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# Optimization of the Abnormal Beckmann Rearrangement: Application to Steroid 17-Oximes

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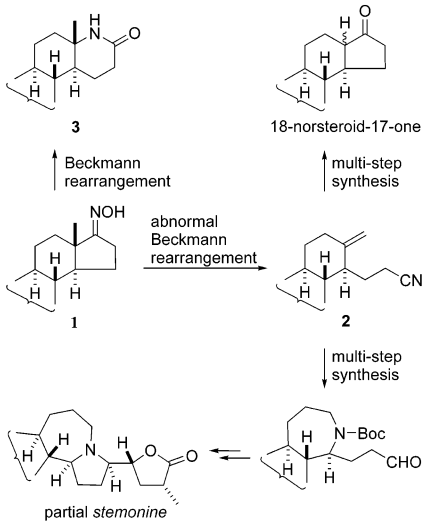
**Abstract:** A novel and practical procedure was developed for the abnormal Beckmann rearrangement of steroid 17-oximes. Treatment of the 17-oximes with TFA/$CH(OMe)_3$ in boiling THF for 2 h gives the corresponding 13,17-seco alkene nitrile products in unprecedented high yields (70−92%). Since the alkene nitriles can be subsequently converted into 18-norsteroids, this general method provides a highly efficient route to these biologically important compounds and, by extension, to other structurally related natural products.

A number of biologically important properties of steroids are dependent upon structural features of the steroid D-ring. Chemical modification of the angular 18-Me provides a way to alter the functional groups, sizes, and stereochemistry of the D-ring, and numerous structure−activity relationships have been established by such synthetic alterations.[1] In particular, methods for the preparation of the noncommercially available 18-norsteroids have received considerable attention.[2,3] Prominent among these synthetic methods are those that use an abnormal Beckmann rearrangement of a steroid 17-oxime (**1**) to yield a ring-cleaved alkene nitrile (**2**) product. Recyclization of the alkene-nitrile by a variety of methods yields the 18-norsteroids. However, a major drawback to this otherwise efficient synthetic approach to 18-norsteroids has been the relatively poor yields obtained because of the competing Beckmann rearrangement that leads to lactam **3** (Scheme 1).[3h−j,4−8]

**SCHEME 1**




In our recent research, several analogues of **2** have been designed as key precursors for the preparation of 18-norsteroid-17-ones[3j] and for the total synthesis of some members of *Stemona* alkaloids (for example, stemonine).[9] Thus, to overcome the low yields associated with the abnormal Beckmann rearrangement of steroid 17-oximes we undertook this study. We report here reaction conditions that accomplish this goal.

Initially, the published methods were scanned on the model compound **1a**. Reagents and solvents investigated

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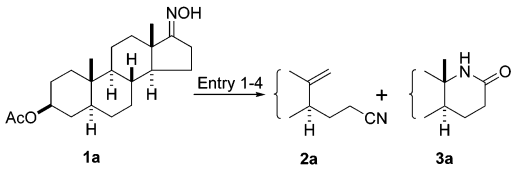
**SCHEME 2**




| Entry | Reaction Conditions | Yield of **2a** (%) | Yield of **3a** (%) |
|---|---|---|---|
| 1 | TFA/DCC/DMSO/$C_6H_6$/rt/3h | 49 | 36 |
| 2 | TFA/CDI/THF/60-70 °C/2h | 70 | 6 |
| 3 | TFA/$CH(OCH_3)_3$/THF/60-70 °C/2h | 80 | 4 |
| 4 | TFA/$CH(OC_2H_5)_3$/THF/60-70 °C/2h | 78 | 4 |

**TABLE 1. Effect of the Ratio of 1a/TFA/$CH(OCH_3)_3$[a]**

| entry | **1a**/TFA/$CH(OCH_3)_3$ (mol) | yield of **2a** (%) |
|---|---|---|
| 1 | 1/1.00/2.75 | 74 |
| 2 | 1/1.20/2.75 | 78 |
| 3 | 1/1.25/2.75 | 80 |
| 4 | 1/1.25/2.25 | 75 |
| 5 | 1/1.25/3.25 | 79 |
| 6 | 1/1.50/2.75 | 80 |

[a] The tests were performed in THF at 65−70 °C for 2 h.

for the reaction were *p*-TsCl−pyridine,[4] TFA−DCC−DMSO,[3f,h−j,5] $PCl_5$−dioxane,[6] $SOCl_2$−dioxane,[7] and TFAA−$CH_2Cl_2$.[8] To our disappointment, none of these reaction conditions minimized the formation of undesirable lactam product and did not give the alkene nitrile product in acceptable yields. The most popularly used reaction medium of TFA−DCC−DMSO−$C_6H_6$ yielded a mixture of **2a** and **3a** in a ratio of 7:5 and was associated with a tedious workup that made a scale-up of the reaction inconvenient (Scheme 2, entry 1).

Realizing that the mechanism of the abnormal Beckmann rearrangement requires reagents having both acidic and dehydration properties, we initially test a combination of TFA and CDI (1,1′-carbonyldiimidazole) as the reaction medium. In agreement with our expection, when **1a** was treated with this new reagent system in boiling THF for 2 h, the ratio of products was improved significantly to give the desired **2a** in 70% yield with lactam **3a** in only 6% yield (Scheme 2, entry 2). Furthermore, the replacement of CDI with $CH(OMe)_3$ achieved an unprecedented high yield for the abnormal Beckmann rearrangement of the steroid 17-oxime. Compound **1a** was converted into **2a** in 80% yield using TFA−$CH(OMe)_3$−THF with a negligible amount of **3a** (less than 4%). Since the $CH(OMe)_3$ was converted into $HCO_2Me$ during the reaction, the procedure also facilitated the workup and scale-up of the reaction (Scheme 2, entry 3). As expected, alternation of $CH(OMe)_3$ by $CH(OEt)_3$ gave a comparable result (Scheme 2, entry 4).

To optimize the reaction conditions, the effect of the ratio of **1a**/TFA/$CH(OMe)_3$ and reaction temperature were studied. As shown in Tables 1 and 2, the reaction gives a satisfactory yield in the ratio of 1/1.25/2.75 for 2 h and excessive TFA and $CH(OMe)_3$ or longer reaction time are not necessary. It was observed that the reaction is quite temperature dependent, and 65−70 °C is recommended. Normally, no reaction occurred below 50 °C and a brown color quickly developed when the reaction temperature was above 70 °C (Table 3).

**TABLE 2. Effect of the Reaction Time[a]**

| entry | time (min) | yield of **2a** (%) |
|---|---|---|
| 1 | 15 | 42 |
| 2 | 30 | 63 |
| 3 | 60 | 76 |
| 4 | 120 | 80 |
| 5 | 240 | 81 |

[a] The tests were performed under the conditions of entry 4 in Table 1.

**TABLE 3. Effect of the Temperature and Solvent[a]**

| entry | *T* (°C) | solvent | yield of **2a** (%) |
|---|---|---|---|
| 1 | <50 | THF | 0 |
| 2 | 60−70 | THF | 80 |
| 3 | 70−80 | $C_6H_6$ | 78 |
| 4 | 100−105 | $CH(OCH_3)_3$ | 79[b] |

[a] The tests were performed under the conditions of entry 4 in Table 1 for 2 h. [b] Deep brown color.

**SCHEME 3**

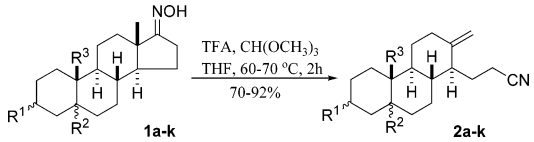



**TABLE 4. Abnormal Beckmann Rearrangement of Steroid-17-one Oximes**

| **1**, **2** | $R^1$ | $R^2$ | $R^3$ | yield of **2** (%) |
|---|---|---|---|---|
| **a** | β-OAc | α-H | Me | 80 |
| **b** | β-OBz | β-H | Me | 88 |
| **c** | β-OAc | $\Delta^{5(6)}$ | Me | 70 |
| **d** | α-OAc | α-H | Me | 88 |
| **e** | α-OAc | β-H | Me | 79 |
| **f** | α-OBz | α-H | Me | 92 |
| **g** | β-OAc | α-H | H | 90 |
| **h** | β-OAc | β-H | H | 74 |
| **i** | α-OBz | α-H | H | 84 |
| **j** | α-OAc | β-H | H | 77 |
| **k** | OMe | $\Delta^{1,3,5(10)}$-triene | | 84 |

Under very similar conditions, the other steroid 17-oximes **1b**−**k** underwent the abnormal Beckmann rearrangement to yield corresponding alkene nitriles **2b**−**k** in 70−92%. As illustrated in Scheme 3 and Table 4, this method is quite general and the yields of **2a**−**k** were not significantly affected by substituents or stereochemistry at C-3, C-5, and C-10.

In summary, a novel and practical procedure was developed for the abnormal Beckmann rearrangement of steroid 17-oximes. When compounds (**1a**−**k**) were treated with TFA/$CH(OMe)_3$ in boiling THF for 2 h, the corresponding 13,17-seco alkene nitriles (**2a**−**k**) were obtained in 70−92% yields. This general method provides high yield access to alkene nitrile compounds which are key intermediates for the preparation of some biologically important 18-norsteroids and structurally related natural products.

## Experimental Section

The $^1H$ NMR spectra were recorded on a Bruker ACF-300 spectrometer with TMS as internal reference. The MS spectra were obtained on a ZAB-HS mass spectrometer with 70 eV. Optical rotations were determined on a Perkin-Elmer 343 polarimeter.

**General Procedure for the Abnormal Beckmann Rearrangement of Steroid-17-one Oximes (1a−k) Promoted by TFA−CH(OMe)$_3$−THF.** To a stirred solution of steroid-17-one oxime (**1**, 10 mmol) and $CH(OMe)_3$ (2.9 g, 27.5 mmol) in anhydrous THF (35 mL) under $N_2$ at 60 °C was added freshly distillated TFA (1.43 g, 12.5 mmol) in one portion. The mixture was then brought to reflux for 2 h, and compound **1** disappeared completely (monitored by TLC). After most of the THF was removed in a vacuum, $CH_2Cl_2$ and 10% aqueous solution of $Na_2CO_3$ were added, respectively. The organic layer was separated, washed with $H_2O$, and dried over $MgSO_4$. Removal of the solvent to give the crude product, which was purified by chromatography [silica gel, 15% EtOAc in petroleum ether (60−90°)] to give the desired product **2** (Table 4).

**17-Cyano-13,17-*seco*-5α-androst-13(18)-en-3*β*-yl acetate (2a):** white crystals; mp 98−99 °C (AcOEt/petroleum ether, lit.[4b] mp 98−99 °C); $[\alpha]^{20}_D = -39.16$ (*c* 0.33, $CHCl_3$); IR *ν* 2220, 1725, 1650 cm$^{-1}$; $^1$H NMR *δ* 4.79 (s, 1H), 4.70 (m, 1H), 4.47 (s, 1H), 2.04 (s, 3H), 0.75 (s, 3H); MS *m*/*z* 329 (M$^+$, 10), 43 (100). Anal. Calcd for $C_{21}H_{31}NO_2$: C, 76.55; H, 9.48; N, 4.25. Found: C, 76.28; H, 9.32; N, 4.20.

**17-Cyano-13,17-*seco*-5*β*-androst-13(18)-en-3*β*-yl benzoate (2b):** white crystals; mp 109−110 °C (AcOEt/petroleum ether); $[\alpha]^{20}_D = -3.65$ (*c* 1.30, $CHCl_3$); IR *ν* 2220, 1730, 1640 cm$^{-1}$; $^1$H NMR *δ* 8.07 (d, *J* = 7.3 Hz, 2H), 7.56 (t, *J* = 7.3 Hz, 1.4 Hz, 1H), 7.46 (t, *J* = 7.2 Hz, 1.3 Hz, 2H), 5.37 (s, 1H), 4.80 (s, 1H), 4.49 (s, 1H), 0.78 (s, 3H); MS *m*/*z* 391 (M$^+$, 0.15), 105 (100). Anal. Calcd for $C_{26}H_{33}NO_2$: C, 79.76; H, 8.49; N, 3.58. Found: C, 79.71; H, 8.46; N, 3.62.

**17-Cyano-13,17-*seco*-androst-5(6),13(18)-dien-3*β*-yl acetate (2c):** white crystals; mp 104−105 °C (AcOEt/petroleum ether, lit.[5a] mp 104−106 °C); $[\alpha]^{20}_D = -149.75$ (*c* 0.80, $CHCl_3$); IR *ν* 2250, 1715, 1645 cm$^{-1}$;$^1$H NMR *δ* 5.39 (t, *J* = 2.4 Hz, 2.3 Hz, 1H), 4.84 (s, 1H), 4.61 (m, 1H), 4.51 (s, 1H), 2.05 (s, 3H), 0.94 (s, 3H); MS *m*/*z* 328 (M + 1, 22), 327 (M$^+$, 100). Anal. Calcd for $C_{21}H_{29}NO_2$: C, 77.02; H, 8.93; N, 4.28. Found: C, 76.98; H, 8.90; N, 4.27.

**17-Cyano-13,17-*seco*-5α-androst-13(18)-en-3α-yl acetate (2d):** white crystals; mp 89−91 °C (AcOEt/petroleum ether); $[\alpha]^{20}_D = -45.07$ (*c* 0.50, $CHCl_3$); IR *ν* 2225, 1720, 1640 cm$^{-1}$; $^1$H NMR *δ* 4.80 (s, 1H), 4.72 (m, 1H), 4.48 (s, 1H), 2.04 (s, 3H), 0.76 (s, 3H); MS *m*/*z* 329 (M$^+$, 12), 85 (100). Anal. Calcd for $C_{21}H_{31}NO_2$: C, 76.55; H, 9.48; N, 4.25. Found: C, 76.24; H, 9.30; N, 4.22.

**17-Cyano-13,17-*seco*-5*β*-androst-13(18)-en-3α-yl acetate (2e):** white crystals; mp 88−90 °C (AcOEt/petroleum ether); $[\alpha]^{20}_D = -6.22$ (*c* 3.04, $CHCl_3$); IR *ν* 2225, 1730, 1640 cm$^{-1}$; $^1$H NMR *δ* 4.79 (s, 1H), 4.75 (m, 1H), 4.46 (s, 1H), 2.04 (s, 3H), 0.84 (s, 3H); MS *m*/*z* 329 (M$^+$, 4), 43 (100). Anal. Calcd for $C_{21}H_{31}NO_2$: C, 76.55; H, 9.48; N, 4.25. Found: C, 76.54; H, 9.28; N, 4.19.

**17-Cyano-13,17-*seco*-5α-androst-13(18)-en-3α-yl benzoate (2f):** white crystals; mp 126−127 °C (AcOEt/petroleum ether); $[\alpha]^{20}_D = -37.28$ (*c* 0.45, $CHCl_3$); IR *ν* 2215, 1720, 1641 cm$^{-1}$; $^1$H NMR *δ* 8.07 (d, *J* = 7.3 Hz, 2H), 7.58 (t, *J* = 7.3 Hz, 1.2 Hz, 1H), 7.48 (t, *J* = 7.2 Hz, 1.4 Hz, 2H), 5.29 (s, 1H), 4.80 (s, 1H), 4.48 (s, 1H), 0.78 (s, 3H); MS *m*/*z* 391 (M$^+$, 2), 166 (100). Anal. Calcd for $C_{26}H_{33}NO_2$: C, 79.76; H, 8.49; N, 3.58. Found: C, 79.70; H, 8.44; N, 3.50.

**17-Cyano-13,17-*seco*-5α-estr-13(18)-en-3*β*-yl acetate (2g):** white crystals; mp 98−99 °C (AcOEt/petroleum ether); $[\alpha]^{20}_D = -20.83$ (*c* 0.36, $CHCl_3$); IR *ν* 2225, 1730, 1640 cm$^{-1}$; $^1$H NMR *δ* 4.81 (s, 1H), 4.72 (m, 1H), 4.49 (s, 1H), 2.03 (s, 3H); MS *m*/*z* 315 (M$^+$, 9), 43 (100). Anal. Calcd for $C_{20}H_{29}NO_2$: C, 76.15; H, 9.27; N, 4.44. Found: C, 76.12; H, 9.22; N, 4.36.

**17-Cyano-13,17-*seco*-5*β*-estr-13(18)-en-3*β*-yl acetate (2h):** white crystals; mp 158−160 °C (AcOEt/petroleum ether); $[\alpha]^{20}_D = -13.95$ (*c* 0.13, $CHCl_3$); IR *ν* 2210, 1715, 1620 cm$^{-1}$; $^1$H NMR *δ* 5.10 (m, 1H), 4.81 (s, 1H), 4.49 (s, 1H), 2.06 (s, 3H); MS *m*/*z* 315 (M$^+$, 2), 43 (100). Anal. Calcd for $C_{20}H_{29}NO_2$: C, 76.15; H, 9.27; N, 4.44. Found: C, 76.08; H, 9.20; N, 4.38.

**17-Cyano-13,17-*seco*-5α-estr-13(18)-en-3α-yl benzoate (2i):** white crystals; mp 128−130 °C (AcOEt/petroleum ether); $[\alpha]^{20}_D = -2.28$ (*c* 0.44, $CHCl_3$); IR *ν* 2225, 1730, 1650 cm$^{-1}$; $^1$H NMR *δ* 8.07 (d, *J* = 7.2 Hz, 2H), 7.56 (t, *J* = 7.2 Hz, 1.3 Hz, 1H), 7.46 (t, *J* = 7.2 Hz, 1.4 Hz, 2H), 5.32 (s, 1H), 4.82 (s, 1H), 4.50 (s, 1H); MS *m*/*z* 377 (M$^+$, 2), 105 (100). Anal. Calcd for $C_{25}H_{31}NO_2$: C, 79.76; H, 8.49; N, 3.58. Found: C, 79.77; H, 8.45; N, 3.50.

**17-Cyano-13,17-*seco*-5*β*-estr-13(18)-en-3α-yl acetate (2j):** white crystals; mp 89−90 °C (AcOEt/petroleum ether); $[\alpha]^{20}_D = +10.97$ (*c* 0.95, $CHCl_3$); IR *ν* 2210, 1720, 1610 cm$^{-1}$; $^1$H NMR *δ* 4.81 (s, 1H), 4.76 (m, 1H), 4.49 (s, 1H), 2.05 (s, 3H); MS *m*/*z* 315 (M$^+$, 12), 43 (100). Anal. Calcd for $C_{20}H_{29}NO_2$: C, 76.15; H, 9.27; N, 4.44. Found: C, 76.10; H, 9.21; N, 4.38.

**3-Methoxy-13,17-*seco*-estr-1,3,5(10),13(18)-tetraene-17-nitrile (2k):**[5a] colorless oil; $[\alpha]^{20}_D = +54.00$ (*c* 0.20, $CHCl_3$); IR *ν* 2200, 1610, 1500 cm$^{-1}$; $^1$H NMR *δ* 7.22 (d, *J* = 8.6 Hz, 1H), 6.75 (m, 1H), 6.65 (d, *J* = 2.7 Hz, 1H), 4.88 (s, 1H), 4.58 (s, 1H), 3.76 (s, 3H); MS *m*/*z* 281 (M$^+$, 43), 161 (100). Anal. Calcd for $C_{19}H_{23}NO$: C, 81.10; H, 8.24; N, 4.98. Found: C, 81.00; H, 8.23; N, 4.88.

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