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Unexpected Formation of 3-Substituted 1,2,3,4-Tetrahydroisoquinolines during Tosylation of *N*,*N*-dibenzylaminols†

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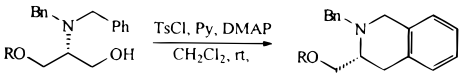
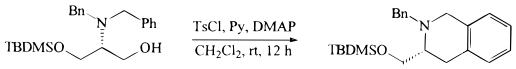
ABSTRACT



An efficient new entry toward the construction of 3-substituted 1,2,3,4-tetrahydroisoquinolines from *N*,*N*-dibenzyl-α-aminols is reported via intramolecular Friedel–Crafts cyclization of in situ generated tosylate intermediate.

Substituted tetrahydroisoquinolines[1] are attributed with broad spectrum of pharmacological properties which range from calcium antagonist[2] and cardiovascular effects,[3] antibacterial[4] and antiplasmodial activity,[5] to neuoromodulating effects.[6] Also the chiral tetrahydroisoquinoline-3-carboxylic acid (Tic) and tyrosine as the dipeptide have been demonstrated to be universal δ-opioid receptor selective antagonists.[7] Incorporation of this unusual amino acid into an opioid peptide dramatically enhances the biological properties.[8] Thus synthesis of this class of compounds has been a prime area of activity at various laboratories. As part of our own interest[9] in the synthesis of unusual amino acids and amino alcohols of biological value, we wanted to tosylate (tosyl chloride, pyridine, DMAP, dichloromethane) the *N*,*N*-dibenzylserinol **1a**. This mild tosylation protocol surprisingly yielded the tetrahydroisoquinoline derivative (**1b**) in 83% yield in 12 h at ambient temperature (Scheme 1).

Scheme 1



To confirm the effectiveness of this unprecedented transformation, several *N*,*N*-dibenzylaminols were prepared using standard protocols[10] (see Table 1) and subjected to tosylation to generate various 3-substituted tetrahydroisoquiolines in excellent yields. Entry 5 gives an access to symmetric isoquinoline derivative **5b** in 70% yield. Similarly, entry 6 describes the formation of the protected tetrahydroisoquinoline carboxylic acid derivative **6b** in 54% yield. This transformation mechanistically may be attributed as tosylation of the alcohol followed by electrophilic cyclization onto the phenyl ring (Friedel−Crafts cyclization).

† IICT nommunication 4334.

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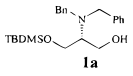
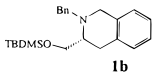
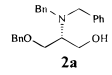
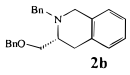
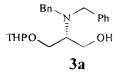
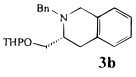
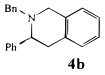
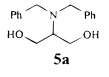
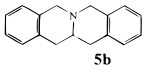
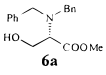
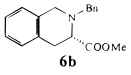
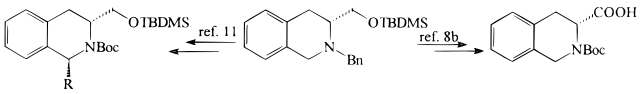
Table 1. Synthesis of 3-Substituted 1,2,3,4-Tetrahydroisoquinolines

Entry	Substrates	reaction time (h)	products[a]	Yield[b] (%)
1	 **1a**	12	 **1b**	83
2	 **2a**	12	 **2b**	77
3	 **3a**	12	 **3b**	72
4	 **4a**	12	 **4b**	68
5	 **5a**	12	 **5b**	70
6	 **6a**	24	 **6b**	54

a : characterised by ^{1}H NMR, IR and mass spectral analysis
b : yields refer to isolated and purified product.

1b is tailor-made for alkylation at C-1with BuLi and electrophile to produce chiral, 1,3-disubstituted tetrahydroisoquinoline.[11] It is understood that the stereochemistry at C-3 dictates the relative chemistry of C-1. Similarly, the same substrate **1b** is a useful chiral precursor for Tic (Scheme 2).

Scheme 2



In conclusion, this Letter describes an unprecedented, but very useful, preparation of tetrahydroisoquinolines which is very useful in organic synthesis.

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Supporting Information Available: Experimental details and ^{1}H NMR spectral data of **1b**, **2b**, **3b**, **4b**, **5b**, and **6b** and HRMS of **1b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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