Stereoselective Synthesis of Novel Δ^5-Androstenoarylpyrazoline Derivatives by $BF_3{\cdot}OEt_2$-Induced Intramolecular 1,3-Dipolar Cycloaddition

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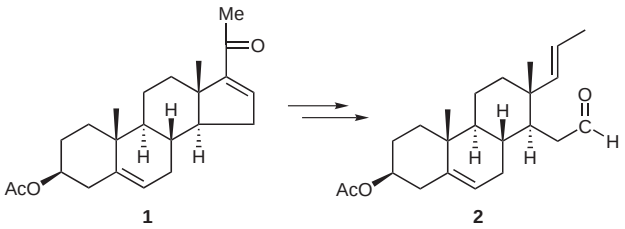
Abstract: The phenylhydrazones of an unsaturated D-*seco*-pregnene aldehyde underwent $BF_3{\cdot}OEt_2$-induced intramolecular 1,3-dipolar cycloaddition to afford new pyrazoline-fused Δ^5-androstene derivatives under extremely mild conditions. The ring closures occurred stereoselectively in good to excellent yields via the corresponding azomethine imine intermediates and showed marked dependence on the electronic feature of the *p*-phenyl substituent.

Key words: steroids, hydrazones, 1,3-dipolar cycloaddition, stereoselectivity, Lewis acid

The thermally induced 1,3-dipolar cycloaddition of hydrazones with multiple-bond systems is a well-known procedure for the formation of N-containing five-membered heterocycles.[1] When protic acid catalysts are used, protonated hydrazone intermediates have been suggested to act as quasi-azomethine imine 1,3-dipoles, which readily react even with nonactivated olefinic dipolarophiles.[2] While inter- and intramolecular Lewis acid catalyzed [3+2] cycloadditions using nitrones or nitrile oxides have been intensively investigated,[3] the corresponding reactions of olefinic hydrazones have less been studied.[4] A dramatic rate acceleration and improvements in diastereoselectivity have been reported for the intramolecular cyclization of a hydrazone/olefin system in the presence of a catalytic amount of $Sc(OTf)_3$ as compared with the thermal reactions.[4a] The use of $BF_3{\cdot}OEt_2$ as Lewis acid, leastwise for intermolecular reactions, proved to enhance the yields of the desired product, but with lower diastereoselectivity.[4b]

The intramolecular cycloadditions of unsaturated hydrazones usually lead to pyrazolidine derivatives. However, these are not always sufficiently stable and they undergo facile dehydrogenation to the corresponding pyrazolines or pyrazoles under the given reaction conditions and/or during the purification procedures.[5] A number of compounds containing a pyrazoline moiety possess marked pharmacological effects; thus, compounds with analgesic, antipyretic, antirheumatic, anti-inflammatory and antidiabetic activities have been described.[6] The wide spectrum of synthetic heterosteroids include pyrazoline[7] and pyrazole derivatives,[8] and some D-ring-fused androstano[17,16-*c*]-5′-arylpyrazolines have recently been reported to exhibit noteworthy in vivo antiandrogenic activity.[9]

The D-*seco*-pregnene aldehyde (**2**), containing a propenyl side chain, can be obtained in several steps from the readily available pregnadienolone acetate (**1**, Scheme 1).[10] This compound was considered to be of use for pyrazoline formation, after preparation of the corresponding phenylhydrazones. Besides study of the stereoselectivity of the $BF_3{\cdot}OEt_2$-catalyzed processes, our present aim was to investigate the electronic effects of different phenyl substituents on the cyclization reactions and to synthesize potentially bioactive androstenopyrazolines. The results of the pharmacological tests will be published elsewhere.



Scheme 1

The reactions of aldehyde **2** with phenylhydrazine **3a** or its *para*-substituted derivatives **3b**–**f**, respectively, in MeOH at room temperature yielded the corresponding (*E*)-phenylhydrazones **4a**–**f** in good to excellent yields (Scheme 2). The ^1H NMR spectra of **4a**–**f**, recorded at different times for each compound, revealed *E*/*Z* isomerization in $CDCl_3$ solution, the amount of the *E*-isomer predominating. As reported earlier, the isomeric ratio of the aldehyde phenylhydrazones in solution is solvent-dependent; equilibration can be observed after a period.[11a] Traces of acids[11b] or free phenylhydrazine[11c] can catalyze the isomerization. The intramolecular cyclization of phenylhydrazones **4a**–**f**, induced by a catalytic amount of $BF_3{\cdot}OEt_2$, led to androstene-fused pyrazoline derivatives **6a**–**f** via the presumed intermediate **5**. No traces of the corresponding pyrazolidine derivatives were observed.

The conversions proceeded in a stereoselective manner to furnish **6a**–**f** as the only diastereomers, with 17-H in the α- and 20-H in the β-position. Comparison of the ^1H NMR spectra of the corresponding pyrazolines **6a**–**f** with those of the phenylhydrazones **4a**–**f**, respectively, demonstrated an upfield shift of the 18-H_3 signal for **6a**–**f**. The aniso-

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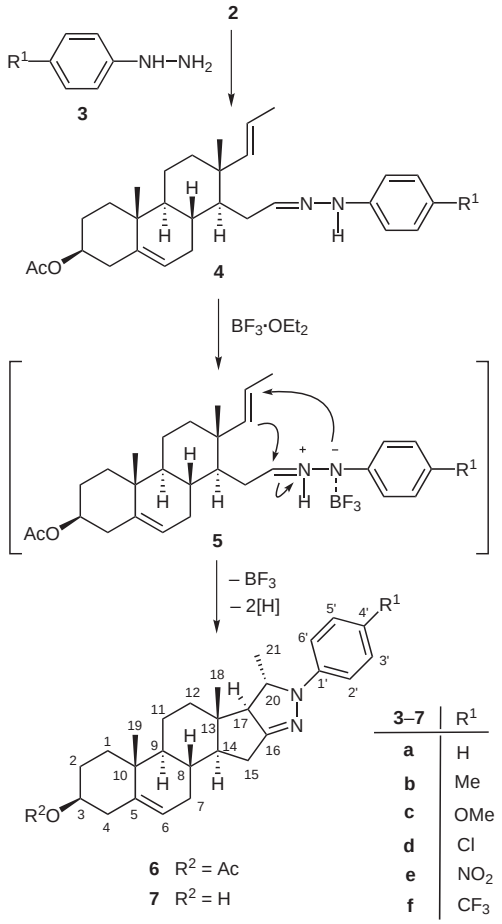

Scheme 2

tropic shielding effect attributed to the N–Ph ring can be observed only when the newly formed pyrazoline ring, together with its N–Ph moiety, is bent towards the C-18 angular methyl group, and 17-H therefore assumes the α-position. The α-orientation of the 21-Me group, and thus the β-position of 20-H, follows from the steric repulsion between the closely situated angular methyl function. The relative configurations were confirmed by NOESY measurement, for **6c**,[12] which indicated a cross-peak between 18-H_3 and 20-H.

The reaction rates and yields of the products **6a**–**f** seemed to depend strongly on the nature of the group R^1 on the Ph moiety in **5**. Internal cyclization of the unsubstituted phenylhydrazone **4a** in the presence of $BF_3{\cdot}OEt_2$ in ice-cold $CHCl_3$, proved to be slow, but after stirring for three hours, the corresponding pyrazoline **6a** could be obtained in good yield besides a minor amount of residual **4a**. Better conversion could be achieved at room temperature after 24 hours (Table 1). In this latter case all of the phenylhydrazone **4a** was converted and, without purification by column chromatography, compound **6a** was obtained in a crystalline form from CH_2Cl_2 after alkaline workup.

The *para*-substituted phenylhydrazones **4b**–**f** were cyclized at the same temperature to give the desired products **6b**–**f**. A yellowish discolouration of the mixtures was observed at the moment the Lewis acid catalyst was added. Compounds **4b** and **4c**, containing electron-donating groups (Me and OMe) were readily involved in pyrazoline formation to furnish **6b** and **6c**[12] in excellent yields. Electron-withdrawing groups (Cl, NO_2 and CF_3), however, seemed to stabilize the related phenylhydrazones **4d**–**f**, decreasing the reaction rate and reducing the yields of the products **6d**–**f**. The reaction time also proved to be important as some polar decomposition products were produced when the pyrazolines **6a**–**f** formed were allowed to stand in the acidic mixtures for longer than the optimum time. Compounds **6a**–**f** were assumed to be formed by autoxidation of the corresponding pyrazolidine derivative during the workup.

Pyrazolines **6a**–**f** were deacetylated in alkaline MeOH to furnish the corresponding 3-OH derivatives **7a**–**f**, which were subjected to pharmacological investigation.

Table 1 Intramolecular 1,3-Dipolar Cycloaddition of **4** in the Presence of a Catalytic Amount of $BF_3{\cdot}OEt_2$

Entry	Phenylhydrazone[a]	R^1	Reaction conditions	Products	Yield (%)	Mp (°C)
1	**4a**	H	0 °C, 3 h[b]	**6a**	71[c]	220–222
2	**4b**	Me	0 °C, 20 min	**6b**	92[d]	194–196
3	**4c**	OMe	0 °C, 20 min	**6c**	95[d]	181–183
4	**4d**	Cl	0 °C, 3 h	**6d**	74[c]	204–206
5	**4e**	NO_2	0 °C, 3 h	**6e**	64[c]	210–212
6	**4f**	CF_3	0 °C, 3 h	**6f**	67[c]	168–170

[a] Synthesized from **2** with phenylhydrazine **3a** or *p*-substituted phenylhydrazines **3b**–**f**, respectively. In cases of **3b**–**f**, the hydrochloride salts were used in basic MeOH.
[b] The yield can be enhances to 78% at r.t. after 24 h.
[c] After purification by column chromatography.
[d] After recrystallization.

In conclusion, we have demonstrated that the stereoselective synthesis of androstenopyrazolines can be achieved by the $BF_3{\cdot}OEt_2$-catalyzed intramolecular 1,3-dipolar cyclization of D-*seco*-hydrazones. The efficacy of pyrazoline formation was strongly influenced by substituents on the phenyl moiety and the reaction conditions.

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(12) **Procedure for the Synthesis of 6c**
A mixture of **2** (359 mg, 1.00 mmol), 4-methoxyphenylhydrazine hydrochloride (**3c**, 175 mg, 1.00 mmol) and NaOAc (200 mg, 2.44 mmol) in MeOH (5 mL) was stirred for 1 h at r.t. The white precipitate was filtered off and dried to give pure **4c** (407 mg, 85%). Compound **4c** was dissolved in CH_2Cl_2 (10 mL) and $BF_3{\cdot}OEt_2$ (0.09 mL, 0.3 mmol) was added dropwise at 0 °C under a nitrogen atmosphere. After 20 min, the reaction was quenched by the addition of 1 M aq $NaHCO_3$ (20 mL). The organic phase was separated, the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic phases were dried over Na_2SO_4. Evaporation in vacuo and recrystallization from CH_2Cl_2–hexane afforded 453 mg (95%) of **6c** as white crystals; R_f = 0.32 (EtOAc–CH_2Cl_2, 10:90). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.76 (s, 3 H, 18-H_3), 1.05 (s, 3 H, 19-H_3), 1.16 (m, 2 H), 1.39 (m, 1 H), 1.44 (d, 3 H, *J* = 6.0 Hz, 21-H_3), 1.51 (m, 1 H), 1.58–1.69 (m, 6 H), 1.80–1.91 (m, 4 H), 2.03 (s, 3 H, 3-Ac-H_3), 2.45 (m, 2 H), 2.49 (m, 1 H), 2.77 (d, 1 H, *J* = 11.2 Hz, 17-H), 3.65 (m, 1 H, 20-H), 3.78 (s, 3 H, 4′-OMe), 4.62 (m, 1 H, 3-H), 5.39 (d, 1 H, *J* = 4.8 Hz, 6-H), 6.85 (d, 2 H, *J* = 8.8 Hz, 2′-H, 6′-H), 7.05 (d, 2 H, *J* = 8.8 Hz, 3′-H, 5′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14. 4 (C-18), 19.3 (C-19), 20.4 (C-21), 20.7 (CH_2), 21.4 (3-Ac-CH_3), 25.4 (CH_2), 27.7 (CH_2), 31.5 (C-8), 31.8 (CH_2), 36.8 (C-10), 36.9 (CH_2), 37.3 (CH_2), 38.1 (CH_2), 40.0 (C-13), 50.0 (C-9), 55.6 (4′-OMe), 57.6 (C-14), 61.3 (C-20), 72.2 (C-17), 73.7 (C-3), 114.3 (2 C, C-2′, C-6′), 118.3 (2 C, C-3′, C-5′), 121.9 (C-6), 139.9 (C-5), 142.3 (C-1′), 154.7 (C-4′), 164.3 (C-16), 170.5 (Ac-CO). MS (EI): *m/z* (relative intensity) = 476 (100) [M^+], 461 (18), 187 (30) [$C_{30}H_{40}N_2O_3$].