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A new route to medium and large heterocyclic compounds

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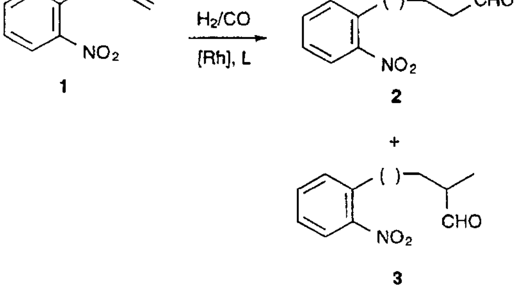
Hydrogenation of nitrobenzenes bearing aldehyde-containing substituents over heterogeneous platinum or palladium catalysts gives medium and/or large heterocyclic amines as a result of simple or dimeric cyclisation in moderate to good yields; a range of heteroatoms can be incorporated into the macrocycles, enhancing their potential as ligands.

The preparation of cyclic amines by hydrogenation of nitroaldehydes or nitroketones over platinum metal catalysts has been well established in the case of 5- and 6-membered heterocycles.[1] Recently the synthesis of a 17-membered cyclic amine has been reported in good yield (66%) by hydrogenolysis of a Cbz-protected aminoaldehyde with subsequent hydrogenation of the resulting cyclic iminium salt.[2] The reactions were carried out at relatively high dilution (4×10^{-3} M) in methanol using moderate amounts of a palladium hydroxide catalyst precursor (3.7×10^{-4} g atom of Pd) relative to substrate (2.3×10^{-1} mmol).

The above chemistry prompted us to explore a general synthesis of medium and large heterocycles based on the ready availability of nitrobenzenes bearing aldehyde-containing side chains **2** and **3** from hydroformylation[3] of the related nitroalkenes **1** (Scheme 1).[3,4] Good regio-control for the terminal aldehydes **2** can often be attained using the bulky bisphosphite ligand, BIPHEPHOS.[5] Use of triphenylphosphine or hydroformylation of allylic ethers[6] led to greater amounts of branched-chain aldehydes **3** but in all cases facile chromatographic separation of the branched and linear aldehydes was possible. The nitroaldehydes were reacted with hydrogen in methanol over 10% Pd/C and/or PtO_2 catalysts (Scheme 2). Standard conditions involved 1 atm H_2, ambient temperature, with Pd (5.6×10^{-5} g atom) for reaction on *ca.* 0.4 mmol scale with substrate concentration of 4.8×10^{-3} M. Larger amounts of Pt (3×10^{-4} g atom) were used, comparable with that described by the Japanese workers.[2] The results are summarised in Table1.

The monomeric compounds **5** and the dimeric compounds **6** were separated from any polymeric material and isolated in pure form by chromatography. Structures were assigned by ^1H and ^{13}C NMR spectroscopy and by electrospray (ESI) mass spectroscopy. Three representative products, the monomer **5n** as its *N*-benzoyl derivative and the dimers **6a** and **6g**, were fully characterised by single crystal X-ray structure determination.† Careful examination of the total product mixture by both adsorption chromotography and HPLC failed to show any evidence for the formation of trimers or other oligomers.



Scheme 1

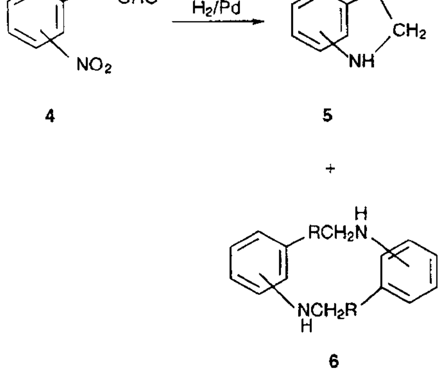
The yields of cyclic products obtained from *ortho*-substituted nitrobenzenes varied both with ring size and the pattern of heteroatom incorporation in the side chain. No clear trends emerged other than that in general compounds containing oxygen as the only heteroatom in the side chain gave lower yields of medium ring compounds, 9–11 membered (0–36%, entries 4–6, 8–10) than larger ring compounds, 13–22 membered (36–75%, entries 1, 4, 5, 9, 10, 13–15). Introduction of other heteroatoms had a marked influence. Reaction of compound **4b** containing sulfur in the side chain led only to an 8-ring monomer (entry 2) and two compounds **4f** and **4j** containing nitrogen in the side chain surprisingly gave only 9- and 11-membered ring compounds (entries 7 and 12). Introduction of ethyleneoxy units into the side chain in general led to improved yields over compounds containing carbon chains of similar lengths, *cf.* reactions of **4k** and **4l** (entries 13–15) with those of **4m** and **4n** (entries 16–18).

The *meta*- and *para*-substituted compounds **4o**–**4s** in all cases gave higher yields of dimeric compounds (entries 19–23).

An attempt was made to influence the yields of products by the addition of potential templating compounds to the reactions. Reactions of the compound **4i** were carried out with additives as summarised in Table 2.

Addition of the heavy metal salts Ag(OTf) and $La(OTf)_3$ dramatically influenced the ratio of products and resulted in exclusive formation of the eleven-membered heterocycle **5i** although the overall recovery of non-polymeric products was reduced. Energy minimisation calculations for interaction of one silver ion with the monomer **5i** and for two silver ions with the dimer **6i** were carried out.[7] The energy of the preferred conformation of the free monomer is similar to that of the preferred conformation when bonded to silver whereas serious distortion of the preferred conformation of the dimer is required in order to attain the conformation most suitable for bonding to two silver ions. Addition of glycine to the reaction had no effect on the yield or product distribution, perhaps not surprising as aqueous methanol was the reaction solvent.

The compounds have potential for use as novel ligands[8–10] and as constituents in molecular switching devices[11,12] and these applications are being evaluated.



Scheme 2

Table 1 Isolated yields of heterocycles from hydrogenation of nitroaldehydes **4**[a]

Entry	Reactant	RCHO	Catalyst	Product yields[b] (%) Monomer **5**	Product yields[b] (%) Dimer **6**
1	**4a**	$2\text{-}O(CH_2)_2CH(CH_3)CHO$	Pd	14(8)	30(16)
2	**4b**	$2\text{-}CH_2SCH_2CH(CH_3)CHO$	Pt	20(8)	—(16)
3	**4c**	$2\text{-}O(CH_2)_3CHO$	Pd	33(8)	8(16)
4	**4d**	$2\text{-}O(CH_2)_4CHO$	Pd	—(9)	64(18)
5	**4d**	$2\text{-}O(CH_2)_4CHO$	Pt	—	75
6	**4e**	$2\text{-}CH_2O(CH_2)_3CHO$	Pd	—(9)	23(18)
7	**4f**	$2\text{-}N(COPh)(CH_2)_4CHO$	Pd	22(9)	–(18)
8	**4g**	$2\text{-}O(CH_2)_5CHO$	Pd	7(10)	20(20)
9	**4h**	$2\text{-}O(CH_2)_2OCH_2CH(CH_3)CHO$	Pd	—(10)	37(20)
10	**4i**	$2\text{-}O(CH_2)_2O(CH_2)_3CHO$	Pd	19(11)	36(22)
11	**4i**	$2\text{-}O(CH_2)_2O(CH_2)_3CHO$	Pt	22	18
12	**4j**	$2\text{-}O(CH_2)_2N(SO_2Me)(CH_2)_3CHO$	Pd	36(11)	—(22)
13	**4k**	$2\text{-}O[(CH_2)_2O]_2CH_2CH(CH_3)CHO$	Pd	56(13)	—(26)
14	**4l**	$2\text{-}O[(CH_2)_2O]_2(CH_2)_3CHO$	Pd	75(14)	6(18)
15	**4l**	$2\text{-}O[(CH_2)_2O]_2(CH_2)_3CHO$	58	—	
16	**4m**	$2\text{-}O(CH_2)_9CH(CH_3)CHO$	Pt	29(15)	18(30)
17	**4n**	$2\text{-}O(CH_2)_{11}CHO$	Pd	27(16)	19(32)
18	**4n**	$2\text{-}O(CH_2)_{11}CHO$	Pd	36	11
19	**4o**	$3\text{-}O(CH_2)_2CH(CH_3)CHO$	Pd	6(9)	39(18)
20	**4p**	$3\text{-}O(CH_2)_4CHO$	Pd	10(10)	17(20)
21	**4q**	$4\text{-}O(CH_2)_5CHO$	Pd	—(12)[c]	11(24)
22	**4r**	$4\text{-}O(CH_2)_2O(CH_2)_3CHO$	Pt	7(13)	22(26)
23	**4s**	$4\text{-}O[(CH_2)_2O]_2((CH_2)_3CHO$	Pt	—(16)	26(32)

[a] Reactions at ambient temperature with H_2 (1 atm, 0.1MPa) using a substrate concentration of 4.76×10^{-3} M in methanol with Pd (5.6×10^{-5} g atom) as 10% Pd on C and Pt (3×10^{-4} g atom) as PtO_2. [b] Ring size in parentheses. [c] Amino alcohol from reduction of CHO and NO_2 groups also formed (45%).

Table 2 Yields of monomer **5** and dimer **6** from hydrogenations of the nitroaldehyde **4i** with additives[a]

Additive	Yield (%)[b] **5i**	Yield (%)[b] **6i**
—	19	36
Ag(OTf) 1 equiv.	30	—
Ag(OTf) 2 equiv.	33	—
$La(OTf)_3$ 1 equiv.	45	—
Glycine 1 equiv.[c]	21	33

[a] Reactions using Pd/C in methanol under conditions in footnote *a* in Table 1. [b] Isolated yield. [c] Glycine dissolved in a minimum amount of water (0.2 ml) and added to reaction in methanol (85 ml).

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Notes and references

† *Crystal data* for **5n**: $C_{25}H_{33}NO_2$, M = 379.54, monoclinic space group $P2_1/n$, a = 9.3905(1), b = 23.1162 (5), c = 10.0908(2) Å, β = 99.648(1)°, U = 2159.46(6) Å^3, Z = 4, D_c = 1.167 g cm^{-3}, crystal dimensions 0.32 $\times$ 0.25 $\times$ 0.17 mm, T = 123(1) K, Mo-Kα, radiation λ = 0.71069 Å, μ = 0.73 cm^{-1}. Data were collected on a Nonius Kappa CCD diffractometer and of the total 15 217 reflections measured, 4843 unique (R_{int} = 0.021). Refinement on F, R_w = 0.039, $R1$ = 0.037 [for 3268 reflections with $I > 3\sigma(I)$]. For **6a**: $C_{22}H_{30}N_2O_2$, M = 354.49, orthorhombic space group $Pbca$, a = 7.045(5), b = 16.646(1), c = 16.866(1) Å, U = 1977.80(2) Å^3, Z = 4, D_c = 1.190 g cm^{-3}, crystal dimensions 0.20 $\times$ 0.18 $\times$ 0.08 mm, T = 173 (1) K, Mo-Kα, radiation λ = 0.71069 Å, μ = 0.76 cm^{-1}. Data were collected on a Nonius Kappa CCD diffractometer and of the total 13313 reflections measured, 2819 unique (R_{int} = 0.106). Refinement on F, R_w = 0.052, $R1$ = 0.064 [for 825 reflections with $I > 3\sigma(I)$]. For **6g**: $C_{24}H_{34}N_2O_2$, M = 382.54, monoclinic space group $P2_1/c$, a = 9.2424(5), b = 5.0502(1), c = 23.455(1) Å, β = 101.075(1)°, U = 1074.42(7) Å^3, Z = 2, D_c = 1.182 g cm^{-3}, crystal dimensions 0.35 $\times$ 0.15 $\times$ 0.11 mm, T = 173(1) K, Mo-Kα, radiation λ = 0.71069 Å, μ = 0.75 cm^{-1}. Data were collected on a Nonius Kappa CCD diffractometer and of the total 6885 reflections measured, 2820 unique (R_{int} = 0.041). Refinement on F, R_w = 0.052, $R1$ = 0.053 [for 1511 reflections with $I > 3\sigma(I)$]. CCDC 182/1323. See http://www.rsc.org.suppdata/cc/1999/1463/ for crystallographic data in .cif format.

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