Synthesis of Unusual Bridged Steroid Alkaloids by an Iminium Ion Induced 1,5-Shift of a Benzylic Hydride**

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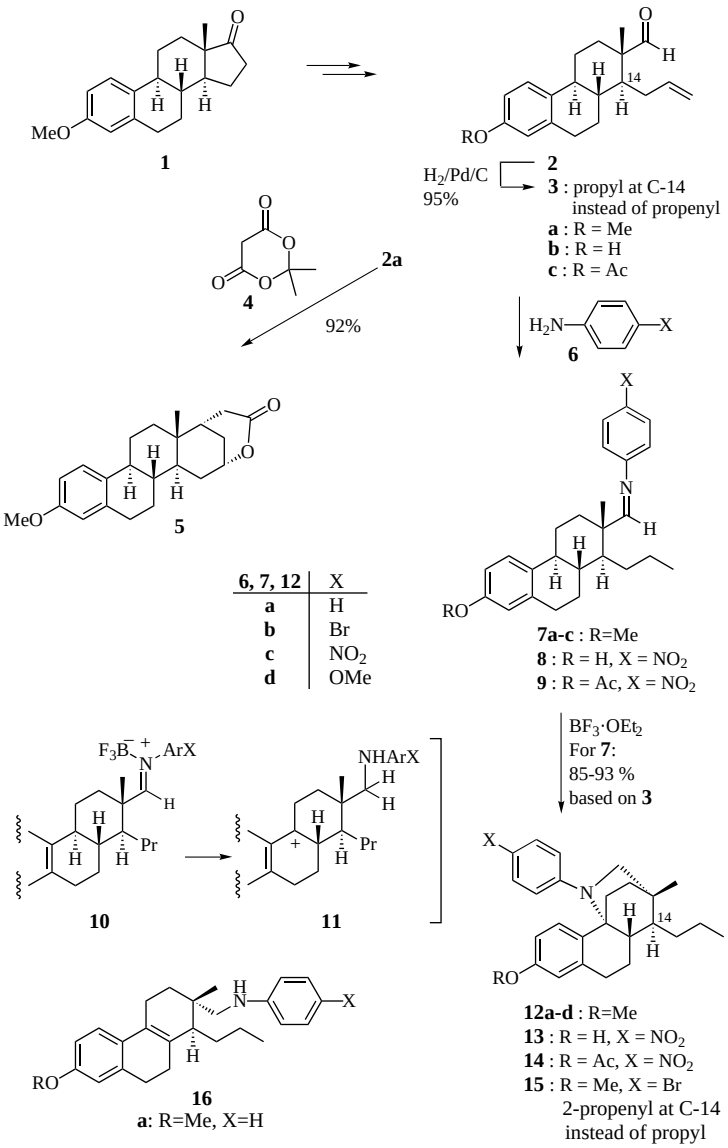
Dedicated to Professor Armin de Meijere on the occasion of his 60th birthday

A main principle in organic synthesis is the displacement of a suitable leaving group or the replacement of a hydrogen atom as a proton in α-position to an electron-withdrawing group. In addition, several examples of intramolecular free radical reactions at unactivated C–H bonds, such as the Barton reaction,[1] are also known. In contrast, a cationic attack at a C–H bond with a hydride shift is rather uncommon. Here we describe a transformation of an iminium ion of a primary amine on a steroid skeleton to give the novel unusually bridged steroid alkaloids **12**–**14**; a reaction that presumably proceeds by a 1,5-hydride shift from a benzylic position to the iminium ion under formation of a carbocation that reacts with the resulting secondary amine.

Recently, we have developed the synthesis of D-homosteroid **5** by a domino Knoevenagel hetero Diels–Alder reaction[2] of Meldrum's acid **4** and the steroid derivative **2a**,[3] which was obtained from estrone 3-methyl ether **1** in four steps.[4] In this sequence a 1-oxa-1,3-butadiene is formed as an intermediate. Similarly, 2-aza-1,3-butadienes can be synthesized by condensation of **2** with aniline derivatives which also undergo a hetero Diels–Alder reaction.[2, 5] However, a completely different pathway dominates if one hydrogenates the propenyl side chain in **2a** first to give the aldehyde **3a**. Reaction of **3a** with aniline **6a** and its derivatives **6b** and **6c**, which contain an electron-withdrawing group in *para*-position, led to the imines **7a**–**c** which are rather unstable and difficult to isolate. Quite unexpectedly, treatment of crude **7a**–**c** with $BF_3 \cdot OEt_2$ in dichloromethane gave the novel unnatural bridged steroid alkaloids **12a**, **12b**, and **12c** in over 80% yield as single diastereomers. The reaction sequence can also be performed more efficiently as a domino process[6] to afford **12a**–**c** in 85–93% yield by preparing the imines in situ. In this way, we have also synthesized the imine **8**, which contains a hydroxyl group at C-3 of the steroid skeleton, and **9**, which contains an acetoxy group at C-3, starting from **6c** and the derivatives **3b** and **3c**, respectively, and treated them with $BF_3 \cdot OEt_2$. In the case of **8**, **13** was obtained in 63% yield together with some unsaturated material **16** within 6 h at room temperature, whereas in the case of **9** after reaction for 24 h at room temperature only 16% of the desired product **14** together with 56% of the starting material was isolated; a compound of type **16** was not found in the reaction of **9**. For the transformation of **3a** and **6c** we have also employed other Lewis acids and Brønsted acids such as $AlCl_3$, $SnCl_4$, $SnMe_2Cl_2$, $TiCl_4$, $HBF_4 \cdot OEt_2$, *p*-TsOH, and trimethylsilyl trifluoromethanesulfonate at room temperature for 24–48 h; however, the yields were much lower and the transformations less clean compared to the reactions with $BF_3 \cdot OEt_2$. Either the reaction did not proceed at all as in the case of $SnMe_2Cl_2$ or the unsaturated derivative **16** is the main compound, which is formed in a



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consequential reaction from **12c** by elimination of the amino function. Thus, treatment of **12a** with $BF_3 \cdot OEt_2$ at room temperature for 24 h led to **16a** in 85% yield. The structures of the steroid azacycles **12a–d**, **13**, and **14** were determined by NMR spectroscopy[7] based on an X-ray crystal structure analysis of **15**.[8]

We assume that during the reaction of the imines **7a–c**, **8**, and **9** with the Lewis acid $BF_3 \cdot OEt_2$ first an iminium ion **10** is formed. This undergoes a 1,5-hydride shift to give **11**, which contains a secondary amine moiety and a carbocation. A 1,2- or a 1,3-hydride shift is not observed, which was to be expected because of the higher activation energy of these rearrangements. Addition of the amino group to the carbocationic center in **11** then yields **12a–c**, **13**, or **14**, The proposed mechanism is consistent with the lower reactivity of **9** compared to that of **7** and **8**, which can easily be explained by a reduced stabilization of the intermediately formed benzylic cation **11**. This again is consistent with the observation that the *p*-methoxybenzyl group, which is used as a protecting group,[9] can easily be removed by an oxidative hydride transfer by using cerium ammonium nitrate (CAN) or other oxidants, whereas a benzyl group without an electron-donating group does not undergo this reaction.

To the best of our knowledge the described domino process is a new type of transformation, though the opposite reaction, namely the formation of an iminium ion from an amine and a carbocation, is a well known process.[10] In addition, examples of a formal insertion of an iminium ion derived from an oxime into a suitably oriented C–H bond have been described.[11] According to the electrophilicity scale, which has recently been published by Mayr and Ofial,[12] the iminium ion **10** is comparable with the tropylium cation and the phenyldiazonium ion. Therefore it is not unexpected that iminium ions obtained from **3a** and an aniline derivative containing an electron-donating group in *para* position such as **6d** gave the corresponding steroid alkaloids **12d** with only 2% yield. Reactions of **3a** with *ortho*-substituted anilines did not lead to the desired products at all, presumably due to steric reasons.

Experimental Section

12a: A mixture of **3a** (298 mg, 1 mmol), freshly distilled aniline (0.9 mL, 1 mmol), and molecular sieves (4 Å, 150 mg) in dichloromethane (10 mL) was stirred under an argon atmosphere for 4 h at 40 °C. After filtration $BF_3 \cdot OEt_2$ (0.15 mL, 0.5 mmol) in dichloromethane (1 mL) was added slowly at room temperature, and stirring was continued for 12 h. After a addition of further $BF_3 \cdot OEt_2$ (0.15 mL, 0.5 mmol) in dichloromethane (1 mL) and stirring until completion (TLC), the reaction was quenched by adding ice-cold 1N NaOH (30 mL). The organic phase was separated, the aqueous phase extracted with dichloromethane (3×30 mL), and the combined organic phases washed with brine and dried over Na_2SO_4. Evaporation in vacuo and purification of the residue by chromatography (silica gel, *tert*-butyl methyl ether/petroleum ether = 1:4) afforded **12a** (319 mg, 85%).

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[7] **12a:** M.p. 61–63 °C; $[\alpha]_D^{20} = +373.9$ ($c = 1.0$, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) $\delta = 0.92$ (t, 3H, $J = 7.2$ Hz, 16a-H_3), 0.93 (s, 3H, 18-H_3), 1.10–1.95 (m, 11H), 2.52 (m, 1H), 2.85 (m, 2H, 6-H_2), 2.94 (dd, 1H, $J = 9.4$ Hz, $J = 2.8$ Hz, N-$CH_{2,ax}$), 3.52 (d, 1H, $J = 9.4$ Hz, N-$CH_{2,eq}$), 3.75 (s, 3H, 3-OMe), 6.31 (d, 2H, $J = 8.3$ Hz, 2′- and 6′-H), 6.52 (m, 2H, 2- and 4′-H), 6.64 (d, 1H, $J = 2.6$ Hz, 4-H), 6.86 (m, 3H, 1-, 3′- and 5′-H); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 14.9$ (C-16a), 22.3, 23.7 (C-18), 26.3, 28.6, 30.5, 33.4, 34.3, 35.0, 46.5 (C-14), 48.8 (C-8), 55.1 (3-OMe), 57.7 (C-9), 61.5 (N-CH_2), 111.8 (C-2), 113.2 (C-4), 116.9 (C-4′), 118.2 (2C, C-2′ and C-6′), 127.6 (2C, C-3′ and C-5′), 129.9 (C-1), 131.7 (C-10), 138.8 (C- 5), 149.1 (C-1′), 158.1 (C-3). **12b**: M.p. 127–129 °C; $[\alpha]_D^{20} = +307.1$ ($c = 1.0$, $CHCl_3$). **12c**: Oil; $[\alpha]_D^{20} = +610.4$ ($c = 1.0$, $CHCl_3$).
[8] Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-102885. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
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Peryleneimidazoloimides: Highly Fluorescent and Stable Replacements of Terrylene**

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Terrylene[1] (**1**) is an important compound for physicochemical investigations,[2] for example for single-molecule spectroscopy,[3] because its UV/Vis absorption spectrum closely matches the operation region of the easily controllable rhodamine 6G dye laser (about 555–560 nm). The preparation of terrylene is however laborious, high purification very difficult, and the chemical persistency low. Moreover, the

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