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Synthesis of chiral N-protected 1,2-dihydro-quinoline-2-carbonitrile and 1,2-dihydro-isoquinoline-1-carbonitrile via an asymmetric Reissert reaction

Mickaël Pauvert,[a,†] Sylvain C. Collet,[a] Marie-Jo Bertrand,[a] André Y. Guingant[a,*] and Michel Evain[b,‡]

[a]*Laboratoire de Synthèse Organique, UMR CNRS 6513, FR CNRS, 2465 Faculté des Sciences et des Techniques, 2, rue de la Houssinière, BP 92208-44322 Nantes Cedex 03, France*
[b]*Institut des Matériaux Jean Rouxel, 2, rue de la Houssinière, BP 92208-44322 Nantes Cedex 03, France*

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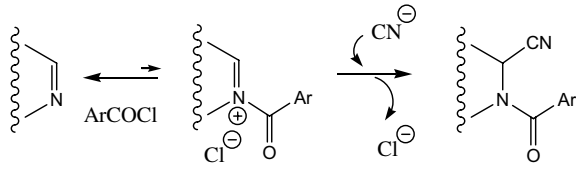
Abstract—Addition of cyanide ion to chiral *N*-acyl-quinolinium and *N*-acyl-isoquinolinium salts led selectively to 1,2-addition products. Removal of the chiral auxiliary affords the title compounds in pure enantiomeric form.

The 1,2 addition of cyanide ion to *N*-benzoyl quinolinium chloride generated in situ by the action of benzoyl chloride on quinoline is known as the Reissert reaction.[1] Other aromatic acid chlorides and nitrogen heterocycles may be used to give the so-called Reissert compounds as depicted in general terms in Scheme 1.

The synthetic potentialities of this venerable reaction[2] have found wide applications in heterocyclic chemistry, particularly since it was recognised that several nucleophiles other than the cyanide ion could be added to the intermediate iminium species.[3] In conjunction with several synthetic projects we became interested in the use of the Reissert reaction to prepare differently substituted 1,2,3,4-tetrahydro-quinoline derivatives. Somewhat surprisingly, the problem of achieving an asymmetric version of the Reissert reaction has not been addressed until quite recently. The first proposed solution was disclosed by Shibasaki and co-workers[4] who discovered that a bifunctional Lewis acid embodying the 2,2′-binaphthol (BINOL) motif was able to catalyse the cyanide addition to variously substituted quinolines (isoquinoline) to give the corresponding Reissert compounds in enantiomeric excesses ranging from 54% to 96%.



Scheme 1.

Following this pioneering work, Liebscher and co-workers[5] showed that the combined action of TMSCN and (−)-(*R*)-menthylchloroformate onto isoquinoline, in the presence of aluminium chloride, delivered the corresponding Reissert compound in greater than 95% diastereoselectivity. The (*S*)-*N*-cbz-alanoyl fluoride was also shown to be equally efficient as chiral inducer. Since the Shibasaki protocol failed to give a high selectivity with isoquinoline, the Liebscher approach complements well the work of the Japanese team. These results prompted us to disclose our own approach to the problem which makes use of an Evans chiral auxiliary to

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* Corresponding author. Tel.: +33 02 51 12 54 13; fax: +33 02 51 12 54 02; e-mail: andre.guingant@chimie.univ-nantes.fr
† Present address: Atlanchim company, 2 rue de la Houssinière, BP 92208-44322 Nantes Cedex 3.
‡ To whom questions regarding X-ray structure should be addressed.

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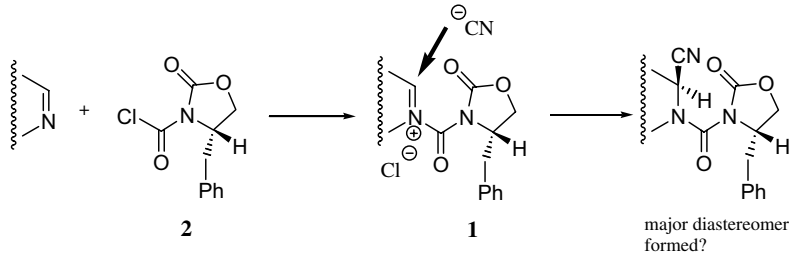


2 **1**

Scheme 2.

reach quinoline- and isoquinoline-derived Reissert compounds with useful diastereoselectivities. We thus envisioned that the bias usually provided by the chiral 4-benzyl-oxazolidin-2-one auxiliary would selectively direct the cyanide anion on one particular diastereotopic face of *N*-acyl (iso)quinolinium chlorides **1** as shown in Scheme 2. The salts **1**, key intermediates to this approach, would be in situ generated by simply reacting (iso)quinoline with the known[6] acid chloride **2**.

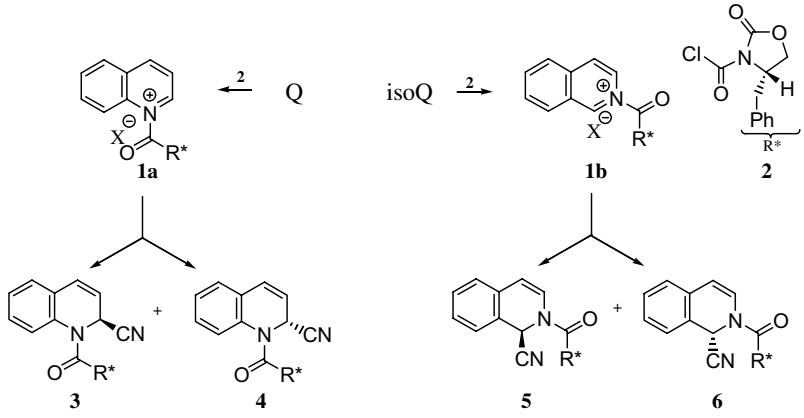
To begin to investigate the behaviour of *N*-acyl salts **1** with cyanide anion, acid chloride **2** was prepared by reacting the sodium salt of (4*S*)-4-benzyl-oxazolidin-2-one with a toluene solution of phosgene (1 equiv) in conditions previously reported.[6] Reaction of **1a** (**1b**), generated by addition of **2** to a solution of quinoline (Q) or isoquinoline (isoQ) in methylene chloride, with TMSCN as a cyanide source, led to the expected formation of diastereomeric Reissert compounds **3** (**5**) and **4** (**6**) as depicted in Scheme 3. The reaction was quite disappointing in terms of selectivity since an almost equal mixture of diastereomers were formed in each case (Table 1, entries 1 and 2). In a second experiment, hoping that the nature of the associated anion would favourably influence the diastereomeric ratio of the nitrile products, exchange of Cl^- for TfO^- was effected prior to the addition of TMSCN. As shown in Table 1 (entries 3 and 4) this operation significantly improved the diastereomeric ratios which increased from ca. 1:1 to ca. 4:1 in both examples.[7] Raising the temperature

Table 1. Reaction of **1a** and **1b** with TMSCN[a]

Entry	Substrate	X^-	*T* (°C)	Products	
				(Diastereomeric ratio)[b]	Yield (%)[c]
1	**1a**	Cl^-	20	**3**:**4** = 55:45	88
2	**1b**	Cl^-	20	**5**:**6** = 60:40	76
3	**1a**	TfO^-	20	**3**:**4** = 83:17	70
4	**1b**	TfO^-	20	**5**:**6** = 15:85	35
5	**1b**	TfO^-	40	**5**:**6** = 29:71	95
6	**1a**	NfO^-	40	**3**:**4** = 84:16	60

[a] All reactions were performed in methylene chloride.
[b] Determined by HPLC analysis (column: Inersil Si Chrompack, 3 × 250 mm; λ = 254 nm; eluent: CH_2Cl_2; flow rate: 0.5 mL/min).
[c] Isolated combined yields after column flash chromatography.

to 40 °C substantially improved the yield of the cyanide addition to isoquinolinium ion although, in that case, the ratio of diastereomeric adducts **5** and **6** was significantly lowered (compare entries 4 and 5). Finally, changing the triflate counterion for the more voluminous nonaflate ion did not affect the diastereomeric ratio of adducts **3** and **4** (entry 6) suggesting that the beneficial role of triflate ion over chloride ion in controlling the course of the reaction finds its origin in electronic rather than in steric effects. Although our results are inferior to those observed in the recent literature it should be pointed out that no elaborated additive is required and that the diastereomeric adducts **3** (**5**) and **4** (**6**) are easily separated by standard silica gel flash chro-



1a **1b** **2**

3 **4** **5** **6**

Scheme 3.

matography, rendering the reaction synthetically useful. Moreover, chiral auxiliary removal can be easily performed in one single operation (vide infra).

Stereochemical assignment was unambiguously accomplished by subjecting each major diastereomer (entries 3 and 4 in Table 1) to X-ray crystal structure analysis. The analysis revealed that these adducts correspond to structures **3**[8] and **6** (Fig. 1),[9] respectively.

The reason for the above stereochemical trends is not clear. A possible pathway that could be envisaged as the major mechanistic possibility leading to adducts **3** and **6** would involve the formation of a stabilising cation–Π complex intermediate.[12] This in turn would then lead to an effective screening of one of the diastereotopic faces of the reacting $C{=}N^+$ double bond. Considering the two potential reactive conformations (**C1**) and (**C2**) for iminium salts **1a** and **1b**, rotations around each of the N–CO bonds are necessary to allow these salts to escape to severe steric interactions (Scheme 4). As a result it became apparent from examination of a model that the establishment of a cation–Π complex is disfavoured in conformations **1a** (**C2**) and **1b** (**C2**) whereas such a stabilising disposition remains easily possible in conformations **1a** (**C1**) and **1b** (**C1**) having the iminium and carbonyl functionalities *trans*-disposed to the single N^+–CO bond. Attack of cyanide ion from the less congested faces of conformations (**C1**) of salts **1a** and **1b** should thus account for the preferential formation of adducts **3** and **6**, respectively. It is not without interest to remark that the conformations displayed by these adducts in the crystalline state structures[13] are closed from conformations (**C2**). Finally, the importance of the associated triflate anion on the diastereoselectivity of the addition process could be that, being less tightly bound to the iminium moiety than the chloride anion, it favours the establishment of the cation–Π complex.

We next focussed our attention on the chiral auxiliary removal operation. To expand the utility of the above reactions for the synthesis of 1,2,3,4-tetrahydro-(iso)quinoline derivatives it appeared useful to remove the chiral auxiliary while, in the same time, protecting the nitrogen atom.

This could be simply and efficiently realised by treatment of adducts **5** and **6** with samarium triflate (0.2 equiv)[14] in a mixture of methylene chloride and methanol at room temperature. Following this procedure, the reaction proceeded cleanly without compromising the chiral centre and led to the 1-cyano-1*H*-isoquinoline-2-carboxylic acid methyl esters (*R*)-**7** and (*S*)-**7**, respectively[15] (Scheme 5).

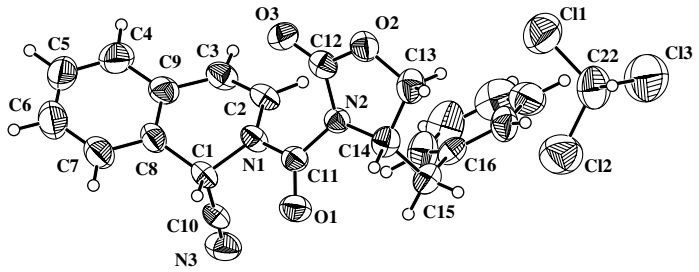
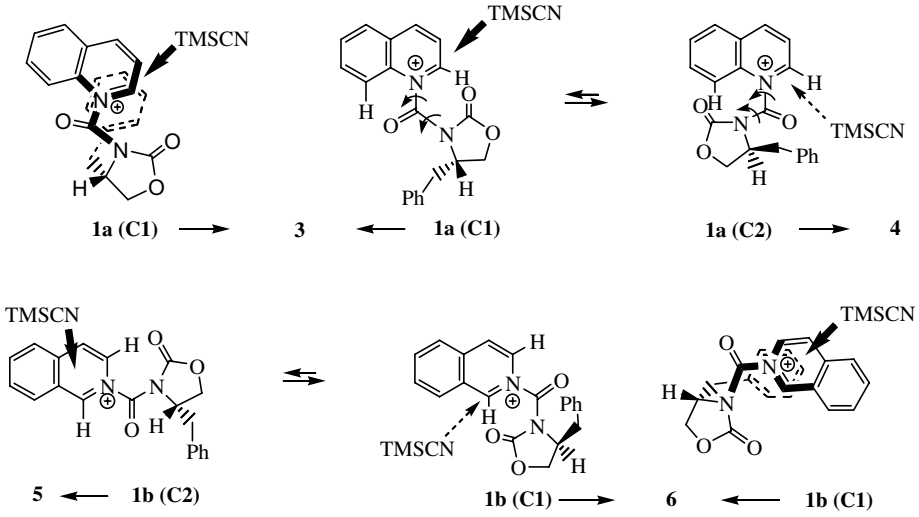
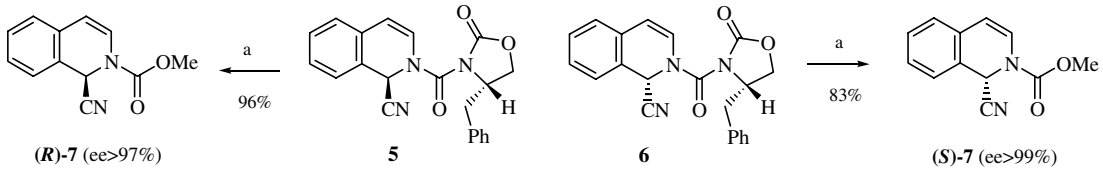


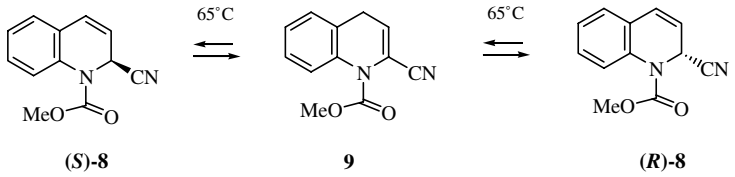
Figure 1. ORTEP drawing of compound **6** complexed with $CHCl_3$.



Scheme 4.



Scheme 5. Reagents and conditions: (a) $Sm(OTf)_3$, 0.2 equiv, CH_2Cl_2/MeOH 1:1, 18 h, rt.



Scheme 6.

If, under similar conditions, the reaction of adduct **3** proceeded as expected to give *N*-protected 2-cyano-2*H*-quinoline (*S*)-**8**,[15] surprisingly, in light of the above results, reaction of adduct **4**, which was conveniently carried out at 40 °C for reasons of solubility, proved to be less satisfying, leading to (*R*)-**8** with a small but detectable erosion of the chirality. To discover the origin of this deleterious effect, compound (*S*)-**8** was taken up in a chloroform–methanol solution and heated at 65 °C. HPLC analyses revealed that the degree of epimerisation gradually increased over time to finally deliver a ca. 1:1 mixture of (*R*)-**8** and (*S*)-**8** after 3 days. Besides, racemic **8** was accompanied with some quantity of compound **9**,[16] which strongly suggested that the epimerisation process arised via the equilibrium depicted in Scheme 6. Since adducts **3** and **4** were recovered without deterioration of their original optical purity, when heated in the same experimental conditions, it thus appears that both (*S*)- and (*R*)-**8** are thermally labile and prone to easy racemisation, most probably via the intermediary of compound **9**.

In conclusion, asymmetric synthesis of Reissert compounds **3**–**6** could be achieved in useful diastereoselectivities. Chiral auxiliary removal from these adducts produced *N*-protected-2-cyano-2*H*-quinolines (*R*)-**8** and (*S*)-**8** as well as 1-cyano-1*H*-isoquinolines (*R*)-**7** and (*S*)-**7**, that are potentially useful intermediates for the synthesis of alkaloids.

Acknowledgements

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Supplementary data

Experimental procedures and analytical data for compounds **3**–**8** are available. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tetlet.2005.03.034.

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7. (a) To the best of our knowledge this constitutes the first observation that exchange of Cl^- for TfO^- can help improve the diastereoselectivity of the Reissert reaction. Triflate ion-promoted Reissert reaction has already been reported, however. For recent exemples, see: Pabel, J.; Hösl, C. E.; Maurus, M.; Ege, M.; Wanner, K. Th. *J. Org. Chem.* **2000**, *65*, 9272–9275; (b) Yamaguchi, R.; Omoto, Y.; Miyake, M.; Fujita, K.-I. *Chem. Lett.* **1998**, 547–548; (c) Yamaguchi, R.; Hatano, B.; Kakayasu, T.; Kozima, S. *Tetrahedron Lett.* **1997**, *38*, 403–406.
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9. X-ray crystallographic analysis for compound **6**: A colorless, rod-like crystal of compound **6**, approximately $0.75 \times 0.25 \times 0.75\ mm^3$ in dimension, was fixed at the tip of a glass Lindeman capillary by means of a silicon glue. All measurements were carried out on a Brüker–Nonius KappaCCD diffractometer with graphite monochromated MoK-$L_{2,3}$ radiation. After the absorption correction (Gaussian integration), the structure was solved by direct methods (Shelxtl)[10] and refined (Jana2000)[11] with anisotropic atomic displacement parameters for all non-H

atoms. All H atoms were defined with fully restrained geometry (angles and distances) and riding isotropic displacement parameters (×1.2). Absolute configuration was unambiguously determined by refining the Flack enantiopole parameter using Friedel pairs. The structure data are as follows: $C_{22}H_{18}Cl_3N_3O_3$, $M_r = 478.8$, orthorhombic, $P2_12_12_1$, $a = 6.19110(10)$, $b = 14.2461(3)$, $c = 25.2042(7)$ Å, $V = 2222.99(9)$ Å^3, $Z = 4$, $D_{calcd} = 1.430$ g × cm^{-3}, $F(000) = 984$, μ(MoK-$L_{2,3}$) = 0.442 mm^{-1}, $T = 293$ K, R(obs) = 0.0728, S(obs) = 1.36 (4996 hkl, 281 parameters, cutoff for observed: $I/\sigma(I) = 2$), Flack's parameter: 0.09(9). Crystallographic details have been deposited at the Cambridge Crystallographic Data Center (deposition number CCDC 258634).

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15. The R_f value of 4(*S*)-benzyl-oxazolidin-2-one on silica TLC plates is significantly different from that of compounds **7** and **8** so that the chiral auxiliary could be recovered and reused, if desired.
16. Selected NMR data for compound **9**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.42 (d, $J = 4.8$ Hz, 2H, CH_2), 3.93 (s, 3H, OCH_3), 6.55 (t, $J = 4.8$ Hz, 1H, C*H*–CH_2), 7.10–7.28 (m, 3H, H–Ar), 7.65 (d, $J = 8.1$ Hz, 1H, H–Ar).