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Nitriles under Palladium-Catalyzed Hydrogenation Conditions as Substitutes for Aldehydes in the Reaction with 1,2-Amino Alcohols: Formation of 1,3-Oxazolidines and Reductive *N*-Alkylation

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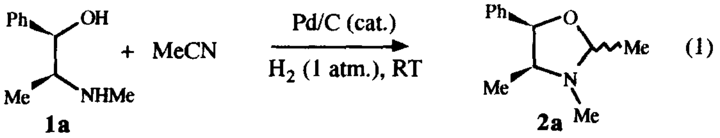
Abstract: At room temperature, the presence of hydrogen and catalytic amounts of Pd/C induced the formation of 1,3-oxazolidines from nitriles and 1,2-amino alcohols. The subsequent reductive cleavage of the NC-O bond of these heterocycles occurred under the same conditions. Thus, this methodology provides a new one-pot *N*-alkylation of 1,2-amino alcohols using nitriles as reagents with yields up to 98%. © 1997 Elsevier Science Ltd.

In the course of studies on the synthesis of optically active ketones in the presence of palladium on charcoal, hydrogen and (-)-ephedrine (**1a**),[1,2] we have isolated small amounts of the 1,3-oxazolidine **2a**[3] when i) acetonitrile was used as solvent and ii) hydrogenation conditions were maintained for a long time. Obviously, **2a** was generated from the reaction between **1a** and acetonitrile mediated by the heterogeneous palladium-catalyzed hydrogenation procedure (Eq. 1). To the best of our knowledge, such a process has never been reported.



Oxazolidines are useful synthetic intermediates; they are usually obtained from the condensation of 1,2-amino alcohols with either aldehydes or their corresponding acetals.[4,5] This urges us to study the formation of oxazolidines under conditions in which a nitrile plays formally the role of an aldehyde.

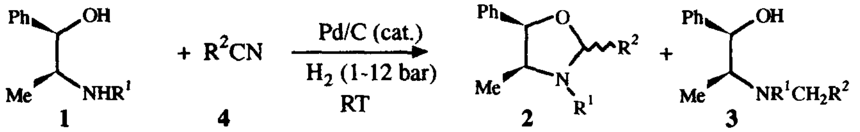
In preliminary experiments, solutions of (-)-ephedrine in acetonitrile containing catalytic quantities of Pd/C[6] were stirred at room temperature under a static hydrogen atmosphere or with a continuous bubbling (1-50 ml/min) of hydrogen into the mixture. Thus, we obtained **2a**[3,7] and also **3a**[8] which corresponds to the *N*-ethylation of **1a** (Eq. 2). The most reproducible conditions were obtained when using a rubber balloon filled with hydrogen. As exemplified by results summarized in Table 1, the conversion of **1a** increased with the amount of catalyst (runs 1 and 2). It also appeared clearly that **3a** was produced by cleavage of the NC-O bond of **2a** since its relative amount increased with time while that of **2a** dropped (runs 2 to 4).[10] In agreement, a solution of **2a** in MeOH (0.12 M) containing Pd/C (0.012 equiv.) stirred under hydrogen (1 atm.) for 24 h provided **3a** with 95% yield.

Table 1. Condensation of (-)-ephedrine with acetonitrile.[a]

Run	Pd/C equiv.	Time	**1a** / **2a** / **3a** Ratio[b]
1	0.004	24 h	21 / 58 / 21
2	0.012	4 h	37 / 50 / 13
3	0.012	7 h	0 / 35 / 65
4	0.012	17 h	0 / 15 / 85

[a]At room temperature, using **1a** (0.6 mmol), MeCN (6 ml), Pd/C and a balloon of hydrogen. [b]Determined by ^1H NMR analysis.[9] The figure "0" means that this compound was not detected.

With butyronitrile (**4b**) instead of acetonitrile, the procedure afforded oxazolidine **2b** (**1a** / **2b** ratio: 75 / 25 in 7 h[9]). In keeping acetonitrile as both solvent and reagent, the exchange of **1a** for (-)-norephedrine (**1c**) provided oxazolidine **2c**[11] and the alkylated adduct **3c**[8] (**1c** / **2c** / **3c** ratios: 56 / 32 / 12 in 7 h, 46 / 27 / 27 in 17 h[9]).



(2)

a: R^1= Me
c: R^1= H

a: R^2= Me
b: R^2= *n*-Pr
d: R^2= Et
e: R^2= $(CH_2)_2OH$
f: R^2= CH_2Ph
g: R^2= *i*-Pr

a: R^1= Me, R^2= Me
b: R^1= Me, R^2= *n*-Pr
c: R^1= H, R^2= Me
d: R^1= Me, R^2= Et
e: R^1= Me, R^2= $(CH_2)_2OH$
f: R^1= Me, R^2= CH_2Ph
g: R^1= Me, R^2= *i*-Pr

With the aim of using lower amounts of the cyano compound, we examined the reaction of **1a** with **4a** in various solvents. The condensation and the accompanying cleavage reaction were indeed obtained (Table 2). Nevertheless, their efficiencies were affected by the nature of solvents (runs 1, 4, 6 and 7) and the amounts of acetonitrile (runs 2 and 3). The complete transformation of **1a** was obtained in 20 to 24 h when using 10 equiv. of **4a** in methanol or toluene (runs 2 and 5). A particularly clean reaction was provided in methanol: **3a** was thus isolated with 95% yield (run 2).

Therefore, the domino reaction[12] described above composes a highly effective one-pot *N*-alkylation of 1,2-amino alcohols. Previously, such a reaction has been carried out either by alkylation with organic halides[8,13] or through two steps: firstly, either a condensation with aldehydes (or their corresponding acetals)[4] or a *N*-acylation[8,14] and secondly, a reduction.[4,15]

Table 2. Influence of the nature of the solvent on the condensation of (-)-ephedrine with acetonitrile.[a]

Run	Solvent	Time	**1a** / **2a** / **3a** Ratio[b]
1	MeOH	7 h	33 / 24 / 43
2	MeOH	24 h	0 / 0 / 100
3	MeOH[c]	24 h	11 / 6 / 84
4	PhMe	7 h	80 / 20 / 0
5	PhMe	20 h	0 / 61 / 39
6	EtOEt	7 h	85 / 15 / 0
7	AcOEt	7 h	88 / 5 / 7

[a] At room temperature, using **1a** (0.6 mmol), **4a** (0.32 ml, 10 equiv.), Pd/C (30 mg, 0.012 equiv.), solvent (5 ml) and a balloon of hydrogen. [b] As in Table 1. [c] The quantity of MeCN was reduced to 5 equiv.

In methanol, the reaction with butyronitrile (**4b**), propionitrile (**4d**) and 3-hydroxypropionitrile (**4e**) was also observed under the present hydrogenation conditions (Table 3, runs 1 to 5). Thus, *N*-alkylated amino alcohols **3b**, **3d** and **3e**[16] have been isolated with fair to high chemical yields (runs 2, 3 and 5[17]). In contrast, benzylcyanide (**4f**) and isopropylcyanide (**4g**) were reluctant to react under these conditions even when the reactions were carried out at 80°C (runs 6 and 7). Nevertheless, the reactivity of **4f** and **4g** was improved when the reaction was performed in a stainless steel bomb under pressure of hydrogen (Table 3, runs 8 to 11). Then, the crude **2g** / **3g** mixture obtained in run 11 was dissolved in methanol; after stirring this solution for 24 h under hydrogen (balloon) in presence of catalytic amounts of Pd/C, **3g**[16] was isolated with 79% yield.

Table 3. Condensation of (-)-ephedrine with various nitriles in methanol.[a]

Run	R^2CN (equiv.)	Hydrogen	t°C	Time	**1a** / **2** / **3** Ratio[b]	**3**: Yield %[c]
1	**4b** (10)	balloon[d]	RT	48 h	32 / 16 / 52	e
2	**4b** (10)	balloon[d]	RT	90 h	0 / 0 / 100	**3b**: 92
3	**4d** (5)	balloon	RT	24 h	0 / 0 / 100	**3d**: 98
4	**4e** (5)	balloon	RT	24 h	39 / 27 / 34	e
5	**4e** (5)	balloon[d]	RT	90 h	0 / 0 / 100	**3e**: 55
6	**4f** (5)	balloon	80	15 h	100 / 0 / 0	0
7	**4g** (10)	balloon	80	15 h	98 / 2 / 0	0
8	**4f** (5)	12 bar	RT	21 h	88 / 12 / 0	e
9	**4f** (5)	12 bar	RT	93 h	29 / 30 / 41	e
10	**4g** (10)	12 bar	RT	15 h	80 / 20 / 0	e
11	**4g** (10)	12 bar	RT	96 h	0 / 40 / 60	**3g**: see text

[a] Using **1a** (0.6 mmol), **4** (5 or 10 equiv.), Pd/C (30 mg, 0.012 equiv.), methanol (5 ml) under hydrogen (1 or 12 bar). [b] As in Table 1. [c] Isolated *N*-alkylated amino alcohol. [d] The rubber balloon was exchanged for a new one filled with hydrogen after each 24 h. [e] Not isolated.

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6. 5% Pd/C Ref. 5011 from Engelhard Company was used throughout this work. This catalyst has a surface area of 1100 m^2/g and contains 50% of water. The carbon type of this catalyst is activated wood (Technical information from Engelhard Company).
7. An almost diastereomerically pure form of **2a** was obtained. The *cis*-relative configuration at C-2 was deduced from literature data: Agami, C.; Rizk, T. *Tetrahedron* **1985**, *41*, 537-540 and ref. therein.
8. Enders, D.; Zhu, J.; Kramps, L. *Liebigs Ann./Recueil* **1997**, 1101-1113.
9. The ratio was determined fom the relative integration of the ^{1}H NMR signals corresponding to the hydrogen *gem* to the phenyl group (doublet for each compound).
10. The metal-catalyzed hydrogenolysis of oxazolidines is already known: ref.^{4}; Engelhardt, T.; Crossley, F.S.; Sprague, J.M. *J. Am. Chem. Soc.* **1950**, *72*, 2718-2722; Eleved, M.B.; Hogeven, H.; Schudde, E.P. *J. Org. Chem.* **1986**, *51*, 3635-3642; Polyak, F.; Dorofeeva, T.; Zelchan, G. *Synth. Commun.* **1995**, *25*, 2895-2900.
11. **2c** was a 75/25 mixture of diastereoisomers; ^{1}H NMR: 0.72 (CH_3CHCH, d, *J* 6.8), 1.56 (CH_3CHO, d, *J* 5.7), 1.87 (NH), 3.60 (CH$_3$CHCH, dq, *J* 7.6, 6.8), 4.72 (CH$_3$CHO, q, *J* 5.7), 4.93 (PhCH, d, *J* 7.6), 7.3 (C$_6H_5$, m) and 0.74 (CH_3CHCH, d, *J* 6,8), 1,40 (CH_3CHO, d, *J* 5.7), 1.87 (NH), 3.73 (CH$_3$CHCH, dq, *J* 6.0, 6.8), 5.01 (PhCH, d, *J* 6.0), 5.2 (CH$_3$CHO, q, *J* 5.7), 7.3 (C$_6H_5$, m).
12. For a highlight definition of the domino reactions, see: Tietze, L.F. *Chem. Rev.* **1996**, *96*, 115-136.
13. See also: Cottineau, F.; Maigrot, N.; Mazaleyrat, J.P. *Tetrahedron Lett.* **1985**, *26*, 421-424. Bradshaw, J.S.; Krakowiak, K.E.; Izatt, R.M. *Tetrahedron Lett.* **1989**, *30*, 803-806. De Souza, S.E.; O'Brien, P. *Tetrahedron Lett.* **1997**, *38*, 4885-4888.
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16. ^{1}H NMR. **3b**: 0.85 (CH_3CH, d, *J* 6.9), 0.91 (CH_3(CH$_2$)$_3$, t, *J* 6.9), 1.3 (CH$_3$CH_2CH$_2$, m), 1.46 (CH$_3$CH$_2$CH_2, m), 2.25 (CH_3N, s), 2.47 (CH_2N, m), 2.81 (CH$_3$CH, dq, *J* 4.2, 6.9), 4.81 (PhCH, d, *J* 4.2), 7.3 (C$_6H_5$, m).

    3d: 0.85 (CH_3CH, d, *J* 7.0), 0.86 (CH_3CH$_2$, t, *J* 7.2), 1.49 (CH$_3$CH_2, sext, *J* 7.2), 2.24 (CH_3N, s), 2.38 (CH_2N, m), 2.80 (CH$_3$CH, dq, *J* 4.2, 7.0), 3.80 (OH), 4.80 (PhCH, d, *J* 4.2), 7.3 (C$_6H_5$, m).

    3e: 0.99 (CH_3CH, d, *J* 6.9), 1.63 (CH$_2$CH_2CH$_2$, m), 2.27 (CH_3N, s), 2.71 (CH_2N, m), 2.87 (CH$_3$CH, dq, *J* 4.6, 6.9), 3.17 (2 OH), 3.65 (CH_2OH, t, *J* 5.3), 4.82 (PhCH, d, *J* 4.6), 7.3 (C$_6H_5$, m).

    3g: 0.88 (CH_3CHN, d, *J* 6.8), 0.89 ((CH_3)$_2$CH, d, *J* 6.5), 1.77 ((CH$_3$)$_2$CH, m), 2.19 (CH_3N, s), 2.24 (CH_2N, m), 2.77 (CH$_3$CHN, dq, *J* 4.6, 6.8), 3.0 (OH), 4.81 (PhCH, d, *J* 4.6), 7.3 (C$_6H_5$, m).
17. The relative low isolated yield of **3e** came from lost of material due to some difficulties in the course of the purification.

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