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A SIMPLE RING ANNELATION OF BI- AND POLYCYCLIC α,β-UNSATURATED KETONES

A FACILE ROUTE TO BENZ[4,5,6]STEROIDS[1]

P. Houdewind,[2] J.C. Lapierre Armande (in part) and U.K. Pandit*
Organic Chemistry Laboratory, University of Amsterdam,
Nieuwe Achtergracht 129, Amsterdam, The Netherlands.

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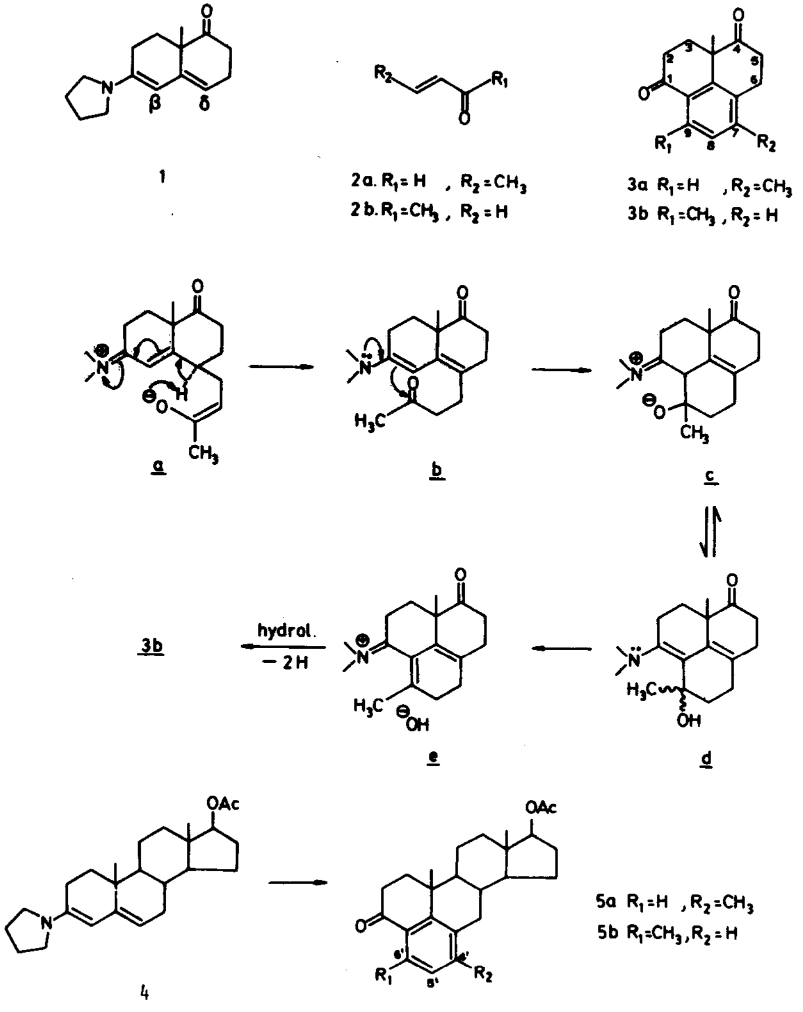
The construction of a new six-membered ring on an existing cyclic system is a problem which has received a great deal of attention in organic synthesis[3]. In the field of steroids considerable effort has been expended in devising elaborate procedures[4a-d] for the attachment of a cyclic (aromatic) moiety across the C_4-C_5-C_6 bonds. This communication describes the accomplishment of such an operation in a convenient, single, practical step.

In connection with our studies on the electrophilic substitution of dienamines[2], we have examined the reaction of linearly conjugated enamines with α,β-unsaturated carbonyl compounds. When dienamine 1 and crotonaldehyde (2a) were heated in toluene (bath temp. 135-140°, 40 h), the mixture gave, following hydrolysis, chromatography (florisil column; eluent: benzene-ethyl acetate 100:1) and crystallization from cyclohexane, diketone 3a, m.p. 118-120°, in 22% yield. The structure of 3a was attested by its spectral data [ν^{KBr} 1700, 1675; δ^{CDCl_3} 1.42 s C_{3a}-CH_3, 2.38 s C_7-CH_3, 7.20 d, J = 8Hz, C_8-H, 7.91 d, J = 8Hz, C_9-H; λ_{max}^{EtOH} 263(13,000)]. The location of the aromatic methyl group was initially assigned by comparison of its chemical shift with that of the analogous methyl group in the benz[4,5,6] steroid described by Ringold[4a]. This was further confirmed by examining the spectral data of the product of reaction of dienamine 1 with methyl vinyl ketone (2b). Crystalline 3b (m.p. 86-87°), which was isolated in a manner similar to that described for 3a, exhibited an NMR spectrum in which the aromatic methyl (C_9-CH_3) appeared as a singlet at δ 2.60. The observed paramagnetic shift is consistent with the proximity of the methyl to the carbonyl function at C_1.


1
β
δ
2a. R_1= H , R_2=CH_3
2b. R_1=CH_3 , R_2= H
3a R_1=H , R_2=CH_3
3b R_1=CH_3 , R_2= H
a
b
c
d
e
H_3C
CH_3
OH
hydrol.
− 2H
3b
OAc
4
5a R_1=H , R_2=CH_3
5b R_1=CH_3, R_2= H

Scheme I

The formation of 3a,b can be visualized as proceeding by the sequence of reactions described for 3b, in Scheme I. A Michael type addition of 1, via the δ-carbon, to electrofilic olefin 2b, would lead to the dipolar intermediate a. The latter would neutralize to b by transfer of a proton involving a six-membered transition state. Enamino Ketone b has ideally situated functionalities for an intramolecular attack of the enamine function on the carbonyl group, to yield intermediates $c \rightleftharpoons d$. Transformation of d to 3b presumably proceeds via e[5], followed by a dehydrogenation step and hydrolysis. The aromatization of the dihydrobenzene system in e (or its hydrolyzed equivalent) might either involve an air-oxidation during workup of the reaction mixture or a disproportionation process. While the yields of the aromatic products - including in the cases to be subsequently discussed - were less than 50%, no compounds containing the di- or tetrahydrobenzene moieties have thus far been identified in the reaction mixtures.

The aforementioned procedure has been applied to the facile conversion of steroidal dienamine 4[6] to benz[4,5,6]androstane derivatives 5a,b, which were isolated as crystalline products. The structures of these compounds is supported by their spectral data.

Compound	m.p.	yield (%)	λ_{max}^{EtOH}	18-CH_3	19-CH_3	$C_{4'}$-CH_3	$C_{6'}$-CH_3
5a	162-164°	11	263 (12,000)	0.88	1.21	2.23	
5b	160-162°	15	261 (9,500)	0.85	1.15		2.51

Although the abovementioned yields compare favourably with the overall yields of similar multistep annelation sequences, it should be noted that no attempt has as yet been made to optimalize the raction conditions and we believe the yields can be improved.

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correct spectral and analytical data have been obtained for all compounds described in this communication.

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*To whom all correspondence may be addressed.

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