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Treatment of *N,N*-Dibenzylamino Alcohols with Sulfonyl Chloride Leads to Rearranged β-Chloro Amines, Precursors to β-Amino Acids, and Not to Tetrahydroisoquinolines

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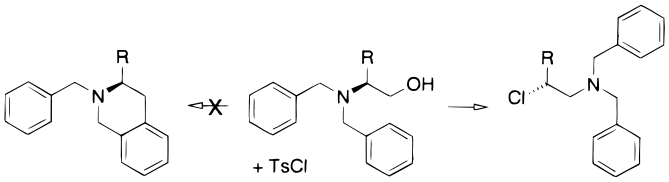
ABSTRACT



Very recently, the unexpected formation of 3-substituted 1,2,3,4-tetrahydroisoquinolines starting from *N,N*-dibenzyl-protected β-amino alcohols was reported. The authors claimed that treatment with tosyl chlorides induced intramolecular Friedel–Crafts alkylation. Reexamination of the reactions in our laboratory clearly proved rearranged chloro amines instead of the initially assumed tetrahydoisoquinoline structures. The chloro amines investigated can be employed as highly useful intermediates for an EPC synthesis of β-amino nitriles and β-amino acids.

N,N-Dibenzyl-protected β-amino alcohols are known as important intermediates for the synthesis of configurationally stable α-amino aldehydes which caused considerable impact on the development of modern ex-chiral pool synthesis. Pioneering work in this field was performed by M. T. Reetz.[1] Furthermore, stereoselective lithiation and *C*-substitution of carbamate derivatives was reported by D. Hoppe.[2] In a series of papers, we have shown that *O*-activation of *N,N*-dibenzyl-protected β-amino alcohols, prepared from asparagine or aspartic acid, by MsCl, Ms_2O, or Tf_2O or by using Mitsunobu conditions and subsequent displacement reactions gives practical access to precursors of enantiomerically pure β-amino acids,[3] diamines,[4] amino lactams,[5] natural product derivatives,[6] and dopaminergic tetrahydroindolizines.[7] In some cases, the β-amino sulfonate intermediates were unstable. Thus, we observed 1,2-migration of the *N,N*-dibenzylamino functionality to give products of type **4** (Scheme 1). Obviously, this reaction sequence proceeds via an aziridinium sulfonate or chloride (**3**).[6] We assume that the preference of the secondary halide (or pseudohalide) structure compared to the primary substituted isomers is thermodynamically driven. In the presence of a nitrile or a second sulfonate as a further functional group, the migration was followed by β-elimination [8] or pyrrolidinium formation, respectively.[9] Although we examined these reactions very

(1) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1531.
(2) Guarnieri, W.; Grehl, M.; Hoppe, D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1734.
(3) (a) Gmeiner, P. *Tetrahedron Lett.* **1990**, *31*, 5717. (b) Gmeiner, P. *Liebigs Ann. Chem.* **1991**, 501.
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(5) Weber, K.; Gmeiner, P. *Synlett* **1998**, 885.
(6) Gmeiner, P.; Junge, D.; Kärtner, A. *J. Org. Chem.* **1994**, *59*, 6766.
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(8) Gmeiner, P. *Arch. Pharm. (Weinheim)* **1991**, *324*, 551.
(9) (a) Gmeiner, P.; Orecher, F.; Thomas, C.; Weber, K. *Tetrahedron Lett.* **1995**, *36*, 381. (b) Thomas, C.; Orecher, F.; Gmeiner, P. *Synthesis* **1998**, 1491.

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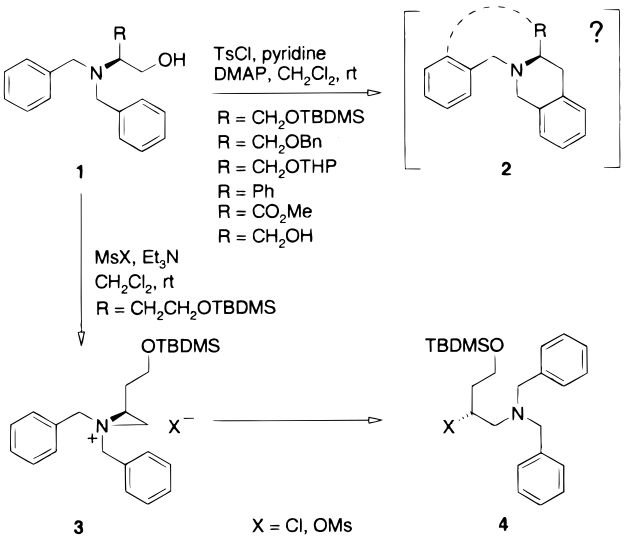
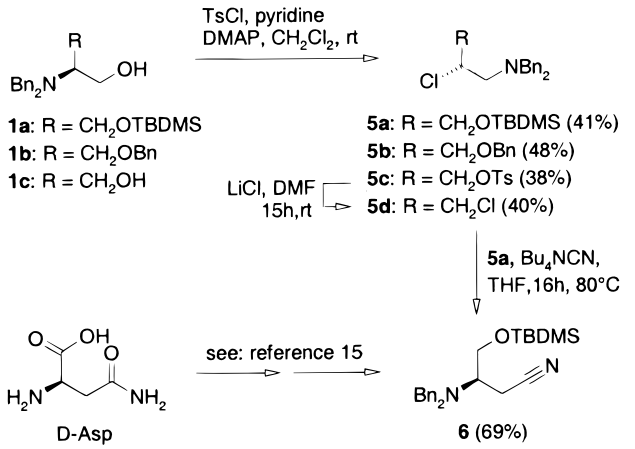
Scheme 1



Scheme 2



carefully, the synthesis of 1,2,3,4-tetrahydroisoquinolines (**2**) by an intramolecular Friedel−Crafts reaction was not detected. Thus, we were surprised by a very recent communication from S. Chandrasekhar and co-workers describing such a cyclization for serine- and phenylglycine-derived *N*,*N*-dibenzyl-protected *β*-amino tosylates.[10] Starting from *N*,*N*-dibenzylserinol, the authors also reported the formation of a tetracyclic 5a-azanaphthacene system involving the alkylation of both benzyl groups. Our comparison of the ^{1}H NMR available as Supporting Information of ref 10, with those of the rearranged *β*-chloro amines of type **4** showed a high similarity and, thus, lead us to the assumption that the authors might have been deceived. This prompted us to reexamine major experiments of the work.

Thus, we reacted the *O*-TBDMS-protected serinol **1a**[11] with TsCl as described. After extraction and chromatography, we isolated a pure product in 41% yield which gave a ^{1}H NMR spectrum basically identical to that published for the potential 2-benzyl-3-silyloxymethyl-1,2,3,4-tetrahydroisoquinoline. However, careful interpretation of our analytical data proved the chloro amine structure **5a** without any doubt (Scheme 2).[12]

In detail, the experimentally determined molecular composition employing both high-resolution mass spectroscopy and combustion analysis (including the measurement of CHN and Cl) corresponded very well to the theoretical values. Besides this, EIMS gave a $(M - Cl)^+$ peak of 368.3 erroneously identified as $(M + H)^+$ by Chandrasekhar et al.[10] Furthermore, ^{13}C NMR spectroscopy in combination with a CH-COSY experiment clearly indicated two magnetically equivalent phenyl substituents without substituents in the ortho positions. The migration of the amino group and the secondary alkyl chloride substructure was elucidated by ^{1}H NMR and mass spectroscopy when the chemical shifts of the vicinally positioned proton signals (2.72/2.93 ppm for CH_2N and 3.90 ppm for C*H*Cl) and a characteristic α-cleavage giving $Bn_2NCH_2^+$ fragmentation in the HRMS were diagnostic.

Starting from the *O*-benzyl-protected amino alcohol **1b**[13] and from the serinol derivative **1c**, reaction with tosyl chloride under identical conditions was also investigated. We observed formation of the chloro amines **5b** and **5c**, respectively, when **5c** showed *O*-tosylation at the second hydroxyl function. Again, analytical data confirmed the chloro amine structure and excluded tetrahydroisoquinoline formation.[14] Whereas the ^{1}H NMR data reported for the benzyloxy derivative corresponded well to our spectra for **5b**, this was not the case for **5c**. Here, the formation of an azanaphthacene through bis-Friedel−Crafts alkylation was

(10) Chandrasekhar, S.; Mohanty, P. K.; Harikishan, K.; Sasmal, P. K. *Org. Lett.* **1999**, *1*, 877.

(11) Laib, T.; Chastanet, J.; Zhu, J. *J. Org. Chem.* **1998**, *63*, 1709.

(12) **5a**: ^{1}H NMR (360 MHz, $CDCl_3$) $\delta = 0.01$ (s, 6H, $SiCH_3$), 0.86 (s, 9H, $C(CH_3)_3$), 2.72 (dd, $J = 13.7$, 6.3 Hz, 1H, NCH_2CH), 2.93 (dd, $J = 13.7$, 6.4 Hz, 1H, NCH_2CH), 3.62 (s, 4H, NCH_2Ph), 3.66 (dd, $J = 10.6$, 5.3 Hz, 1H, OCH_2), 3.76 (dd, $J = 10.6$, 5.4 Hz, 1H, OCH_2), 3.90 (dddd, $J = 6.4$, 6.3, 5.4, 5.3 Hz, 1H, *C*HCl), 7.21−7.38 (m, 10H, ar); ^{13}C NMR (63 MHz, $CDCl_3$) $\delta = -5.3$ (SiCH_3) 18.3 (*C*$(CH_3)_3$), 25.8 (CCH_3), 57.3 (NCH_2-CH), 59.0 (NCH_2Ph), 60.7 (*C*HCl), 65.8 (OCH_2), 127.1 (*C*H-ar), 128.2 (*C*H-ar), 128.9 (*C*H-ar), 139.1 (*C*-ar) (the interpretation of the data is based on CH-COSY experiments). Anal. Calcd for $C_{23}H_{34}ClNOSi$: C, 68.37; H, 8.48; Cl, 8.77; N, 3.47. Found: C, 68.40; H, 8.53; Cl, 8.72; N, 3.43. HRMS (EI). Calcd 403.2098 (M^+), 210.1282 ($Bn_2NCH_2^+$). Found: 403.2091 (M^+), 210.1288 ($Bn_2NCH_2^+$).

(13) Beaulieu, P. L.; Wernic, D. *J. Org. Chem.* **1996**, *61*, 3635.

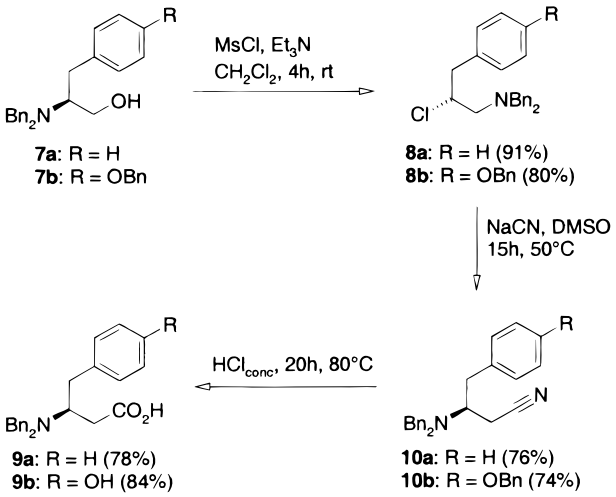
(14) **5b**: ^{1}H NMR (360 MHz $CDCl_3$) $\delta = 2.75$ (dd, $J = 13.7$, 6.2 Hz, 1H, NCH_2CH), 2.91 (dd, $J = 13.7$, 7.5 Hz, 1H, NCH_2CH), 3.47 (dd, $J = 10.5$, 6.3 Hz, 1H, OCH_2CH), 3.57 (d, $J = 13.4$ Hz, 2H, NCH_2Ph), 3.65 (d, $J = 13.4$ Hz, 2H, NCH_2Ph), 3.71 (dd, $J = 10.5$, 6.3 Hz, 1H, OCH_2CH), 3.95−4.05 (m, 1H, *C*HCl), 4.44 (d, $J = 12.0$ Hz, 1H, OCH_2Ph), 4.51 (d, $J = 12.0$ Hz, 1H, OCH_2Ph), 7.22−7.39 (m, 15H, ar). $C_{24}H_{26}ClNO$: HRMS (EI). Calcd 379.1703 (M^+), 210.1282 ($Bn_2NCH_2^+$). Found: 379.1712 (M^+), 210.1273 ($Bn_2NCH_2^+$). **5c**: ^{1}H NMR (360 MHz $CDCl_3$) $\delta = 2.44$ (s, 3H, CH_3), 2.72 (dd, $J = 13.7$, 5.5 Hz, 1H, NCH_2CH), 2.80 (dd, $J = 13.7$, 8.2 Hz, 1H, NCH_2CH), 3.51 (d, $J = 13.4$ Hz, 2H, NCH_2Ph), 3.62 (d, $J = 13.4$ Hz, 2H, NCH_2Ph), 3.82−3.95 (m, 1H, *C*HCl), 3.91 (dd, $J = 10.0$, 7.3 Hz, 1H, OCH_2CH), 4.30 (dd, $J = 10.0$, 6.9 Hz, 1H, OCH_2CH), 7.22−7.35 (m, 12H, ar), 7.72−7.78 (m, 2H, ar). $C_{24}H_{26}ClNO_3S$: HRMS (EI). Calcd 443.1322 (M^+), 210.1282 ($Bn_2NCH_2^+$). Found: 443.1327 (M^+) 210.1293 ($Bn_2NCH_2^+$). **5d**: ^{1}H NMR (360 MHz, $CDCl_3$) $\delta = 2.80$ (dd, $J = 13.8$, 5.8 Hz, 1H, NCH_2CH), 2.98 (dd, $J = 13.8$, 8.1 Hz, 1H, NCH_2CH), 3.62 (d, $J = 13.4$ Hz, 2H, NCH_2Ph), 3.65 (dd, $J = 11.9$, 5.8 Hz, 1H, ClCH_2-CH), 3.68 (d, $J = 13.4$ Hz, 2H, NCH_2Ph), 3.78 (dd, $J = 11.9$, 4.5 Hz, 1H, ClCH_2CH), 3.88−4.00 (m, 1H, *C*HCl), 7.23−7.40 (m, 10H, ar). $C_{17}H_{19}$-Cl_2N: HRMS (EI). Calcd 307.0895 (M^+), 210.1282 ($Bn_2NCH_2^+$). Found: 307.0902 (M^+), 210.1280 ($Bn_2NCH_2^+$).

reported. However, after displacement of the tosylate function of **5c** with LiCl in DMF giving the dichloride **5d** the spectra showed high correspondence. Therefore, we assume that the experiments of S. Chandrasekhar et al. resulted in further chloride displacement during the reaction or brine extraction. Thus, dichloride **5d** appeared to show the azanaphthacene formation expected by the authors of ref 10.

Upon reaction of the secondary chloride **5a** with Bu_4NCN, the nitrile **6** was formed, giving analytical data (^{1}H NMR, optical rotation) identical to those of a sample which we synthesized from D-asparagine by benzylation, dehydration of the carboxamide, reduction, and subsequent silylation of the primary alcohol.[15]

Starting from *N*,*N*-dibenzyl-protected amino alcohols, which can be readily obtained from natural amino acids, the combination of *O*-activation and subsequent introduction of a cyano substituent can be used for the synthesis of β-amino nitriles.[16] Further hydrolysis gives access to suitably protected β-amino acids and, thus, demonstrates a highly practical homologation sequence for amino acids.[17] To demonstrate this, we reacted the phenylalanine- and tyrosine-derived β-amino alcohols **7a** and **7b**[13,18] with MsCl using Et_3N as a base Scheme 3). This combination of reagents is more

Scheme 3



suitable than TsCl/pyridine since the product separation from the excess of sulfonyl chloride is more convenient and the yields are generally higher, at least in our hands. Activation of the amino alcohol **7b** resulted in formation of the rearranged chloride **8b**, exclusively.[19] On the other hand,^{1}H NMR based analysis of crude product obtained from **7a** gave a mixture of both the primary and the regioisomeric secondary chloride. However, after chromatograpy and storage, the thermodynamic situation was achieved when only the secondary chloride **8a** could be detected. Reaction of **8a**,**b** with NaCN proceeded again through an aziridinium intermediate which is regioselectively opened at the sterically less demanding CH_2 position to give the amino nitriles **10a**,**b** (kinetic control).[20, 21] Transformation into the protected β-homophenyl alanine **9a** and the β-homo tyrosine **9b** could be realized by treatment of **10a**,**b** with hydrochloric acid in 78 and 84% yields, respectively.

The configurational integrity of the reaction sequence was established by comparing optical rotation data of the protected homophenylalanine **9a** with those reported for a differentially synthesized product[8] and by esterification, *N*-deprotection, and derivatization of the homotyrosine **9b** with enantiomerically pure 1-phenylethyl isocyanate.[22] Subsequent ^{1}H NMR studies indicated that the synthetic material was isomerically pure.

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(15) Gmeiner, P.; Hummel, E.; Haubmann, C. *Liebigs Ann. Chem.* **1995**, 1987.

(16) For a prevoius synthesis of β-amino nitriles, see: Reetz, M. T.; Kayser, F.; Harms, K. *Tetrahedron Lett.* **1994**, *35*, 8769.

(17) For previous homologations of amino acids, see: Podlech, J.; Seebach, D. *Liebigs Ann. Chem.* **1995**, 1217. Caputo, R.; Cassano, E.; Longobardo, L. Palumbo, G. *Tetrahedron* **1995**, *51*, 12337 and references therein.

(18) (a) Reetz, M. T.; Drewes, M. W.; Schmitz, A. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1141. O'Brien, P.; Powell, H. R.; Raithby, P. R. Warren, S. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1031.

(19) **8b**: ^{1}H NMR (200 MHz, $CDCl_3$) δ = 2.56 (dd, J = 14.4, 9.0 Hz, 1H, NCH_2CH), 2.80 (d, J = 7.0 Hz, 2H, CHCH_2Ar), 3.23 (dd, J = 14.4, 4.2 Hz, 1H, NCH_2CH), 3.58 (d, J = 13.6 Hz, 2H, NCH_2Ph), 3.72 (d, J = 13.6 Hz, 2H, NCH_2Ph), 3.92−4.02 (m, 1H, *CH*Cl), 5.04 (s, 2H, CH_2O), 6.85−6.89 (m, 2H, ar), 6.97−7.01 (m, 2H, ar), 7.19−7.46 (m, 15H, ar). Anal. Calcd for $C_{30}H_{30}ClNO$: C, 79.02; H, 6.63; N, 3.07. Found: C, 78.51; H, 6.47; N, 3.74.

(20) **8a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.59 (dd, J = 14.4, 9.1 Hz, 1H, NCH_2CH); 2.78−2.84 (m, 2H, CHCH_2Ph), 3.30 (dd, J = 14.4, 4.0 Hz, 1H, NCH_2CH), 3.59 (d, J = 13.6 Hz, 2H, NCH_2Ph), 3.71 (d, J = 13.6 Hz, 2H, NCH_2Ph), 3.99−4.06 (m, 1H, *CH*Cl), 7.00−7.10 (m, 2H, ar), 7.18−7.40 (m, 13H, ar). Anal. Calcd for $C_{23}H_{24}ClN$: C, 78.95; H, 6.92; N, 4.00. Found: C, 78.80; H, 6.73; N, 4.34. 1-Chloro-2-dibenzylamino-3-phenylpropane (recorded together with **8a** from crude product): ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.78−2.84 (m, 1H, CH_2Ph), 3.01 (dd, J = 13.8, 6.7 Hz, 1H, CH_2Ph), 3.16−3.24 (m, 1H, *CH*N), 3.53 (dd, J = 11.5, 5.5 Hz, 1H, CH_2Cl), 3.69 (dd, J = 11.5, 6.8 Hz, 1H, CH_2Cl), 3.72 (d, J = 13.8 Hz, 2H, NCH_2Ph), 3.78 (d, J = 13.8 Hz, 2H, NCH_2Ph), 7.00−7.10 (m, 2H, ar), 7.18−7.40 (m, 13H, ar).

(21) **10a**: ^{1}H NMR and optical rotation data were consistent with those reported in ref 8 for a differentially synthesized product. **10b**: ^{1}H NMR (200 MHz, $CDCl_3$) δ = 2.41 (dd, J = 10.5, 8.3 Hz, 1H, CH_2CN), 2.50−2.63 (m, 2H, CH_2CN, CH_2Ar), 3.08 (dd, J = 13.6, 5.5 Hz, 1H, CH_2Ar), 3.17−3.31 (m, 1H, *CH*N), 3.66 (d, J = 13.7 Hz, 2H, NCH_2), 3.78 (d, J = 13.7 Hz, 2H, NCH_2), 5.05 (s, 2H, OCH_2), 6.88−6−92 (m, 4H, ar), 7.20−7.46 (m, 15H, ar). Anal. Calcd for $C_{31}H_{30}N_2O$: C, 83.37; H, 6.77; N, 6.27. Found: C, 83.05; H, 6.85; N, 6.46.

(22) A solution of **9b** in MeOH and concentrated aqueous HCl was heated for 12 h at 80 °C. After extraction under basic conditions and evaporation, the residue was dissolved in MeOH and stirred under H_2 in the presence of catalytic amounts of $Pd(OH)_2$. After 15 h the mixture was filtrated and evaporated. The residue was dissolved in THF and coupled with (*S*)-1-phenylethylisocyanate (1 h, rt). After evaporation the crude urea was investigated by ^{1}H NMR spectroscopy (400 MHz). The procedure was repeated with racemic 1-phenylethyl isocyanate. Diagnostic signals: δ = 3.61 ppm (OCH_3) for the (3*S*,2′*S*)-configured urea; δ = 3.66 ppm (OCH_3) for the (3*S*,2′*R*)-configured urea. The synthetic material proved isomerically pure.