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Enantiomerically pure dihydroimidazoisoquinolinones by reaction of isoquinoline with amino acid fluorides†

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Abstract

Reaction of isoquinoline with *N*-tosylated (*R*)- or (*S*)-amino acid fluorides **2** or **5** gives access to novel optically active dihydroimidazoisoquinolinones **4** or **6**, respectively, by *N*-acylation and attack of the deprotonated tosylamino group at position 1 of intermediate 2-tosylaminoacylisoquinolinium salts. © 2000 Published by Elsevier Science Ltd.

Isoquinoline (**1**) and related six-membered *N*-heterocycles, e.g. as pyridines or quinolines, can react with carboxylic acid derivatives such as acid chlorides to form cyclic *N*-acyliminium salts. These products can be used as activated carboxylic acid derivatives in acylation reactions of nucleophiles by losing the heterocyclic moiety. On the other hand, nucleophiles can add to the iminium carbon atom affording dihydro derivatives of the starting *N*-heteroaromatic compound such as in the formation of Reissert compounds.[1] We took an interest in applying *N*-acylation of six-membered *N*-heterocycles with chiral carboxylic acids, in particular α-amino acid derivatives, in order to achieve asymmetric additions to the C–N double bond. Such reactions have not been found in the literature. Here we report our preliminary results of the reaction of isoquinoline (**1**) with amino acid fluorides. The latter were introduced into peptide synthesis by Carpino et al.[2] and can be synthesised from α-amino acids by treatment with cyanuric fluoride or DAST. As compared with amino acid chlorides they are less sensitive to racemisation but still reactive enough for the introduction of amino acyl groups into nucleophiles. When we reacted isoquinoline (**1**) with amino acid fluorides **2** or **5** in the presence of catalytic amounts of $AlCl_3$ and TMSCl the expected *N*-acylation occurred, but corresponding *N*-(α-aminoacyl)iminium salts such as **3** could not be observed. Instead, further cyclisation by attack of the acidic NH group on the iminium carbon atom, i.e. at position 1 of the isoquinoline ring occurred affording novel 1,10b-dihydro-imidazo[2,1-*a*]isoquinolin-3(2*H*)-ones **4** and **6** in enantiomerically pure form. The cyclisation took

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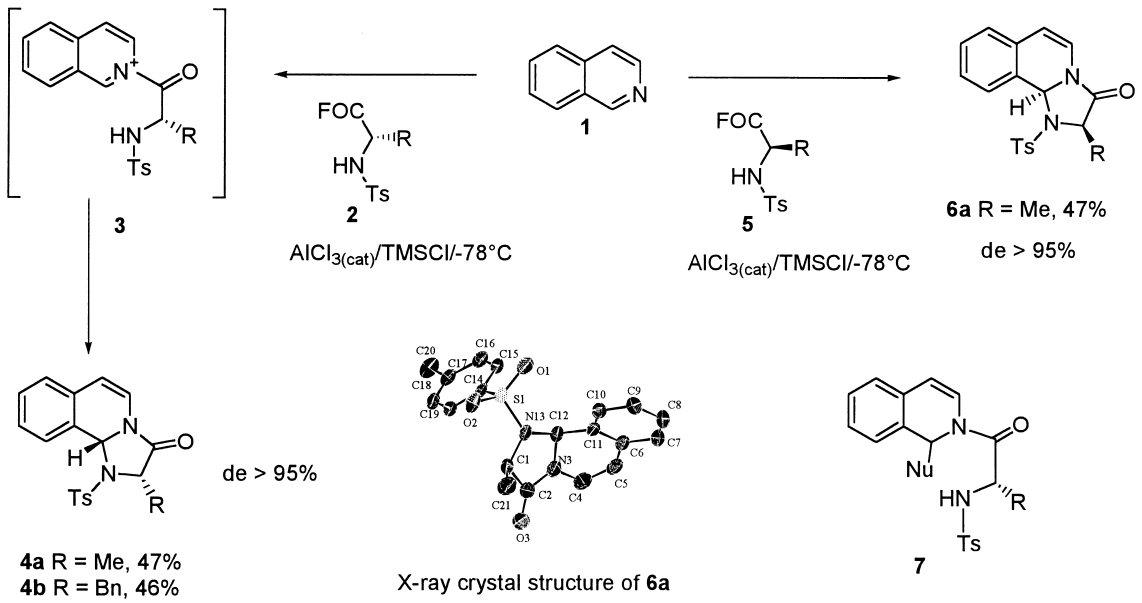
place from the α-face thus giving the (*ul*)-isomers **4** and **6**. The structure of products was proved by X-ray crystal analysis of compound **6a**[3] and NMR spectroscopy (Scheme 1).[4] Fully aromatic imidazo[2,1-*a*]isoquinolines and corresponding bicyclic imidazo[1,2-*a*]pyridines as well as corresponding fully saturated analogues are frequently reported in the literature[5] but dihydroimidazo[2,1-*a*]isoquinolin-3(2*H*)-ones and 1,8a-dihydroimidazo[1,2-*a*]pyridin-3(2*H*)-one are generally unknown.



Scheme 1.

The application of the optically active imidazoisoquinolinones **4** in further asymmetric syntheses such as of ring opened adducts **7**, as well as the application of amino acid fluorides with other *N*-protective groups such as Fmoc or Z, directly affording adducts **7** in the presence of nucleophiles such as cyanide are presently under investigation.

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2. (a) Carpino, L. A.; Mansour, E. M. E.; El-Faham, A. *J. Org. Chem.* **1993**, *58*, 4162. (b) Carpino, L. A.; Beyermann, M.; Wenschuh, H.; Bienert, M. *Acc. Chem. Res.* **1996**, *29*, 268.
3. Full data of the X-ray crystal structure determination have been deposited with the Cambridge Crystallographic Data Centre, Cambridge, UK, as supplementary publication no. CCDC-145074.

4. Selected data for **4a**: Colourless crystals, mp. 143–144°C; $[\alpha]_D^{20} = +159.5$ (*c* 1, CH_2Cl_2); δ_H (300 MHz, $CDCl_3$ *J*/Hz) 1.40 (d, $J = 7.2$, 3H), 2.39 (s, 3H), 4.09 (q, $J = 7.0$, 1H), 5.91 (s, 1H), 6.19 (d, $J = 7.5$, 1H), 7.09–7.79 (m, 8H). δ_C (75 MHz, $CDCl_3$) 20.54, 21.65, 57.53, 72.09, 116.45, 120.90, 124.76, 125.24, 128.08, 128.87, 128.98, 130.18, 130.46, 130.89, 132.28, 145.28, 168.77.
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