Transition Metal-catalysed N-Alkylation of Amines by Alcohols†

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Summary Primary and secondary alcohols effect alkylation of primary and secondary amines in the presence of rhodium, iridium, and ruthenium compounds at ⩽100 °C, whereby selective monoalkylation of primary amines can be achieved, and heterocyclic rings can be constructed by both inter- and intra-molecular processes.

THE N-alkylation of primary and secondary amines by reaction with alcohols can be achieved under forcing conditions by a number of metal catalysts, *e.g.* nickel,[1] nickel–rhenium compounds,[2] thorium salts,[3] silica–alumina,[4] metal alloy catalysts,[5] and mixed oxides of copper, barium, and chromium.[6] Our work[7] on metal-catalysed hydrogen transfer from alcohols to organic substrates suggested that similar catalyst systems should effect N-alkylation of amines by alcohols. We have accordingly studied such processes using both metal halide–triphenylphosphine mixtures, to generate phosphine complexes *in situ*, and preformed metal–phosphine complexes as catalysts.

The N-methylation of pyrrolidine by methanol was examined using *in situ* metal–phosphine complex formation (molar ratio of metal salt : phosphine 1 : 5). The catalytic activity (5 mol % catalyst) was found to decrease in the order $IrCl_3.H_2O$–PPh_3 > Na_2IrCl_6–PPh_3 > $RhCl_3.3H_2O$–PPh_3 > $RuCl_3.3H_2O$–PPh_3 ⩾ 5% Pd–C. 5% Rh–C did not show any catalytic activity. Thus, iridium trichloride gave an 80% yield (73% of pyrrolidine consumed) of *N*-methylpyrrolidine after boiling with a solution of pyrrolidine in methanol for 13 h. In comparison, 5% Pd–C gave a 6% yield (59% of pyrrolidine consumed) after 46 h. N-Alkylation using preformed metal–phosphine complexes as catalysts resulted in a significant increase in rate (Table 1), with $RhH(PPh_3)_4$ being the most active catalyst. Other amines and alcohols have been studied and some representative examples are shown in Table 2.

TABLE 1. N-Methylation of pyrrolidine by methanol.[a]

Catalyst	Time/h	Yield of *N*-methylpyrrolidine (%)
$RhH(PPh_3)_4$	4	97
$IrCl(PPh_3)_3$	5	87
$RhCl(PPh_3)_3$	8	92
mer-$IrH_3(PPh_3)_3$	24	47
$RuH_2(PPh_3)_4$	48	15

[a] Reactions carried out in boiling methanol using 5 mol % catalyst.

Metal complexes of the type studied in the present work are known to dehydrogenate primary and secondary alcohols to aldehydes and ketones respectively. The N-alkylation process can thus be represented as in the Scheme.

$$R^1CH(OH)R^2 + M \rightleftharpoons R^1COR^2 + MH$$

$$R^1COR^2 + HNR^3R^4 \rightleftharpoons R^1R^2C(OH)NR^3R^4 \rightleftharpoons R^1R^2C{=}\overset{+}{N}R^3R^4 + OH^-$$

$$R^1R^2C{=}\overset{+}{N}R^3R^4 + MH \rightleftharpoons R^1R^2CHNR^3R^4 + M$$

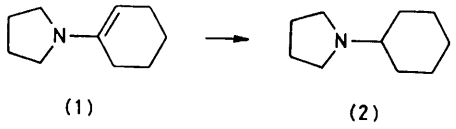
SCHEME

No imines were detected by g.l.c., suggesting that either carbinolamine formation or iminium ion formation was rate determining.‡ Pyrrolidine is known to form iminium species with carbonyl compounds with particular ease.[8] We have previously shown that $RhH(PPh_3)_4$ is an efficient catalyst for the reduction of imines by catalytic hydrogen-transfer from propan-2-ol.[9] Furthermore, both the $RhCl_3$–PPh_3 (1 : 5) and $IrCl_3$–PPh_3 (1 : 5) catalytic systems effect the reduction (**1**) → (**2**) by hydrogen transfer from propan-2-ol. The iridium system is superior, giving (**2**) in 87% yield (g.l.c.).

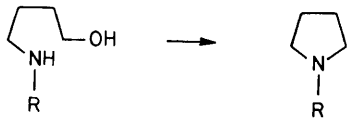
TABLE 2. Catalytic N-alkylations using $RhH(PPh_3)_4$ (5 mol %).

Amine	Alcohol	Time/h	Product (yield/%)[a]
Bu^nNH_2	MeOH	8	Bu^nNHMe (98)
Bu^nNHMe	MeOH	96	Bu^nNMe_2 (86)
Cyclohexylamine	MeOH	10	$C_6H_{11}NHMe$ (99)
Cyclohexylamine	MeOH	22[b]	$C_6H_{11}NHMe$ (88)
Pyrrolidine	EtOH	6	C_4H_8NEt (74)
Pyrrolidine	$PhCH_2OH$	4	$C_4H_8NCH_2Ph$ (99)
Pyrrolidine	Pr^iOH	240[c]	$C_4H_8NPr^i$ (37)
$PhNH_2$	MeOH	72	PhNHMe (39)
Piperazine	MeOH	160[c]	*N*-Methylpiperazine (52), *NN'*-Dimethylpiperazine (13)

[a] Yields determined by g.l.c. using mesitylene as internal standard. [b] 1 mol % $RhH(PPh_3)_4$. [c] $IrCl_3.3H_2O$–PPh_3 (1 : 5 mol. ratio; 5 mol % $IrCl_3.3H_2O$).



(1) (2)



(3) (4)

a; R = Bu^n a; R = Bu^n

b; R = CH_2Ph b; R = CH_2Ph

† British patent pending to R. Grigg; European Patent Application No. 81,300,598, U.S.A., 234,803.

‡ Amine attack (carbinolamine formation) is rate determining under acidic conditions, whilst dehydration of the carbinolamine (iminium ion formation) is rate determining at pH values near or above neutrality: W. P. Jencks, *Prog. Phys. Org. Chem.*, 1964, **2**, 63.

The catalytic N-alkylation procedure can also be applied to ring synthesis. Thus the amines (**3a**) and (**3b**) are cyclised to the pyrrolidines (**4a**) (56% isolated yield) and (**4b**) (82% by g.l.c.), respectively, by 5 mol % $RhH(PPh_3)_4$ in boiling dioxan. In a similar manner butane-1,4-diol and benzylamine (10:1 mol. ratio) in boiling dioxan give (**4b**) (31% by g.l.c.).

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