Efficient Asymmetric Synthesis of Reissert Compounds

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Dedicated to Erhard Matthes on the occasion of his 80th birthday.

Abstract: Asymmetric synthesis of Reissert compounds **5**, **12** was achieved using chiral acyl halides such as amino acid fluorides or (–)-(*R*)-menthylchloroformate and TMSCN. These are the first cases of asymmetric synthesis of unsubstituted isoquinoline-derived Reissert compounds with high stereoselectivities. The chiral Reissert compound **12** could be alkylated in position 1 affording 1-substituted Reissert compound **13** highly stereoselectively. The products are potential starting materials for unnatural amino acids and alkaloid analogues.

Key words: Reissert compounds, asymmetric synthesis, isoquinolines, amino acid fluorides, menthylchloroformate

Reissert compounds formed by addition of cyanide in the presence of acyl chlorides to the C-N double bond of isoquinolines, quinolines or pyridines via intermediate *N*-acyliminium salts have found wide synthetic application.[1] Their α-acylamino nitrile moiety can be hydrolysed to cyclic amino acids, they can be alkylated in position 1 and were used in ring annelations affording alkaloid related structures. It was just recently that asymmetric synthesis of Reissert compounds was developed. Thus Shibasaki et al. reported a catalytic version using achiral acyl chlorides and chiral Lewis acids derived from BINOL.[2] Although high asymmetric induction could be achieved with quinolines and with 1-substituted isoquinolines the method revealed drawbacks with respect to isoquinolines. 3-Methyl-isoquinoline gave just an ee of 71% and even less satisfactory results were obtained with isoquinoline itself.[3] Further 1-alkylation of such Reissert compounds obtained by asymmetric catalysis would undoubtly result in racemisation because the deprotonated intermediates are not chiral. Thus, the problem of satisfactory asymmetric synthesis of Reissert compounds of isoquinolines has not yet been solved.

Our prior attempts to the asymmetric synthesis of Reissert compounds using α-tosylaminoacyl fluorides **2** (PG = Ts) of natural α-amino acids as chiral inducer in the presence of anhydrous $AlCl_3$ and TMSCN provided dihydroimidazoisoquinolones **4** rather than the anticipated cyano compounds **5**.[4] Obviously, the *N*-acylisoquinolinium salts **3** primarily formed did not add cyanide but cyclised by intramolecular nucleophilic attack of the deprotonated tosylamino group at position 1 of the isoquinoline ring. Interestingly, *N*-arylsulfonylamino acid chlorides could be used by Ohsawa et al. for asymmetric 1,2-addition of silylenol ethers or allylstannane to isoquinolines.[5] We surmised that less acidifying protective groups at the amino acid fluoride **2** would prevent the intramolecular attack affording **4** and thus could open the way to the addition of cyanide to obtain the anticipated Reissert compounds such as **5**.

Indeed, treatment of Z- or FMOC-protected amino acid fluorides **2** (PG = Z or FMOC) with isoquinoline, $AlCl_3$ and TMSCN according to the procedure previously applied for the synthesis of **4** afforded Reissert compounds **5** in a stereoselective manner (Scheme 1, Table 1).[6,7] Proof for the configuration of these products could be provided by stepwise transformation of **5a** into the FMOC-protected tetrahydroisoquinoline-1-carboxylic acid **8**, which is commercially available and has been obtained by separation of the racemate so far.[8] The transformation of **5a** into **8** (Scheme 1) includes basic hydrolysis to the amide **6**, catalytic hydrogenation of the enamine moiety to **7**, acid hydrolysis of both, the peptide and the amide group, and introduction of the FMOC protective group. From the configuration of products **5** it can be deduced that the attack of the cyanide is likely to occur via the conformation of *N*-acyliminium salt **3** shown in Figure 1.

We further applied commercially available (–)-(*R*)-methylchloroformate **10** and its enantiomer in the asymmetric

Table 1 Reissert Compounds **5**, **12** and Methylation Product **13**

Product	R or R[1]	PG	Yield[a] (%)	dr[b]
5a	Me	Z	89[c]	>95:5
5b	Me	FMOC	44	71:29
5c	*i*-Pr	FMOC	47	70:30
5d	CH_2Ph	Z	51	82:18
12a	H		98	>95:5
12b	Br		96	>95:5
13	H		87	<95:5

[a] Isolated yields after chromatography, crude yields >90%.
[b] Stereoisomers separable by column chromatography.
[c] Crude yield.

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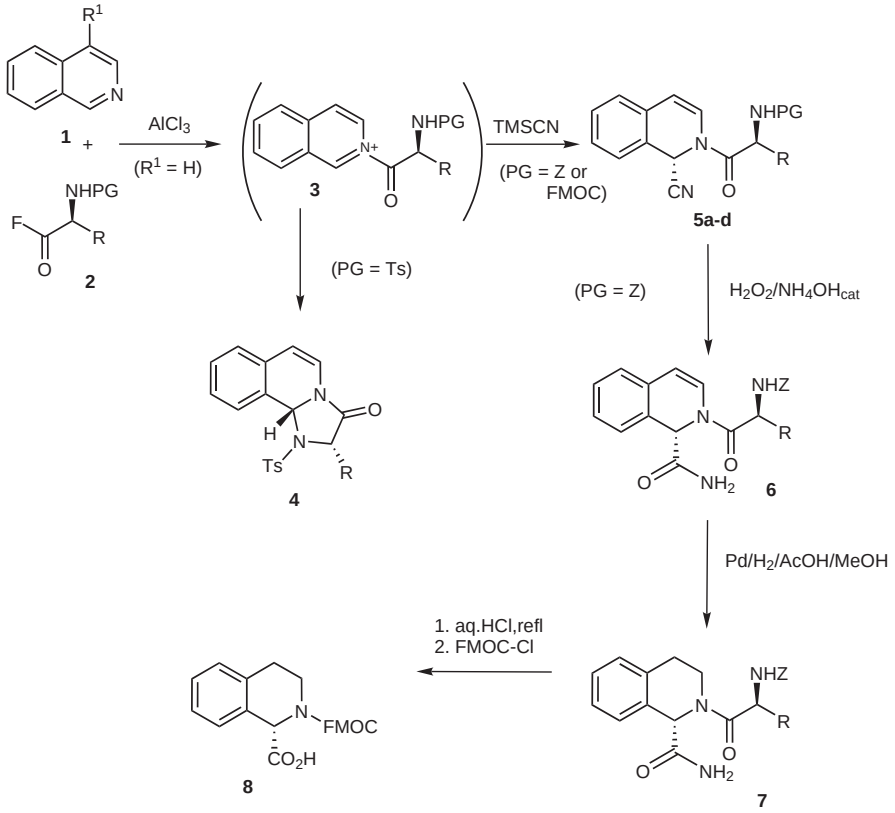


Scheme 1

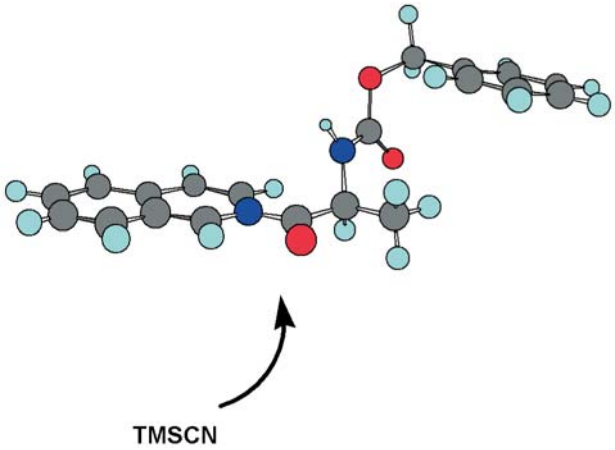


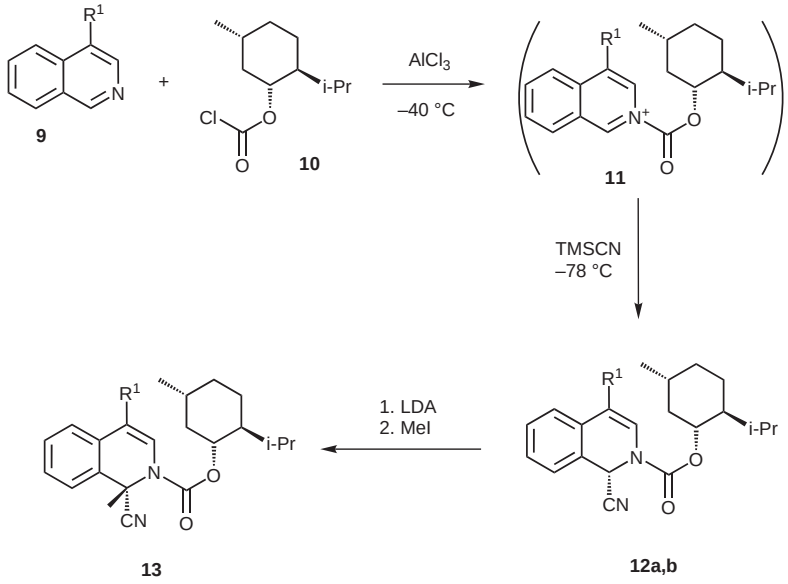
Figure 1 MM2-Optimized structure of *N*-acylisoquinolinium salt **3** (R = Me, PG = Z) attacked by TMSCN

synthesis of Reissert compounds (Scheme 2). (8-Phenylmenthyl)-chloroformate was successfully used in asymmetric 1,2-addition of Grignard reagents to isoquinoline via intermediate *N*-acyliminium salts by Comins et al.[9] This chloroformate as well as **10** were also useful in analogous Grignard reactions in the pyridine series.[9]

Our investigations revealed that reaction of isoquinolines **9** with **10** and $AlCl_3$ in dichloromethane or THF at –40 °C gave the corresponding iminium salts **11**, which could be isolated, or, more conveniently, were directly treated with TMSCN at –78 °C. The desired Reissert compounds **12** were obtained in excellent yields and stereoselectivities (dr >95%, Table 1).[6,10]

The configuration of **12** was deduced by comparison of experimental and theoretical optical rotation (OR). Recently, it has been shown[11] that reliable theoretical predictions for the OR of large chiral molecules can be obtained by time-dependent density functional response theory (TDDFT). According to our computations,[12] **5a** has an $[\alpha]_D$ of –158 which is in good agreement with the experimental value of –118.7 demonstrating the reliability of our theoretical approach. Applying the same treatment to **12a** gives a $[\alpha]_D$ of –392 and –437 for two different conformers (rotation around C-N-bond). The measured value of **12a** has the same sign (–59.6). On the other hand, the 1-(*R*) epimer of **12a** gives a calculated α-value of +503. These results show that the sign of the OR is mainly determined by the configuration at position 1 of the dihydroisoquinoline ring and give evidence for the configuration of **12a**.

The chiral menthylcarbonyl substituent in the Reissert compounds **12** should further allow diastereoselective introduction of alkyl substituents in position 1 by deprotonation followed by alkylation with alkyl halides. Indeed, treatment of **12a** with LDA and methyl iodide gave the anticipated alkylation product **13** in excellent yield and stereoselectivity (Scheme 2). It has to be mentioned that the reaction of 1-methylisoquinoline with amino acyl



Scheme 2

fluorides and TMSCN as an alternative way to Reissert compounds with alkyl substituents in position 1 failed. This fact underlines the importance of the alkylation method resulting in **13**. In addition, such 1-substitued isoquinoline starting materials are not readily available. Thus it is very convenient to start with the unsubstituted isoquinoline and to introduce both, the cyano group and the alkyl rest in stereoselective fashion.

Ongoing investigations of the synthetic utility of menthylchloroformate **10** in other asymmetric 1,2-additions to isoquinolines have given first promising results with Grignard reactions and organostannanes as well as with aldehydes.

In summary, we have developed a straightforward asymmetric route to Reissert compounds using chiral acyl halides. The achieved stereoselectivities are high and 1-unsubstituted isoquinoline gives excellent results. Products similar to **8**, **12**, **13** but with opposite configuration at position 1 of the isoquinoline ring should also be accessible by our method using the other enantiomer of chiral acyl halides **2** and **10**. The latter is commercially available too.

Since most of the optically active products **5**, **8**, **12**, **13** either represent precursors for bridged chiral α-amino acids, which are interesting building blocks for peptidomimetics or are promising starting materials for new alkaloid analogues we presently investigate the scope of the 1,2-addition to other isoquinolines and other heterocycles at one side and synthetic transformations of the products on the other side.

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(7) **Reissert Compound 5a:** Anhyd $AlCl_3$ (30 mg, 0.2 mmol) was added to a solution of (*S*)-*N*-cbz-alanoyl fluoride (500 mg, 2.22 mmol) in anhyd CH_2Cl_2 (50 mL) at –40 °C. A solution of isoquinoline (300 mg, 2.32 mmol) in anhyd CH_2Cl_2 (10 mL) was added at –40 °C over a period of 30 min. After stirring at this temperature for 2 h, the temperature was lowered to –78 °C and a solution of TMSCN (230 mg, 2.32 mmol) in anhyd CH_2Cl_2 (10 mL) was added at this temperature over a period of 1 h. After 4 h stirring at –78 °C and combining with ice water (100 mL) the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with sat. aq NH_4Cl and 5% aq $NaHCO_3$, dried ($MgSO_4$) and concentrated under vacuum. Yield 830 mg (93%). Further purification by flash chromatography (CH_2Cl_2–MeOH) is possible but causes decomposition of a part of the product. $[\alpha]_D^{20}$ –118.7 (*c* 1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.40 (d, *J* = 7.16 Hz, 3 H, CH_3), 4.72 (q, *J* = 7.16 Hz, 1 H, CH_3CH), 5.00 (s, 2 H, CH_2), 6.06 (d, *J* = 7.54 Hz, 1 H, CHCH-N), 6.57 (s, 1 H, CH-CN), 7.11 (d, *J* = 7.54 Hz, 1 H, CHCH-N), 7.20 (m, 1 H, NH), 7.25 (m, 5 H, CH_{ar}), 7.32–7.27 (m, 4 H, CH_{ar}). ^{13}C

NMR (75 MHz, $CDCl_3$): δ = 18.3 (CH_3), 43.7 (CH), 46.9 (CH), 67.1 (CH_2), 112.2 (CH), 116.1 (CN), 124.3 (C_q), 126.1 (CH), 126.7 (CH), 128.0 (CH), 128.2 (CH), 128.2 (CH), 128.4 (CH), 128.5 (CH), 128.8 (CH), 129.4 (C_q), 130.2 (CH), 151.8 (CO), 170.7 (CO). HRMS calcd for $C_{21}H_{19}N_3O_3$: 361.1426. Found: 361.1420.

(8) Observed $[\alpha]_D^{20}$ +27.4 (*c* 1.05, Et_2O), reference sample provided from Catalogue *Special amino acids, building blocks of Neosystem groupe SNPE*, Strasbourg, France: $[\alpha]_D^{20}$ 25.8 (*c* 1, DMF)

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(10) **Preparation of Reissert Compounds 12:** The isoquinoline **9** (2.0 mmol) dissolved in CH_2Cl_2 (50 mL) was slowly added to a solution of (–)-(*R*)-menthylchloroformate (2.2 mmol) and $AlCl_3$ (20 mol%) in CH_2Cl_2 (20 mL) under argon at –40 °C. After 30 min the yellow solution was cooled to –78 °C and a solution of TMSCN (2.0 mmol) in CH_2Cl_2 (1 mL) was slowly added. After stirring for 3 h, the colourless solution was brought to r.t. and poured onto ice/water. The organic phases were separated, dried over $MgSO_4$ and concentrated. Crude products could be purified by column chromatography (silica, dichloromethane). **12a:** $[\alpha]_D^{20}$ –59.6 (*c* 1, CH_2Cl_2).

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(12) All quantum chemical calculations have been performed with the TURBOMOLE suite of programs: (a) *TURBOMOLE* (Vers. 5.5): Ahlrichs, R.; Bär, M.; Baron, H.-P.; Bauernschmitt, R.; Böcker, S.; Ehrig, M.; Eichkorn, K.; Elliott, S.; Furche, F.; Hase, F.; Häser, M.; Horn, H.; Huber, C.; Huniar, U.; Kattannek, M.; Kölmel, C.; Kollwitz, M.; May, K.; Ochsenfeld, C.; Öhm, H.; Schäfer, A.; Schneider, U. Treutler, O.; von Arnim, M.; Weigend, F.; Weis, P.; Weiss, H. Universität Karlsruhe **2002**. The structures of **5** (Ph substituent replaced by a methyl group) and **12** have been fully optimised at the density functional (DFT) level employing the BP86 functional (b), a Gaussian AO basis of valence-double-zeta quality including polarisation functions (SVP) (c)and the RI-approximation for the two-electron integrals (d). The structures have been used in subsequent calculations of the frequency-dependent optical rotatory dispersion ([α]) at the sodium-D-line wavelength. These calculations have been performed in the framework of time-dependent DFT (e)as described in detail in (f). In the TDDFT approach the SVP basis sets augmented with diffuse basis functions (C, O: [1s1p1d], H: [1s1p]) have been used. (b) Becke, A. D. *Phys. Rev. A.* **1988**, *38*, 3098. (c) Perdew, J. P. *Phys. Rev. B* **1986**, *33*, 8822. (d) Schäfer, A.; Horn, H.; Ahlrichs, R. *J. Chem. Phys.* **1992**, *97*, 2571. (e) Eichkorn, K.; Treutler, O.; Öhm, H.; Häser, M.; Ahlrichs, R. *Chem. Phys. Lett.* **1995**, *240*, 283. (f) Bauernschmitt, R.; Ahlrichs, R. *Chem. Phys. Lett.* **1996**, *256*, 454. (g) Grimme, S.; Furche, F.; Ahlrichs, R. *Chem. Phys. Lett.* **2002**, *361*, 321.