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Heterogeneous Rhodium-Catalyzed Hydrogenation Conditions for the Highly Effective Synthesis of 1,3-Oxazolidines from 1,2-Amino Alcohols and Nitriles .[1#]

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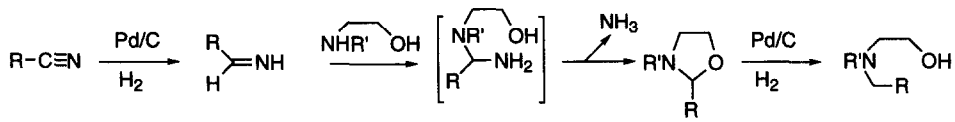
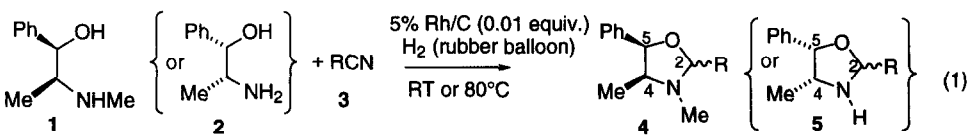
Abstract: A procedure easily to carried out for the synthesis of 1,3-oxazolidines in high yields using 1,2-amino alcohols, nitriles, an atmospheric pressure of hydrogen and catalytic quantities of rhodium on carbon powder is presented. This reaction probably involves the semi-hydrogenation of the nitrile followed by condensation with the amino alcohol. The process may constitute the key step in a two-step sequence for reducing a nitrile into the corresponding aldehyde. © 1998 Elsevier Science Ltd. All rights reserved.

Recently, we reported a one-pot *N*-alkylation procedure of 1,2-amino alcohols through their reaction with nitriles in the presence of palladium on charcoal and hydrogen. Under these conditions, 1,3-oxazolidines are formed as intermediates and they undergo hydrogenolysis of the NC-O bond to afford *N*-alkylated-amino alcohols.[2] We suspect that the heterocyclization involves firstly hydrogenation of the nitrile to the corresponding imine,[3,4] and secondly trapping of this imine by the amino alcohol competing with its further reduction (Scheme 1).



Scheme 1

1,3-Oxazolidines are usually obtained from the condensation of 1,2-amino alcohols with either aldehydes or their corresponding acetals.[5] They are useful as intermediates in organic synthesis.[5,6] Moreover, it has been recently shown that non-racemic, chiral 1,3-oxazolidines can be effective ligands for metal-catalyzed enantioselective procedures.[7] Therefore, it would be desirable to find appropriate conditions to selectively and effectively synthetize oxazolidines from amino alcohols and nitriles in a one-pot procedure. With this aim, we have examined the use of heterogeneous catalysts other than palladium in the above reaction. We are now delighted to report that this goal has been attained by using rhodium on carbon powder (Eq. 1).



R: CH_3 (**a**), CH_2CH_3 (**b**), $(CH_2)_2CH_3$ (**c**), $(CH_2)_3CH_3$ (**d**), CH_2Ph (**e**), Ph (**f**), $(CH_2)_8CH_3$ (**g**), *c*-C_6H_{11} (**h**), $CH(CH_3)_2$ (**i**).

This paper is dedicated to Pr J.-P. Pète on the occasion of his 60th birthday.

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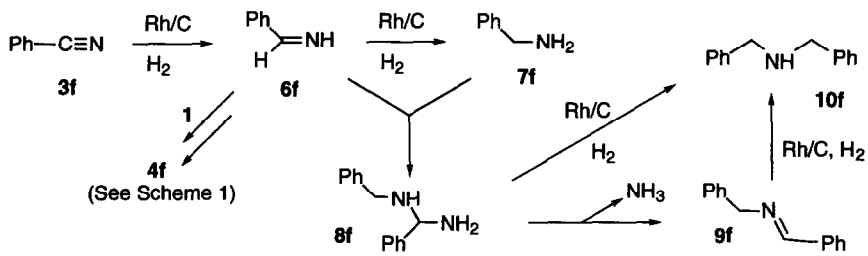
When a solution of (-)-ephedrine **1** (0.12 M) in acetonitrile containing catalytic quantities of Rh/C[8] was stirred at room temperature under an atmosphere of hydrogen, complete consumption of the amino alcohol was observed after 7 h. Filtration of the mixture over a short pad of silica gel and evaporation of the solvents gave oxazolidine **4a**[9] in 95% yield. When using a solvent such as toluene and an amount of **3a** reduced to 10 equiv. (with respect to **1**), the reaction remained very effective, since a 92% yield of the desired product was recovered (Table 1, run 1). As outlined by runs 2-4 and 14-17, similar results were obtained with propionitrile, *n*-butyronitrile and valeronitrile in reaction with either **1** or **2**. In contrast, the use of heavier (runs 5, 7 and 10) or secondary nitriles (run 12) led to a sluggish condensation under analogous conditions: the conversion of **1** was greatly reduced and this was similarly observed when exchanging toluene for methanol or ethyl acetate. Nevertheless, satisfying results were obtained when the reactions in ethyl acetate were performed at reflux instead of room temperature. These conditions provided a 100% consumption of **1** with virtually quantitative formation of **4** even when only 5 equiv. of **3** were used (runs 6, 8, 9, 11 and 13).

The observed diastereomeric ratios obtained for oxazolidines **4** and **5** (Table 1) suggest a thermodynamically controlled reaction: the tautomeric equilibrium between oxazolidines and their open form is in favour of the *cis*-heterocyclic diastereomer as demonstrated by studies on **4a**[9], **4f**[11] and **5f**.[16] In fact, we were unable to identify the open form of **5a-5d** among the reaction products when **2** was used as aminoalcohol.

Nevertheless, careful analysis of the ^{1}H NMR spectrum of the crude reaction mixture obtained from **1** and **3f** showed the presence of *N*-benzylidenebenzylamine (δ: 4.81 and 8.37 ppm) and dibenzylamine (δ: 3.85 ppm) as side-products while benzylamine (δ: 3.80 ppm) was not detected. As mentioned above, hydrogenation of nitriles and imines into amines are competing reactions to the trapping of imines.[17] In the present reaction, the imine **6f**, formed by hydrogenation of **3f**, is reduced to the primary amine **7f** or trapped either by the amino alcohol giving **4f** or by the amine **7f** leading to **8f** (Scheme 2). Compound **8f** gave **10f** either by hydrogenolysis[4] or *via* the imine **9f**.[4,20] These observations led us to investigate the hydrogenation of **3f** in the absence of **1** (**3f**: 3 mmol, Rh/C: 30 mg, AcOEt, 80°C): a slow reaction took place (the conversion of **3f** was incomplete after 80h) to afford the substituted imine **9f** and the secondary amine **10f**; as above, no primary amine was detected. The large increase in the **10f/9f** ratio with time (16 h: 0.3, 80 h: 4.9) suggested that **10f** was at least in part derived from **9f**.[4,20] The comparison of the competing reactions showed that the hydrogenation steps were much slower than those of the imine condensation.



Scheme 2

Oxazolidines are masked aldehydes, the latter being produced by hydrolysis of the former.[5,21] Therefore, we examined the possibility of reducing nitriles into the corresponding aldehydes *via* oxazolidines. For this purpose, an excess of amino alcohol *versus* nitrile was required. Thus, benzonitrile was reacted with

10 equiv. of either (-)-ephedrine or *N*-methylaminoethanol for 48 h (Rh/C: 0.012 equiv., EtOAc, 80°C). After elimination of the catalyst by filtration over Celite and concentration, the crude mixture was hydrolyzed[21b] leading to benzaldehyde with respectively 71 or 65% overall yields. In conclusion, this two-step procedure offers an efficient alternative to other methods of reducing nitriles.[22]

Table 1.: Condensation of various nitriles with (-)-ephedrine (**1**) and (+)-norephedrine (**2**).

Runs	Amino alcohol	RCN (equiv.)	Method[a]	Time h	Conversion % of **1** or **2**	Oxazolidine yield %	*cis* / *trans*[10]
1	**1**	**3a** (10)	A	8	100	**4a**[9]: 92[b]	93 / 7
2	"	"	"	10	"	**4b**[12]: 91[b]	88 / 12
3	"	**3c** (10)	"	20	"	**4c**[13]: 94[b]	92 / 8
4	"	**3d** (10)	"	"	"	**4d**: 89[b]	89 / 11
5	"	**3e** (5 or 10)	"	16	~ 37	**4e**: n.d.[c]	n.d.[c]
6	"	**3e** (5)	B	8	100	**4e**[14]: 95[d]	91 / 9
7	"	**3f** (5)	A	20	74	**4f**: n.d.[c]	82 / 18
8	"	**3f** (3)	B	16	100	**4f**[11]: 96[d]	91 / 9
9	"	**3g** (5)	"	15	"	**4g**: 97[d]	91 / 9
10	"	**3h** (5)	A	24	22	**4h**: n.d.[c]	86 / 14
11	"	**3h** (5)	B	21	100	**4h**: 92[d]	91 / 9
12	"	**3i** (10)	A	20	70	**4i**: n.d.[c]	n.d.[c]
13	"	**3i** (10)	B	15	100	**4i**[12,15]: 91[b]	88 / 12
14	**2**	**3a** (10)	A	7	"	**5a**: 99[b]	73 / 27
15	"	**3b** (10)	"	7	"	**5b**: 97[b]	75 / 25
16	"	**3c** (10)	"	24	"	**5c**: 97[b]	72 / 28
17	"	**3d** (10)	"	"	"	**5d**: 99[b]	68 / 32

[a]The mixture of amino alcohol (0.6 mmol), nitrile (1.8-6 mmol), Rh/C (30 mg) and solvent (5 ml) was stirred under an atmosphere of hydrogen (rubber balloon); A: in toluene at RT; B: in ethyl acetate at 80°C. [b]Isolated yields. [c]Not determined. [d]Yields determined by ^{1}H NMR using dibenzylether (δ: 4.55 ppm) as internal standard.

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    ^1H NMR:
    - *cis* **5a**: 0.73 (*Me*(4), d, *J* 6.9), 1.57 (*Me*(2), d, *J* 5.3), 1.84 (N*H*, m), 3.63 (*H*(4), m), 4.73 (*H*(2), q, *J* 5.3), 4.94 (*H*(5), d, *J* 7.6), 7.25 (*Ph*, m).
    - *trans* **5a:** 0.74 (*Me*(4), d, *J* 6.9), 1.42 (*Me*(2), d, *J* 5.7), 1.84 (N*H*, m), 3.74 (*H*(4), m), 5.02 (*H*(5), d, *J* 6.5), 5.20 (*H*(2), d, *J* 5.7), 7.25 (*Ph*, m).
    - *cis* **5b**: 0.73 (*Me*(4), d, *J* 6.5), 1.13 (*Me*CH_2, t, *J* 7.6), 1.89 (*CH*2Me, m), 1.89 (N*H*, m), 3.63 (*H*(4), m), 4.52 (*H*(2), t, *J* 5.7), 4.90 (*H*(5), m), 7.25 (*Ph*, m).
    - *trans* **5b:** 0.74 (*Me*(4), d, *J* 6.9), 1.03 (*Me*CH_2, t, *J* 7.6), 1.69 (*CH*2Me, m), 1.89 (N*H*, m), 3.69 (*H*(4), m), 4.90 (*H*(5) and *H*(2), m), 7.25 (*Ph*, m).
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