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N-Alkylation of phenethylamine and tryptamine

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Abstract—A clean and efficient method for the N-alkylation of tryptamine and phenethylamine, employing alcohols as the alkylating agents, has been developed. The reaction proceeds via catalytic electronic activation, involving an iridium catalyst which activates the alcohol by borrowing hydrogen from the substrate, returning it later in the catalytic cycle. Some examples of N-heterocyclisation have been performed employing a diol as the substrate.
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The ability to prepare a large number of synthetically useful and pharmacologically active compounds, either by traditional or high throughput methods, is becoming increasingly important. Herein we report an efficient, atom economic, one-pot method for the N-alkylation of tryptamine and phenethylamine, giving water as the only by-product.

The tryptamine sub-structure is present in numerous naturally occurring and synthetic compounds, many of which exhibit important pharmacological activity. For example, a number of 5-alkyltryptamine derivatives (collectively known as 'triptans', e.g., sumatriptan)[1] are used as antimigraine drugs, binding to the 5-HT$_{1D}$, 5-HT$_{1B}$ and 5-HT$_{1F}$ receptors with high affinities.[2] Some N,N-disubstituted tryptamines have been reported to show psychotomimetic activity, although there is evidence to suggest that the tryptamine derivatives are metabolised in vivo to more active forms.[3] Bis(phenylalkyl)amines have been tested following reports that nylidrin, a nonpiperidine analogue of ifenprodil, was a potent NR2B-selective N-methyl-D-aspartate receptor antagonist (potentially useful as neuroprotectants, anti-convulsants, analgesics and agents that augment the effects of L-DOPA for the treatment of Parkinson's disease) (Fig. 1).[4]

As part of our continued interest into catalytic electronic activation, we recently reported a method for the conversion of alcohols 1 into phenylamines 2 using the com-
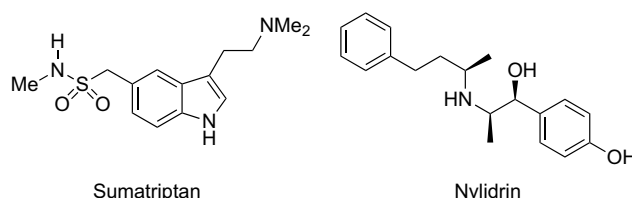

Figure 1.

mercially available iminophosphorane 3.[5] The reaction proceeds via a strategy of 'borrowing hydrogen', which we have previously exploited in other procedures such as the conversion of alcohols to longer chain alkanes.[6] As shown in Scheme 1, hydrogen is temporarily removed from the alcohol 1 to afford an intermediate aldehyde 4, which undergoes an aza-Wittig reaction with the iminophosphorane 3 to afford the imine 5. The hydrogen is then returned by the catalyst, reducing the imine 5 to an amine 2.
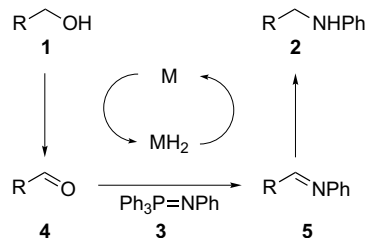
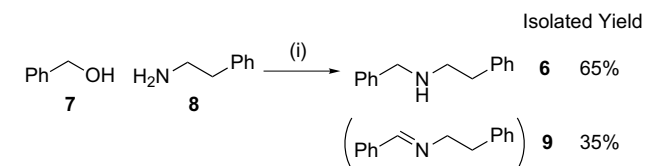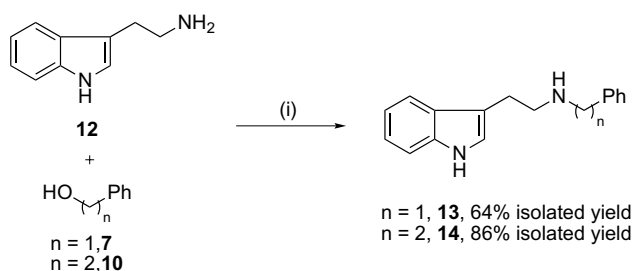Scheme 1. Borrowing hydrogen in the synthesis of amines via an aza-Wittig reaction.

Whilst this strategy was used successfully for the preparation of β-aminoarenes, it proved to be difficult to remove the triphenylphosphine oxide that was formed during the reaction. Imines are readily formed by the reaction of an aldehyde or ketone with an amine, and are traditionally driven to completion by the azeotropic removal of water. We therefore turned our attention to the use of free amines, which we hoped would form imines in situ with only the formation of water as a byproduct. Preliminary results indicated that this reaction was possible, and indeed the removal of water with the use of molecular sieves enabled these reactions to achieve higher yields. The *N*-alkylation of amines with alcohols has been reported previously with ruthenium catalysts, though more forcing conditions were required.[7]

N-Benzylphenethylamine **6** was prepared by two related routes, as shown in Scheme 2. The iridium catalysed reaction of benzyl alcohol **7** with phenethylamine **8** provided the expected product (65%) as well as a quantity of the nonreduced imine **9** (35%). An alternative synthesis employing phenethyl alcohol **10** with benzylamine **11** also afforded the desired product **6**, though in this case without any trace of the corresponding imine, in 93% isolated yield.[8]

As previously mentioned, our particular interests were in the preparation of *N*-alkylated tryptamine derivatives (vide supra). The reaction of tryptamine **12** with benzyl alcohol **7** and with phenethyl alcohol **10** proceeded without any over-alkylation. However, the reaction employing benzyl alcohol resulted in a lower yield, presumably as a consequence of the formation of a small amount of imine that had not been reduced (Scheme 3).
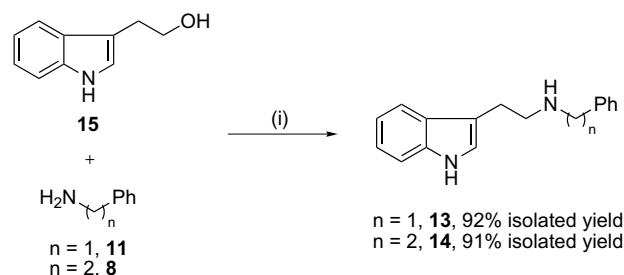
The *N*-alkylated tryptamine derivatives **13** and **14** could also be prepared by the reaction of tryptophol **15** with amines. Indeed, using this approach with benzylamine **11** allowed us to prepare *N*-benzyltryptamine **13** in 92% isolated yield with no trace of the intermediate imine (Scheme 4).

Whilst we had observed no formation of tertiary amines in any of the preceding reactions, we reasoned that the use of diols with primary amines would lead to the formation of *N*-heterocycles. Indeed, there is precedent for this reaction under forcing conditions,[9] and during the preparation of this manuscript Fujita et al. reported the *N*-heterocyclisation of primary amines with diols using a Cp*Ir catalyst.[10] As shown in Scheme 5, a diol **16** could undergo dehydrogenation to provide a monoaldehyde **17**, which undergoes reductive amination to **19**. The aminoalcohol **19** is then oxidised to generate the aminoaldehyde **20** which cyclises in situ to the enamine **21** (or iminium salt), which in turn is reduced to the heterocycle **22**. During the catalytic cycle, there is no net oxidation or reduction, but the temporary removal of hydrogen is required in order for the reaction to proceed.

n = 1, **13**, 92% isolated yield
n = 2, **14**, 91% isolated yield

Scheme 4. Reagents and conditions: (i) 5 mol % [Ir(COD)Cl]$_2$, 5 mol % dppf, 3 Å molecular sieves, PhMe, 24 h.

Isolated Yield

6 65%

9 35%

6 93%

Scheme 2. Reagents and conditions: (i) 5 mol % [Ir(COD)Cl]$_2$, 5 mol % dppf, 3 Å molecular sieves, PhMe, reflux, 24 h.

n = 1, **7**
n = 2, **10**

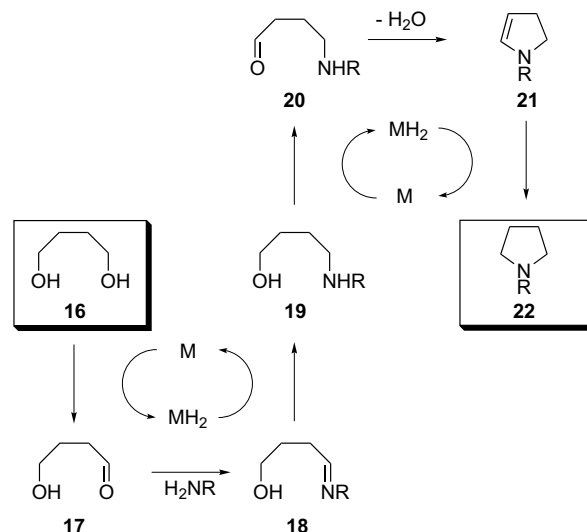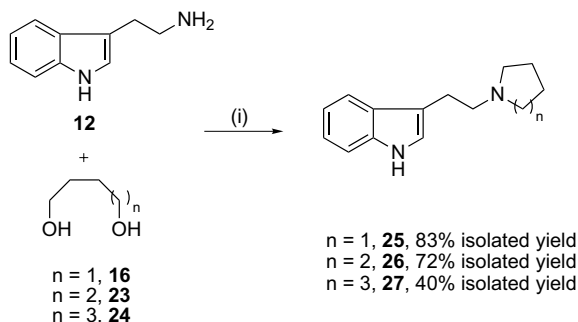n = 1, **13**, 64% isolated yield
n = 2, **14**, 86% isolated yield

Scheme 3. Reagents and conditions: (i) 5 mol % [Ir(COD)Cl]$_2$, 5 mol % dppf, 3 Å molecular sieves, PhMe, 24 h.

Scheme 5. A proposed mechanism for the conversion of diols to cyclic amines.

Scheme 6. Reagents and conditions: (i) 5 mol % [Ir(COD)Cl]₂, 5 mol % dppf, 3 Å molecular sieves, PhMe, 24 h.

We were pleased to find that reaction of tryptamine (**12**) with the appropriate diol (**16**, **23** and **24**) resulted in good conversion to the corresponding pyrrolidine **25**, and piperidine **26**, and in reasonable isolated yield into azepane **27** (Scheme 6).

In conclusion, a simple strategy for *N*-alkylation of amines has been developed and applied to the preparation of tryptamine derivatives. The work has also been extended to provide a simple procedure for the elaboration of tryptamine into heterocyclic derivatives.

References and notes

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8. The procedure for the preparation of **6** is typical: To a nitrogen purged pressure tube containing [IrCl(COD)]₂ (16 mg, 0.02 mmol), dppf (27 mg, 0.05 mmol), K₂CO₃ (6 mg, 0.05 mmol) and benzyl amine (109 μL, 1.00 mmol), was added phenethyl alcohol (120 μL, 1.00 mmol), followed by anhydrous toluene (1 mL). The tube was sealed and then heated at 110 °C for 24 h. After cooling to room temperature the reaction was quenched with wet diethyl ether (10 mL) and poured into water (50 mL) and diethyl ether (50 mL). The ether layer was separated and remaining aqueous layer further extracted with diethyl ether (3 × 50 mL). The combined organic extracts were washed with saturated brine (50 mL), dried (MgSO₄), filtered and concentrated in vacuo. Purification by flash column chromatography on silica using petroleum ether (bp 40–60 °C)/dichloromethane/ethyl acetate (2:1:1) as the eluent afforded *N*-benzyl-2-phenethylamine **6** as a pale yellow liquid (0.232 g, 100% conversion, 93% isolated yield): ^{1}H NMR (300 MHz, CDCl₃, 25 °C): δ = 2.17 (br s, 1H, NH), 2.79 (m, 4H, 2 × CH₂), 3.73 (s, 2H, CH₂), 7.09–7.26 (m, 10H, CHAr); ^{13}C NMR (75.4 MHz, CDCl₃, 25 °C): δ = 36.8, 51.0, 54.3, 126.5, 127.3, 128.5, 128.8, 128.9, 129.18, 140.5, 140.7; IR (liquid film): ν_{max} (cm^{-1}) 3313 (NH), 3060 (C$_{Ar}$–H), 2922 (N–CH₂), 2846 (C–H), 1718 (C$_{Ar}$–C$_{Ar}$), 1454 (C$_{Ar}$–C$_{Ar}$), 1354 (C$_{Ar}$–C$_{Ar}$); MS (EI+, 70 eV): *m/z* (%) 211 (16), [M$^{·+}$], 120 (65) [(M−(C₈H₉$^·$))$^+$], 91 (100) [(M−((C₉H₈)−CH₂NH$^·$))$^+$] 65 (10).
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