Pergamon

Tetrahedron Letters 40 (1999) 5597–5600

TETRAHEDRON LETTERS

A Direct Route to Medium and Large Cyclic Amines from Aminoalkenes

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Received 27 April 1999; accepted 19 May 1999

Abstract

Rhodium-catalysed reactions of aminoalkenes with H_2/CO give cyclic amines with a range of medium and large ring sizes in yields up to 85%. High regioselectivity for non-branched products can be obtained when BIPHEPHOS is used as a ligand in the hydroformylation reaction.

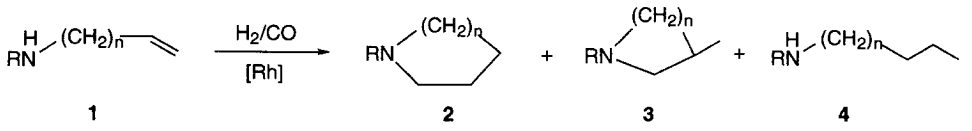
Keywords: Hydroformylation, Regiochemistry, Nitrogen heterocycles, Medium-ring heterocycles.

The formation of medium and large ring amines by cyclisation of aminoaldehydes and subsequent reduction of the intermediate iminium salts has been demonstrated either using sodium borohydride [1] or hydrogen and a palladium catalyst [2] as reductants. It has been previously demonstrated that metal-catalysed reactions of unsaturated amines with H_2/CO can give 5- and 6-membered lactams in high yields as a result of carbonylation reactions [3]. Hydroformylation of other unsaturated amines leads to aminoaldehydes which can cyclise to give iminium salts which in turn can be trapped by an additional amine substituent in the molecule leading to bicyclic diamines in high yield [4]. Coordination of the amino function to the rhodium metal catalyst has been shown to occur rapidly [5,6] and it thus seemed possible that, as only very low ratios of rhodium to substrate are used (typically 1:100 or greater), then hydroformylation should result in formation of an aldehyde in close proximity to the rhodium-coordinated amine function thus promoting cyclisation to give a cyclic imine or iminium salt rather than polymerisation. However, rhodium-catalysed reactions of some alkenyloxybenzylamines with H_2/CO gave polymeric material in all cases [7] suggesting that either polymerisation was more rapid than cyclisation or that the cyclic imines or iminium salts were themselves susceptible to polymerisation under the reaction conditions.

In this paper we describe attempts to achieve rapid *in situ* reduction of any cyclic intermediate before it has a chance to polymerise. A recent paper has described an intermolecular version of this reaction leading to the formation of secondary and tertiary amines [8].

Initial attempts involving rhodium-catalysed reactions of 10-undecenamine **1a** with H_2/CO (1:1) gave polymeric material on work up. However, immediate reduction of the initial hydroformylation product with sodium borohydride followed by acetylation gave a mixture of *N*-acetyl derivatives of **2a** and **3a** in modest

0040-4039/99/$ - see front matter
PII: S0040-4039(99)01020-5



1 2 3 4

a R = H, n = 9
b R = Bn, n = 9
c R = (*o*-Tol)CH_2, n=9
d R = *n*-Bu, n = 9
e R = Bn, n = 6
f R = Bn, n = 4
g R = PhCH(Me), n = 3

yield (38%). Reactions of the *N*-benzyl-10-undecenamine **1b** under the same conditions directly gave a mixture of the cyclic amines **2b** and **3b** derived from linear and branched products without the need for borohydride reduction consistent with recent observations that enamines hydrogenate more rapidly than imines [9]. Use of the bulky bisphosphite ligand BIPHEPHOS [10] and a 9:1, H_2/CO gas ratio led to high regio- and chemoselectivity resulting in the formation of *N*-benzylazacyclotridecane **2b** in excellent yield (85%). These conditions were thus applied to the reactions of other linear unsaturated amines **1b-1g** and the results are summarised in Table 1 together with the results of reactions using other ratios of H_2:CO.

Table 1

Rhodium-catalysed reactions of unsaturated amines **1** with H_2/CO[a]

Entry	Reactant	R	n	Ratio H_2/CO	Product yield[b] 2	4	Ring size of **2**
1	**1b**	Bn	9	1 : 1	47	-	13
2	"	"	"	9 : 1	85	-	"
3	**1c**	(*o*-Tol)CH_2	9	1 : 5	28	-	"
4	**1d**	*n*-Bu	9	1 : 1	40	-	"
5	"	"	"	9 : 1	82	-	"
6	**1e**	Bn	6	1 : 1	25	35	10
7	"	"	"	9 : 1	25	35	"
8	**1f**	Bn	4	1 : 1	43	-	8
9	**1g**	PhCH(Me)	3	1 : 5	60	-	7
10	"	"	"	9 : 1	20	40	"

a Reactions of **1** were carried out for 20 h at 80°C with an initial gas pressure (H_2 + CO) of 2.76 MPa (400 psi) in the presence of $[Rh(OAc)_2]_2$ and BIPHEPHOS in molar ratio 200 : 1 : 4.

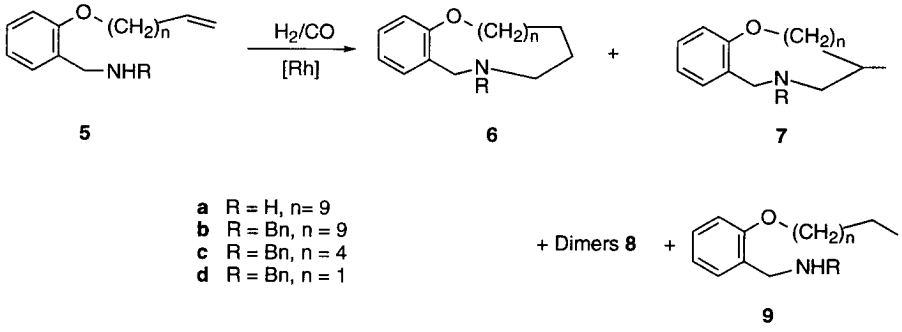
b Yields of material purified by selective extraction and/or chromatography

Although excellent yields of *N*-benzyl and *N*-butyl azacyclotridecanes were obtained using a H_2/CO ratio of 9:1 (entries 2 & 5), hydrogenation of the starting alkene prior to hydroformylation became an increasing problem as the chain length of the alkenylamine **1** became shorter. Thus reaction of *N*-benzyl-7-octenamine **1e** gave *ca.* 35% of *N*-benzyloctylamine **4e** and reaction of *N*-(α-phenylethyl)-4-pentenamine **1g** gave *ca.* 40% of the saturated linear amine **4g** (entries 7 and 10). The hydrogen content of the gas mixture was decreased in an attempt to minimise this hydrogenation initially to 1:1 and then to 1:5 after publication of Rische and Eilbracht's paper [8]. Reactions of the undecenamines **1b,c** and **d** with 1:1 H_2/CO gave

decreased yields of cyclic amine (47 and 40%, entries 1 and 4) and an even lower yield (28%) when a 1:5 H_2/CO ratio was used (entry 3).

It appears that hydrogenation of an initially formed 13-membered cyclic iminium salt or enamine is crucial to obtaining high yields of the 13-membered cyclic amine and that hydrogenation of the long chain terminal alkene is relatively slow even when the gas mixture has a high H_2 content. In contrast, lowering the hydrogen content in the gas mixture led to an increased yield of cyclic amine in reaction of *N*-(α-phenylethyl)-4-pentenamine **1g**. Reaction using a 1:5, H_2/CO mixture gave 60% of the cyclic amine (entry 9). A reaction of *N*-benzyl-5-hexenamine **1f** also gave a moderate yield of cyclic amine (43%) when a 1:1 gas mixture was used (entry 8).

Similar reactions were carried out using a limited range of 2-alkenyloxybenzylamines **5**. A reaction of **5a** using 1:1, H_2/CO and PPh_3 as ligand gave only polymeric material but immediate reduction of the initially



formed product with sodium borohydride followed by acetylation gave a mixture of the *N*-acetyl derivatives of the cyclic amines **6a** and **7a** in 36% yield. Reactions of the *N*-benzyl analogues **5b,c** and **d** are summarised in Table 2. A reaction of **5b** using PPh_3 as ligand and a 1:1, H_2/CO ratio directly gave a low yield of cyclic products **6b** and **7b** (10%) (entry 11) again confirming the beneficial effect of *N*-benzyl substitution. Use of BIPHEPHOS as ligand with a H_2/CO ratio of 1:1 led to almost complete regioselectivity for the product **6b** arising from terminal hydroformylation but in contrast to reactions of the aliphatic amines **1** a significant amount of the product was dimeric **8b**, (entry 12). A similar result was obtained using a 1:5, H_2/CO ratio (entry 14). An attempt to increase the amount of monomeric cyclic product by raising the H_2/CO ratio to 9:1 was not successful in this case giving a similar amount of **6b** but with an increase in the amount of dimeric product (to 44%) and a significant amount of hydrogenated material **9b** (16%).

Reactions of the homologous alkene **5c** with H_2/CO ratios of 1:1 or 9:1 gave no cyclic amines. A reaction using BIPHEPHOS as ligand would have been expected to mainly give a terminal aldehyde which on cyclisation would give a strained twelve membered ring. However, reaction using a 1:5, H_2/CO ratio led to monomeric cyclic products **6c** and **7c** in yields of 30 and 10% respectively. No dimeric products **8c** nor the product of hydrogenation **9c** were observed. It appears that the regioselective influence of the BIPHEPHOS ligand is not as effective when a H_2/CO ratio of 1:5 is used.

Reactions of the allyloxy compound **5d** were more complex. Use of PPh_3 as a ligand gave only the phenol arising from hydrogenolysis of the allyl group and the benzoxazine arising from a previously noted rearrangement [7] (entry 18). A similar reaction but using BIPHEPHOS as ligand gave the 7-membered ring **6d** (33%) and its dimer **8d** (19%), (entry 19).

Table 2
Rhodium-catalysed reactions of *N*-benzyl 2-alkenyloxybenzylamines **5**; R=Bn with H_2/CO[a]

Entry	Reactant	n	Ligand	Gas Ratio H_2/CO	Product (yields %)[b] 6	7	8	9
11	**5b**	9	PPh_3	1 : 1		10	-	-
12	"	"	BIPHEPHOS	1 : 1	34	-	20	-
13	"	"	"	9 : 1	38	-	44	16
14	"	"	"	1 : 5	20	-	10	-
15	**5c**	4	"	1 : 1	-	-	-	20
16	"	"	"	9 : 1	-	-	-	20
17	"	"	"	1 : 5	30	10	-	-
18	**5d**	1	PPh_3	1 : 1	-	-	-	-[c]
19	"	"	BIPHEPHOS	1 : 1	33	-	19	-[d]

a Reaction conditions as for reactions in Table 1

b Yields of material purified by selective extraction and/or chromatography

c 2-Benzylaminomethylphenol (25%) and 3-benzyl-2-(1-methylethyl)-3,4-dihydro-2*H*-1,3-benzoxazine (19%) were isolated

d 2-Benzylaminomethylphenol (18%) was also isolated.

In summary, it can be seen that the hydroformylation of *N*-substituted alkenylamines can give monomeric cyclic products in fair (entry 8) to good (entry 9) to very good (entries 2 and 5) yields. However, important side reactions including dimerisation and polymerisation of intermediates or hydrogenation in preference to hydroformylation of the starting aminoalkenes **1** and **5** can lead to undesirable products.

Acknowledgements

We thank the Australian Research Council for support and for provision of an Australian postgraduate award (to DJB) and Johnson Matthey Pty Ltd for a loan of rhodium.

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