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Partial hydrogenation of substituted pyridines and quinolines: a crucial role of the reaction conditions

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Abstract—Hydrogenation of pyridyl and quinolyl compounds 2-substituted with a carbonyl group (**1a–c** and **2b**,**c**) using PtO_2 and 1 equiv. of HCl (conditions **A**) provides clean and total formation of the desired amino alcohol (hydrogenation of the heterocyclic ring and of the carbonyl) while under conditions $\mathbf{B_1}$ and/or $\mathbf{B_2}$ (concentrated HCl or pure CF_3CO_2H) the heterocyclic ring remains untouched and other aromatic parts are hydrogenated providing complex mixtures. When the heterocyclic ring is substituted by an alkyl group (quinaldine **3**) conditions **A** provide mixtures while under conditions $\mathbf{B_2}$ (pure CF_3CO_2H) the benzene ring is cleanly hydrogenated leading to a pure product.

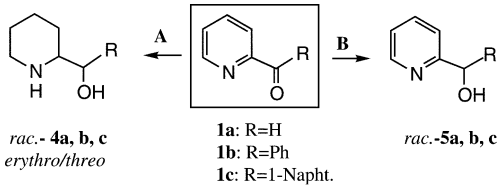
1. Introduction

The selectivity of catalytic hydrogenation of substituted pyridines[1–3] and of quinolines bearing aryl substituents,[1,4] with reduction of the heterocyclic ring or of the substituent according to which product is desired, has been studied and acidic conditions proved to be the most suitable.[3,5]

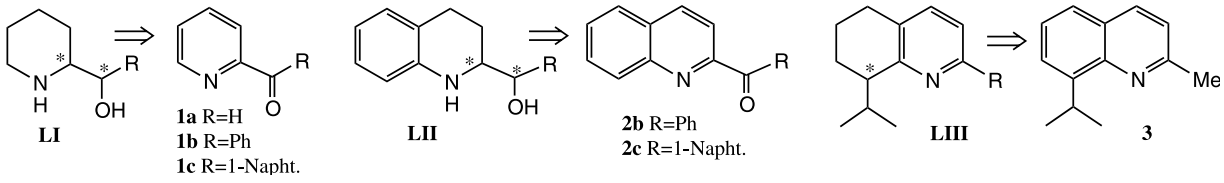
As part of our work toward the synthesis of various new chiral ligands of types **LI**–**LIII**, we studied the simultaneous reduction of the carbonyl group and of the heterocyclic ring in **1a–c** pyridyl and **2b**,**c** quinolyl compounds, as well as hydrogenation of the benzene ring of the 8-substituted quinaldine **3**.

We report here that, using PtO_2/H_2, the results depended strongly on the conditions (Schemes 1–3 and Tables 1–3). The **A**, $\mathbf{B_1}$ and $\mathbf{B_2}$ conditions which were used are **A**: Solvent = EtOH, 1 equivalent of HCl (compared to the substrate) and 55 bar of H_2; $\mathbf{B_1}$: Solvent = concentrated HCl and 10 bar H_2 and $\mathbf{B_2}$: Solvent = CF_3CO_2H and 10 bar of H_2.

Substrates **1a–c**[6] under conditions **A** provide the desired pure piperidyl compounds **4a–c**[7] with hydrogenation of both the heterocyclic ring (pyridyl ring) and the carbonyl group (Table 1, entries 1, 3 and 5)



Scheme 1.



Keywords: hydrogenation; aminoalcohol; arylpyridylketones; arylquinolylketones; quinaldines.
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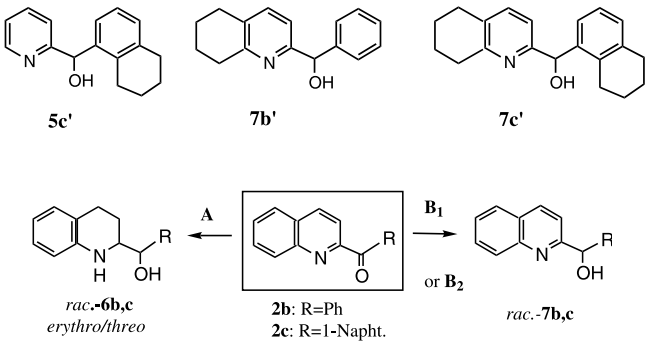
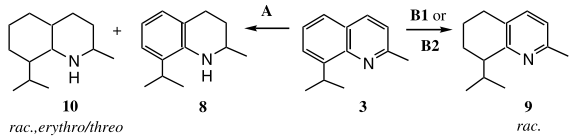


Scheme 2.



Scheme 3.

while under conditions $\mathbf{B_1}$ and/or $\mathbf{B_2}$ only the carbonyl group was reduced with formation of compounds **5a**–**c**.[7] Traces (~10%) of a product assigned to be **5c′** corresponding to partial hydrogenation of the naphthyl-group was also observed in the case of **1c**, but the heterocyclic ring had not been modified. It is worth noting that piperidyl alcohols **4b** and **4c** (Table 1, entries 3 and 5) have been obtained as diastereomers mixtures, the *erythro* isomer being major.

Substrates **2b** and **2c**[8] under conditions **A** were also cleanly hydrogenated at the heterocyclic ring and the carbonyl group leading quantitatively to pure amino alcohol **6b** and **6c**[9] (Table 2, entries 1 and 4) as diastereomeric mixtures highly enriched in the *erythro* isomer. Under conditions $\mathbf{B_1}$ and/or $\mathbf{B_2}$ complex mixtures were obtained from which 40 and 30% of compounds of type **7**[9] were isolated, Table 2 (entries 2 and 5). Compounds **7b′** and **7c′**, in which hydrogenation of some aromatic sites together with hydrogenation of the carbonyl had occurred, were also observed, but the heterocyclic ring remained untouched.

Hydrogenation of 8-*iso*-propyl-2-methyl quinoline **3**[10] under condition **A** provided a **8**/**10**/**9**[11] mixture. However the desired compound **9**[11] (hydrogenation of the benzene ring) was quantitatively obtained using condition $\mathbf{B_2}$. It is worth noting that, in this case, condition $\mathbf{B_1}$ was not efficient, requiring a longer reaction time for only 10% conversion.

Table 1. Partial hydrogenation of pyridines **1a**–**c** (Scheme 1)

Entry	Subst.	Cond.	React. time (h)	Conv.[a] (%)	**4**[a]	**4**[a] **I**/**II**	**5**[a]	**1**[a] start
1	**1a**	**A**	16	100	**100**	–	0	0
2	**1b**	**A**	10	100	**100**	70/30	**0**	0
3	**1b**	$\mathbf{B_2}$	5	80	**0**	–	**80**	20
4	**1c**	**A**	15	100	**100**	85/15	0	0
5	**1c**	$\mathbf{B_2}$	18	86	0	–	≥**66**[b]	14

[a] Determined by ^{1}H NMR analysis of crude reaction products.
[b] Side product observed (cf. text).

Table 2. Partial hydrogenation of quinolines **2b**,**c** (Scheme 2)

Entry	Subst.	Cond.	React. time (h)	Conv.[a] (%)	**6**[a]	**6**[a] **I**/**II**	**7**[a]	**1**[a] start
1	**2b**	**A**	10	100	**100**	77/23	0	0
2	**2b**	$\mathbf{B_1}$	16	80	**0**	–	**40**[b]	20
3	**2b**	$\mathbf{B_2}$	16	84	0	–	32	16
4	**2c**	**A**	15	100	**100**	90/10	**0**	0
5	**2c**	$\mathbf{B_2}$	16	100	**0**	–	**30**[b]	0

[a] Determined by ^{1}H NMR analysis of crude reaction products.
[b] After chromatographic purification.

Table 3. Partial hydrogenation of **3** (Scheme 3)

Entry	Subst.	Cond.	React. time (h)	Conv.[a] (%)	**8**[a]	**9**[a]	**10**[a]	**1**[a] start
1	**3**	**A**	16	100	57	22	21	0
2	**3**	**A**	6	100	77	12	11	0
3	**3**	$\mathbf{B_1'}$[b]	24	10	0	10	–	90
4	**3**	$\mathbf{B_2'}$[b]	12	**100**	0	**100**	–	0

[a] Determined by ^{1}H NMR analysis of crude reaction products.
[b] Reaction under 5 bar hydrogen and product composition determined by GC.

2. Conclusion

It appears that, when the heterocyclic ring is substituted with a carbonyl group (**1a–c** and **2b,c**), conditions **A** (1 equiv. of HCl and probable formation of the hydrochloride of the substrate) provide clean and total formation of the desired amino alcohol as *erythro*/*threo* mixtures highly enriched (85–90%) in the *erythro* isomer (hydrogenation of the heterocyclic ring and of the carbonyl) while under conditions $\mathbf{B_1}$ and/or $\mathbf{B_2}$ the heterocyclic ring remains untouched (although other aromatic parts are hydrogenated providing complex mixtures).

When the heterocyclic ring is substituted by a alkyl group (the quinaldine **3**) conditions **A** provide mixtures while under conditions $\mathbf{B_2}$ the benzene ring is cleanly hydrogenated leading to a pure product.

Acknowledgements

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   5a is commercially available. For **5b**, see: Gros, P.; Fort, Y.; Caubère, P. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3597–3600. **5c**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.40 (s, 1H, CHOH), 6.40 (s, 1H, CHOH), 7.06 (d, 1H, J=8.5 Hz), 7.22 (m, 1H), 7.44–7.58 (m, 5H), 7.82–7.89 (m, 2H), 8.12 (d, 1H), 8.66 (d, 1H, J=5 Hz).
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10. **3** ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.37 (d, 6H, J=7 Hz), 2.73 (s, 3H), 4.47 (sept., 1H, J=7 Hz), 7.28 (d, 1H, J=8 Hz), 7.46 (t, 1H, J=8 Hz), 7.63 (m, 2H), 8.03 (d, 1H, J=8 Hz).
11. **8** ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (d, 3H, J=5 Hz), 1.27 (d, 3H, J=6.5 Hz), 1.29 (d, 3H, J=5 Hz), 1.61 (m, 1H), 1.95 (m, 1H), 2.85 (m, 3H), 3.46 (m, 1H), 6.66 (t, 1H, J=7.5 Hz), 6.88 (d, 1H, J=7.5 Hz), 7.0 (d, 1H, J=7.5 Hz).
    9 ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.64 (d, 3H, J=7 Hz), 1.04 (d, 3H, J=7 Hz), 1.62 (m, 2H), 1.92 (m, 2H), 2.49 (s, 3H), 2.66 (m, 2H), 2.77 (m, 1H), 2.83 (bs, 1H), 6.85 (d, 1H, J=8 Hz), 7.21 (d, 1H, J=8 Hz).