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Facile C_{21} functionalization through a novel functional group transfer reaction in 16α,17α-epoxy-3β-hydroxypregn-5-en-20-one and its applications

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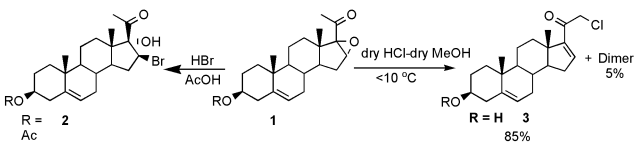
A novel functional group transfer reaction in 16α,17α-epoxy-3β-hydroxypregn-5-en-20-one by treatment with dry HCl affords 21-chloro-3β-hydroxy-pregn-5,16-dien-20-one, which has been utilized to obtain a number of C_{21}-substituted derivatives.

The functionalization at C_{21} in steroidal-20-ones has fascinated the many researchers due to its significance in the synthesis of various medicinally important molecules of the adenocorticoid[1] series as well as other C_{21}-substituted steroids of medicinal significance.[2] The various strategies that have been developed suffer from either low yields or tedious chemical transformations.[1–3]

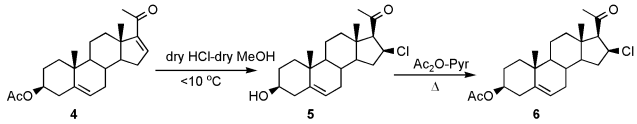
It has been discovered that in contrast to the reported conversion of epoxide (**1**)[3a] to bromohydrin (**2**, Scheme 1) by treatment with HBr–AcOH,[3] treatment of **1** with dry-HCl in anhydrous methanol leads to 21-chloro-3β-hydroxy-pregn-5,16-dien-20-one (**3**, 85%)† in high yields, besides a yet to be characterized dimeric product (5%).

Thus, reaction of **1** with dry HCl in dry MeOH led to the formation of a major product, which was isolated and characterized as 21-chloro-3β-hydroxy-pregn-5,16-dien-20-one (**3**, > 85%) along with dimeric product, which could not be characterized, and no chlorohydrin was formed. The assigned structure of **3** as 21-chloro-3β-hydroxy-pregn-5,16-dien-20-one has been established by detailed spectroscopic analysis (^{1}H and ^{13}C NMR, IR and mass).[4] The olefinic region of its ^{1}H NMR revealed a double-doublet at δ 6.77 (J 2.01, 3.43 Hz), which is assigned to C_{16}-H, besides the C_6-H resonance at δ 5.34. The most characteristic feature of the ^{1}H NMR spectrum was the absence of a resonance for C_{21}-methyl anticipated around δ 2.00 and the presence of an AB-quartet at δ 4.40–4.24 (J_{AB} 14.18 Hz), which is attributed to C_{21}-Hs. In its ^{13}C NMR, the olefinic region revealed four resonances at δ 152.61 (q, C_{17}), 145.13 (CH, C_{16}), 141.58 (q, C_5) and 120.91 (CH, C_6); the chemical shift of C_{20} (δ 189.01) was also characteristic of an α,β-unsaturated carbonyl. The structure was also supported by mass spectrometry (M^+ at m/z 348, 20%, as well as peaks at m/z 351 (M^+ + 3, 10%), 350 (M^+ + 2, 15%) and 349 (M^+ + 1, 18%) and IR spectroscopy (band at 1698 cm^{-1}, C=O).

To confirm that the observed transformation of epoxide (**1**, R = H) to **3** is an intramolecular functional group transfer reaction and is not a consequence of any other reaction involving Cl_2 *etc.* generated under the reaction conditions, it was decided to subject 16-dehydropregenolone acetate (**4**) to similar treatment with dry-HCl in dry-MeOH (Scheme 2). Under these conditions **4** was converted to 3β-hydroxy-16β-chloropregn-5-en-20-one (**5**, 94%), which was acetylated to 3β-acetoxy-16β-chloropregn-5-en-20-one (**6**)[5] and no chlorination occurred at C_{21}.

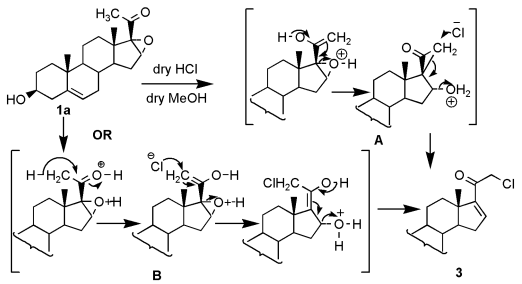


Scheme 1



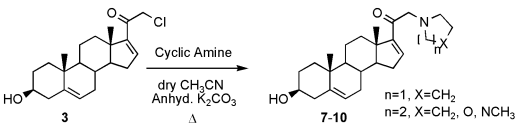
Scheme 2

The steroid 21-chloro-3β-hydroxypregna-5,16-dien-20-one (**3**) is derived from an interesting intramolecular functional group transfer reaction. The probable mechanisms, based on some related transformations reported in the case of 16α,17α-epoxy-16β-methylandrostane-17β-carbothioic acid[6] are outlined in Scheme 3.



Scheme 3

In view of the overwhelming importance of C_{21}-substituted steroids,[2] the usefulness of this serendipitously discovered transformation has been demonstrated by subsequent exploitation of **3** to obtain a number of C_{21}-substituted molecules‡ (Scheme 4 and Table 1).



Scheme 4

Table 1 Reactions of 21-chloro-3β-hydroxypregna-5,16-dien-20-one (**3**) with various cyclic amines‡

Product	Reactant	Temp./°C	Time/h	Yield (%)
7	Morpholine[5]	60	8	62
8	Pyrrolidine	60	7	67
9	Piperidine	60	5	54
10	*N*-Methylpiperazine	60	8	53

Various products (**7**–**10**) have been characterized by detailed spectroscopic analysis. It may be mentioned here that besides obtaining C_{21}-substituted steroids in the pregnane series, the reported transformation will be highly useful in the area of adrenocorticoids.

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Notes and references

† The reaction was carried out by dissolving epoxide **1** (200 mg, 0.57 mmol) in dry MeOH (50 ml) and dry HCl was bubbled through the solution until the solution became wine red; at this point bubbling of HCl was stopped. The contents were poured into a saturated solution of $NaHCO_3$ and stirred until the evolution of CO_2 gas ceased. The precipitated product was filtered through Whatmann filter paper, dried under reduced pressure in a desiccator over fused $CaCl_2$ and recrystallized from MeOH to obtain off-white granules of 21-chloro-3β-hydroxypregna-5,16-dien-20-one (**3**). It may be mentioned here that several immediate attempts did not reproduce the results, until the proper conditions for formation of **3** were worked out and reproducibility of the results was guaranteed. After several attempts, it was found that bubbling of HCl should be stopped immediately as soon as the color of reaction solution becomes wine red; at this stage no epoxide is left and the amount of any side product is minimal. However, if HCl is bubbled beyond this point it leads to the formation of a number other side products, which, probably, include addition of HCl to the C_{16},C_{17}-π bond in **3**.

‡ The reactions of **3** with various cyclic amines were carried out by stirring equimolar, dry acetonitrile solutions of the steroid and the corresponding amines in the presence of anhydrous K_2CO_3, at 60 °C, until the reaction was complete (TLC). Removal of solvent under vacuum followed by column chromatography [silica gel, 60–120 mesh, ethyl acetate–hexane (1:10) as eluent] afforded a single product in each case, which was characterized by detailed spectroscopic analyses.

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5 *21-Chloro-3β-hydroxypregna-5,16-dien-20-one* **3**: yield 85%, mp 198 °C; ν_{max}(KBr)/cm^{-1} 3510, 2988, 2940, 2890, 1698, 1580; δ_H($CDCl_3$, 200 MHz) 6.73 (dd, 1H, *J* 2.00, 3.43 Hz, C_{16}-Hs), 5.36 (d, 1H, *J* 5.08 Hz, C_6-H), 4.40–4.20 (AB q, 2H, *J* 14.18 Hz, C_{21}-Hs), 3.54 (m, 1H, C_3-H), 2.44 (steroidal hump having singlets at δ 1.04, 0.96 of CH_3 overall 24 H); δ_C($CDCl_3$, 50 MHz) 189.01 (C_{21}), 152.61 (C_{17}), 145.13 (C_{16}), 141.589 (C_5), 120.91 (C_6), 96.01 (CCl_4), 71.66 (C_3), 56.22 (C_{21}), 50.54, 46.69, 45.75, 42.30, 37.21, 36.76, 34.46, 32.71, 31.72, 31.57, 30.36, 20.74, 19.37, 15.73; *m*/*z* 351 (M^{+}+ 3, 7.6%), 350 (M^{+}+ 2, 9.9%), 349; Anal. Calc. $C_{22}H_{29}ClO_2$: C, 72.29; H, 8.38. Found: C, 72.87; H, 8.16%; $[\alpha]_D^{18}$ −33.08 (*c* 0.136%; $CHCl_3$). *3β-Acetoxy-16β-chloropregna-5,16-dien-20-one* **6:** yield 90%, mp 216–218 °C; ν_{max}(KBr)/cm^{-1} 3300, 2985, 2930, 2890, 1740, 1720, 1442, 1370, 1255, 1188, 1145, 1038, 990, 970, 920, 856, 828; δ_H($CDCl_3$, 200 MHz) 5.37 (d, 1H, *J* ~ 4.09 Hz, C_6-H), 4.86–4.79 (dt, δ 4.80, $J_{15,16}$ ~ 6.58, $J_{16,17}$ ~ 7.12 Hz, C_{16}-Hs), 4.61–4.45 (m, 1H, C_3-H), 2.91 (d, 1H, *J* 7.12 Hz, C_{17}-H), 2.33–0.61 (steroidal hump having singlets at δ 2.17, 2.06, 1.00 & 0.61 of CH_3 overall 29 H); δ_C($CDCl_3$, 50 MHz) 205.51 (C_{21}), 170.12 (CH_3CO_2–), 139.66 (C_5), 121.93 (C_6), 74.98 (C_3), 73.58 (C_{16}), 56.58 (C_{21}), 54.47, 49.63, 45.71, 38.60, 36.88, 36.56, 31.67, 31.46, 31.11, 27.66, 27.05, 21.34, 20.79, 20.67, 19.27, 13.82; *m*/*z* 349 (M^+ − 49 (≡ AcO), 3%), 335, 334, 333, 332, 330; Anal. Calc. for $C_{23}H_{33}ClO_3$: C, 70.30; H, 8.46. Found: C, 70.62; H, 8.09%; $[\alpha]_D^{26}$ −13.25 (*c* 0.445%; $CHCl_3$). **7**: Yellow needles, yield 62%, mp 210–214 °C; ν_{max}(KBr)/cm^{-1} 3360, 2940, 2886, 1670, 1630, 1445, 1360, 1240, 1210, 1135, 1080; δ_H($CDCl_3$, 200 MHz) 6.78 (q, 1H, C_{16}-H), 5.32 (br d, 1H, C_6-H), 3.77–3.36 (br m, 7H, C_3-H, OCH_2 × 2 of morpholine and C_{21}-Hs), 2.90–2.79 (split t, 2H, NCH_2), 2.55–2.50 (split t, 2H, NCH_2), 2.25–0.9 (steroidal hump having singlets at δ 1.03, 0.92 of CH_3, overall 24 H); δ_H($CDCl_3$, 50 MHz) 193.69 (C_{20}), 153.57 (C_{17}), 144.90 (C_{16}), 141.03 (C_5), 121.90 (C_6), 71.40, 67.13 (OCH_2 of morpholine), 66.34, 63.72, 56.04, 50.22, 46.55 (NCH_2 of morpholine), 42.12, 36.60, 34.49, 31.46, 27.45, 20.59, 19.24, 15.76; *m*/*z* 313 [M^+ − 86 (C_4H_8NO), 1%), 302, 301, 300, 298, 296, 287, 284, 279, 271, 269, 256, 255, 241; Anal. Calc. for $C_{25}H_{37}NO_3$: C, 75.15; H, 9.33; N, 3.51. Found: C, 74.60; H, 8.89; N, 4.01%; $[\alpha]_D^{25}$ −20.34 (*c* 0.069%; EtOH).

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