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# Regio- and stereoselective thermal cycloaddition of α-aryl-*N*-phenylnitrones to 16-dehydropregnenolone acetate: π-facial selective addition of the minor rotamers of the nitrones

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**Abstract**

Thermal cycloaddition of α-aryl-*N*-phenylnitrones to the C16–C17 π-bond in 16-dehydropregnenolone-3β-acetate (**1**) involves only the minor rotamer (*E*-form) of the nitrones and occurs regio-, stereo- and π-facial-selectively to afford steroido[16,17-*d*]isoxazolidines (**3**) in high yield. 

*Keywords:* nitrone; pregnenolone; stereoselective; 1,3-dipolar cycloaddition; regioselective.

Cycloadditions of nitrones to a variety of unsaturated systems have been extensively exploited to synthesize isoxazoline/isoxazolidine rings.[1] Recently, useful antiinflammatory, analgesic, and sedative properties have been ascribed to molecules possessing such heterocyclic functionalities.[2] In general 1,3-dipolar cycloaddition to unsaturated steroidal systems are reported to be inefficient and various strategies have been adopted to improve the yields of the cycloadducts.[3] Though the 16,17-double bond in 16-dehydro-20-one steroidal systems has been more frequently targeted[3] for obtaining hetero-annulated pentacyclic-steroids, the only available report of a successful 1,3-dipolar cycloaddition of a nitrone relates to addition, under high pressure (14 kbar, 30°C), of a dipolar nitronic ester[3a,b] to 16-dehydropregnenolone acetate, affording a mixture of diastereomeric adducts. In view of the reported medicinal importance of steroidal systems bearing additional heterocyclic rings,[3,4] we have investigated the thermal cycloaddition of a number of α-aryl-*N*-phenylnitrones (**2a**–**e**) to 16-dehydropregnenolone acetate (**1**) and report that the addition of nitrones is highly regio- and stereoselective and affords steroido[16,17-*d*]isoxazolidines (**3**) in high yields (Scheme 1, Table 1).

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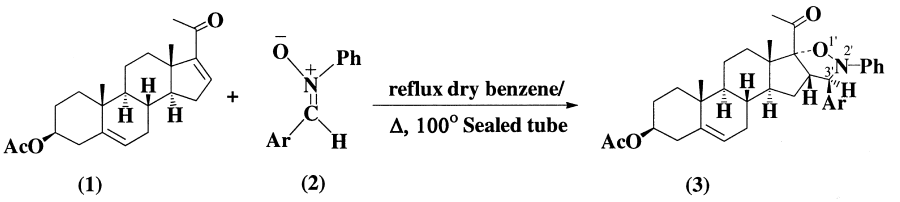



Scheme 1.

Table 1
Reactions of 16-DPA (**1**) and nitrone (**2**)

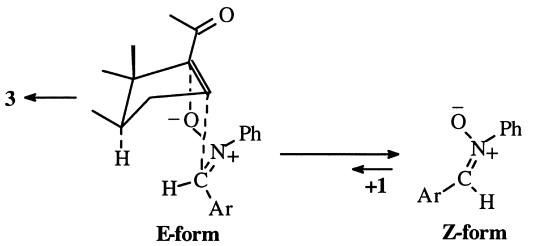
| S. No. | Ar | % Yield of **3** (reaction time) | |
|---|---|---|---|
| | | Reflux (h) | Δ Sealed tube (h) |
| a | Ph | 80 (65) | 85 (36) |
| b | *p*-$NO_2$Ph | 82 (64) | 83 (30) |
| c | *p*-ClPh | 82 (70) | 85 (37) |
| d | *p*-MeOPh | 74 (43) | 74 (24) |
| e | 3-Furanyl | 73 (72) | 83 (32) |

Thus, refluxing a solution of 16-DPA (1.4 mmol) and the nitrone (2.8 mmol) in dry benzene (20 ml) until all the steroid was consumed (TLC), followed by column chromatographic separation of the residue (silica gel 60–120 mesh, 20% ether in hexane eluent) afforded cycloadducts (**3**). Alternatively, a solution of 16-DPA (0.56 mmol) and the nitrone (1.12 mmol) in dry benzene (10 ml) was sealed in a Pyrex glass tube which was heated at 100°C for varied periods (24–36 h)[5] and the products isolated in a similar manner.

The assigned structures (**3a**–**e**) are based on detailed spectroscopic analysis and microanalytical data.[6] The NMR data clearly established the presence of a single stereoisomer even in the crude thermolysate. The involvement of the 16,17-π bond in the cycloaddition was established, inter alia, by the absence of a C16–H (olefinic) resonance in the $^1$H NMR spectrum (observed in the case of 16-DPA at $\delta$ 6.68). The regiochemical mode of addition was assigned on the basis of the presence of a tertiary carbon resonance[6] at $\sim\delta$ 99.0 (C17) consistent with its linking to an oxygen.[4f,7] The *trans* arrangement around C16–C3′ is based[cf.3a,8] on $^3J_{16,3'}$ (4.5–6.5 Hz).[9] The *cis*-relationship between the C17-acetyl function and the C13-methyl is based[3a,10] on the $^1$H chemical shift value of the C13-methyl protons ($\sim\delta$ 0.70); critical $^1$H and $^{13}$C NMR assignments in the case of **3a** and **3e** are included.[6]

The addition is frontier-orbital controlled (dipole-LUMO and dipolarophile-HOMO) as evidenced by the regiochemistry of addition.[11] The successful addition of the nitrones and stereochemical outcome are a consequence of equilibration of the (*E*) and (*Z*) forms of the dipole with the minor rotamer (*E*-form) of the dipole adding to the less hindered face of the C16–C17 π-bond as depicted in Scheme 2. Such equilibration of the (*E*) and (*Z*) forms of nitrones to give major products of cycloaddition using the less favoured *E*-form of the nitrones is precedented.[11d] Here the addition of the *E*-form of the nitrone is dictated by steric constraints imposed by the steroidal nucleus. The overall addition can be described as *endo*- as far as the C-17 acetyl function is concerned, though this *endo*-orientation is of no consequence, because

the stereochemistry of the addition is controlled by the *exo*-orientation of the steroidal bulk. The stereoselective addition of only the minor rotamer of the nitrone in the present case is in sharp contrast to the reported isolation of mixtures of diastereomers from addition of nitronic esters,[3a,b] which results from both *endo*- as well as *exo*-modes of addition involving both (*E*) and (*Z*) forms of the dipole.




Scheme 2.

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5. Attempts have been made to optimise the varied periods of refluxing/heating the reactants in a sealed tube for best yields of the adducts from different nitrones
6. **3a**: Pale yellow solid (ether–hexane, 1:5). Mp 158°C. $[\alpha]_D^{25}$ –42.69 (0.4%, $CHCl_3$). Anal. calcd for $C_{36}H_{43}NO_4$: C (78.12), H (7.77), N (2.53); found C (78.17), H (7.84), N (2.54). $\nu_{max}$ ($CHCl_3$): 3030.5 (s), 2990 (s), 1725 (b), 1710 (s), 1599.2 (m), 1491.2 (s), 1454.5 (m), 1255.8 (b), 1194.1 (w), 1099.6 (m), 1032 (m) $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 200

MHz): $\delta$ 7.30–6.85 (bm, 10H, aromatic-Hs) 5.38 (d, *J* 4.53 Hz, C6–H), 4.62 (bm, C2–H), 3.70 (d, *J* 6.49 Hz, C3′–H), 3.61 (dd, *J* 7.6 and 6.58 Hz, 1H, C16–H), 2.40–0.70 (bm, with methyl singlets at $\delta$ 2.40, 2.0, 1.03 and 0.70). $^{13}$C NMR ($CDCl_3$, 50 MHz): $\delta$ 210.50 (C20), 170.17 ($CH_3CO_2$), 149.21 (quat. arom.), 140.60 (quat. arom.), 139.75 (C5), 128.91 (CH), 128.44 (CH), 127.85 (CH), 127.50 (CH), 123.52 (CH), 122.10 (C6), 118.18 (CH), 99.66 (C17), 80.48 (C3′), 73.72 (C3), 58.22, 50.76, 49.55, 45.83, 38.09, 37.00, 36.68, 31.99, 31.64, 31.35, 29.73, 27.77, 26.98, 21.35, 20.63, 19.34, 14.94. Mass (*m*/*z*): 554 (20, $M^+$+1), 553 (12.6, $M^+$), 313 (7.7), 297 (11.8), 296 (10.4), 284 (3.2). **3e**: Light yellow needles (methanol). Mp 132°C. $[\alpha]_D^{25}$ −14.16 (0.32%, $CHCl_3$). Anal. calcd for $C_{34}H_{41}NO_5$: C (75.16), H (7.63), N (2.54); found C (75.19), H (7.67), N (2.57). $\nu_{max}$ ($CHCl_3$): 2961.6 (s), 2940.3 (s), 2918.9 (m), 2876.2 (m), 2384.6 (w), 1777.7 (w), 1722.1 (s), 1717.9 (s), 1602.5 (w), 1593.9 (w), 1495.6 (w), 1457.1 (w), 1444.3 (w), 1380.2 (m), 1269.1 (s), 1256.2 (s), 1205.0 (m), 1200.7 (m), 1038.3 (w). $^1$H NMR ($CDCl_3$, 200 MHz): $\delta$ 7.40–7.39 (m, 1H), 7.36–7.11 (m, 4H), 7.06–6.97 (m, 2H), 6.37 (d, 1H, *J* 1.25, furanyl–H), 5.73 (d, 1H, *J* 4.31 Hz, C6–H), 4.50 (m, 1H, C3–H), 3.65 (d, 1H, *J* 5.65 Hz, C3′–H), 3.58 (dd, 1H, *J* 5.6 and 3.23 Hz, C16–H), 2.34–0.71 (broad, having singlets at $\delta$ 2.34, 2.03, 0.98 and 0.71) $^{13}$C NMR ($CDCl_3$, 50 MHz): $\delta$ 210.21 (C20), 170.09 ($CH_3CO_2$), 143.87 (quat. arom.), 139.91 (C5), 136.83 (CH), 128.46 (CH), 124.76 (quat.), 124.12 (CH), 122.11 (C6), 118.69 (CH), 116.47 (CH), 109.5 (CH), 99.51 (C17), 73.71 (C3), 72.38 (C3′), 56.31, 50.94, 49.61, 45.78, 38.13, 37.03, 36.72, 32.04, 31.87, 31.36, 29.75, 27.81, 26.85, 21.39, 20.64, 19.38, 14.97. Mass (*m*/*z*): 544 (30, $M^+$+1), 543 (40, $M^+$), 312 (20), 298 (25), 283 (60), 265 (68), 241 (3), 227 (2). **3b**; mp 169°C. **3c**; mp 162°C. **3d**; mp 135°C.

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9. Calculations of the coupling constant $^3J_{16,3'}$ by extended Karplus equations,[12] based on the dihedral angles obtained by molecular modelling (dtmm Version-2), of both **3** and the corresponding C16,C3′ *cis*-adduct, gave values of *J* 2.8–5.5 Hz for the *trans* arrangement and *J* 6.8 to ~9.0 Hz for *cis* arrangement; the variations are due to different nitrogen invertomers. A comparison of the values of $^3J_{16,3'}$ in **3a**–**e** with the calculated and reported values of $^3J_{3,4}$ for a large number of isoxazolidines,[8] particularly, with the reported values of $^3J_{16,3'}$ for the steroidal isoxazolidines closely related to **3**,[3a] indicates that the presently obtained values are well on the lower side, corresponding to a *trans* arrangement.
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