 1 Mechanism for amine alkylation with alcohols.

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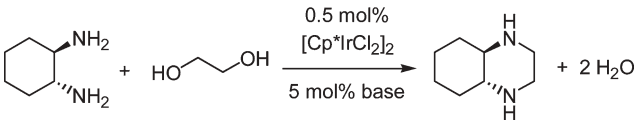
† Electronic supplementary information (ESI) available: General procedure, characterisation data and copies of ^1H and ^{13}C NMR spectra for all the prepared piperazines. See DOI: 10.1039/b712685a



Scheme 2 Iridium catalysed synthesis of a bicyclic piperazine.

complex $[Cp^*IrCl_2]_2$ was chosen since this catalyst has previously shown high reactivity in the coupling of primary amines with both primary and secondary alcohols.[10] First, we examined several different solvents with sodium bicarbonate as the base (Table 1, entries 1–5). Rewardingly, the desired reaction proceeded very well in toluene and water while dioxane gave a slightly lower yield. It is quite remarkable that water is a highly effective solvent for this transformation since the reaction goes through two imines. Apparently, the formation of these imines is not the rate limiting step in the overall transformation.

A number of experiments were then carried out in order to investigate the influence of the base. In the absence of a base, the reaction resulted in a lower yield due to incomplete conversion of the starting materials (entries 6 and 7). Lower yields were also observed when sodium carbonate or sodium acetate were employed while triethylamine gave a similar yield to sodium bicarbonate (entries 8–12). Experiments were also carried out with an acid as the additive. When the reaction in Scheme 2 was carried out in water in the presence of 10% of trifluoroacetic acid, the product piperazine was isolated in 98% yield. This is an interesting result and shows that the cyclocondensation can be promoted by both acids and bases. For general use, however, we selected the more convenient sodium bicarbonate as the additive with either toluene or water as the solvent.

We then turned our attention to other substrates in order to explore the scope of the cyclocondensation reaction (Table 2). Propane-1,2-diol showed a similar reactivity to ethylene glycol in

Table 1 Solvent and base screening for the reaction in Scheme 2

Entry	Solvent	Base	Temp./°C	Yield[a] (%)
1	THF	$NaHCO_3$	67	5
2	Heptane	$NaHCO_3$	98	13
3	Dioxane	$NaHCO_3$	100	86
4	Toluene	$NaHCO_3$	110	94
5	Water	$NaHCO_3$	100	96
6	Toluene	None	110	78
7	Water	None	100	41
8	Toluene	Na_2CO_3	110	63
9	Water	Na_2CO_3	100	24
10	Toluene	NaOAc	110	53
11	Water	NaOAc	100	48
12	Toluene	Et_3N	110	94

[a] Isolated yield.

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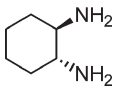
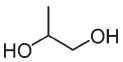
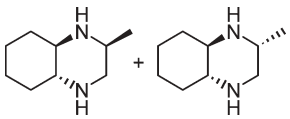
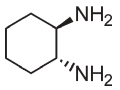
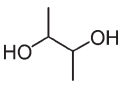
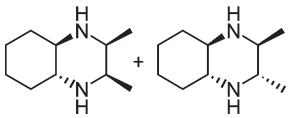
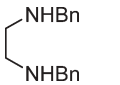
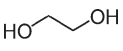
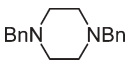
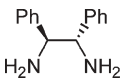
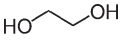
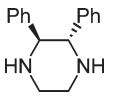
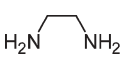
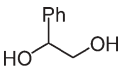
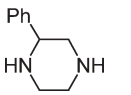
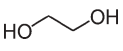
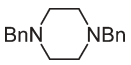
Table 2 Synthesis of substituted piperazines[a]

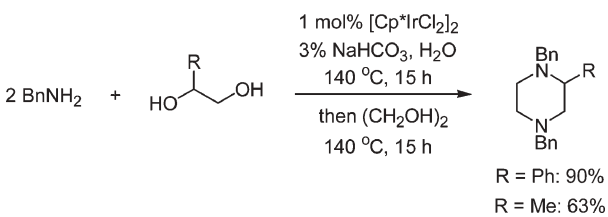
Entry	Amine	Diol	Product(s)	Solvent	Temp./°C	Yield[b] (%) (dr)[c]
1				Toluene	110	87 (3 : 1)
				Water	100	98 (>20 : 1)
2				Toluene	140	79 (1 : 1)
				Water	140	81 (3 : 1)
3				Toluene	140	74
				Water	140	73
4				Toluene	110	54[d]
				Water	100	60[d]/86[e]
5				Water	120	Quant.
6	$BnNH_2$			Neat	160[f]	94

[a] Reactions were performed overnight with equimolar amounts of amine and diol in the presence of 0.5 mol% $[Cp^*IrCl_2]_2$ and 5% of $NaHCO_3$. [b] Isolated yield. [c] Determined from ^1H NMR spectroscopy. [d] Reaction time 64 h. [e] 10% of trifluoroacetic acid was used instead of $NaHCO_3$. [f] Reaction time 6 h.

the reaction with *trans*-1,2-diaminocyclohexane and good yields were obtained in both toluene and water (entry 1). A new stereocentre is introduced in this reaction and the diastereoselectivity is highly dependent on the solvent. Butane-2,3-diol also reacted with an equimolar amount of 1,2-diaminocyclohexane, but in this case the reaction was slower and required a higher temperature in order to go to completion (entry 2). The reaction gave mainly two diastereomers which were identified as the *cis* and the *trans* product, with the former being the major product in water. Additional substituents were also allowed in the diamine and this was shown by the reaction between *N*,*N*′-dibenzyl-1,2-diaminoethane and ethylene glycol to give 1,4-dibenzylpiperazine (entry 3). The reactions in entries 2 and 3 required a temperature around 140 °C for full conversion which shows that secondary amines and secondary alcohols react significantly slower than the corresponding primary amines and alcohols. The addition of trifluoroacetic acid did not improve the reactions with the substituted substrates and in both entries 2 and 3 the cyclocondensation proceeded poorly with the acid as an additive. The reaction in water in entry 3 should be noted since the transformation with the secondary amine must go through an iminium ion/enamine and this does not seem to be severely hampered by the aqueous media. Optically pure (1*S*,2*S*)-1,2-diamino-1,2-diphenylethane also participated in the cyclisation reaction with ethylene glycol, and the product showed no sign of racemisation according to the optical rotation (entry 4). This diamine reacted slower than 1,2-diaminocyclohexane and required almost 3 days for complete conversion. Notably, the reactivity and the yield could be improved in this case by using an acid as the additive. On the other hand, the simple diamine, 1,2-diaminoethane, reacted smoothly with (±)-1-phenylethane-1,2-diol to give 2-phenylpiperazine in quantitative yield (entry 5).

1,4-Dibenzylpiperazine in entry 3 is a symmetric molecule that could also be generated from benzylamine and ethylene glycol. This reaction was investigated in entry 6 and the initial experiments were performed in toluene or water at 140 °C. However, the reaction was slower than in entry 3 under these conditions and only gave about 45% yield. Therefore, it was attempted to leave out the solvent which required the reaction to be performed at 160 °C to ensure full conversion. Under these conditions, dibenzylpiperazine was obtained as a crystalline material and isolated in 94% yield after washing with water and filtration.‡

To further expand the scope of the reaction and to develop an alternative route to substituted piperazines we carried out a sequence where two different diols would participate in the cyclocondensation with a primary amine (Scheme 3). This was performed as a one-pot protocol where 1-phenylethane-1,2-diol or propane-1,2-diol was first allowed to react to completion with 2 equiv. of benzylamine to produce the corresponding 1,2-bis(benzylamino) compound. Since a secondary amine is converted much slower than a primary amine, the starting diol will



Scheme 3 Synthesis of 1,2,4-trisubstituted piperazines from two diols.

predominately react with benzylamine. Subsequently, ethylene glycol is added to the mixture and the reaction is heated again until full conversion into the piperazine is achieved. In this way, 1,4-dibenzyl-2-phenylpiperazine was formed in 90% yield from 1-phenylethane-1,2-diol while 1,4-dibenzyl-2-methylpiperazine was obtained in 63% yield from propane-1,2-diol. The lower yield in the latter case is due to a lower selectivity in the initial reaction between benzylamine and the diol. Both reactions were carried out in water at 140 °C which gave a higher yield than performing the reactions in neat conditions at 160 °C.

In summary, we have developed a new method for the synthesis of piperazines by using an iridium catalysed cyclocondensation of diols with either a primary amine or a 1,2-diamine. This constitutes a green and atom-economical transformation that can be performed in aqueous media and only produces water as a by-product.

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Notes and references

‡ **Synthesis of 1,4-dibenzylpiperazine (Table 2, entry 6)**: to a 5 mL screw-top vial were added $[Cp^*IrCl_2]_2$ (48 mg, 0.06 mmol), benzylamine (1.31 mL, 12.0 mmol), ethylene glycol (0.67 mL, 12.0 mmol) and $NaHCO_3$ (23 mg). The vial was flushed with argon, sealed and heated to 160 °C for 6 h. After cooling to room temperature, the flask was stored at 5 °C overnight. The solid reaction mixture was washed with water and filtered, and the filter cake was rinsed with a small amount of ether to give 1.50 g (94%) of the target compound as white crystals, mp 87–90 °C (lit.[11] mp 90–92 °C). δ_H (300 MHz, $CDCl_3$): 7.35–7.21 (m, 10H), 3.52 (s, 4H), 2.49 (bs, 8H); δ_C (75 MHz, $CDCl_3$): 138.2, 129.4, 128.3, 127.1, 63.2, 53.2.

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