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A Facile and Versatile Synthesis of Heteropolycyclic Compounds from 4-Amino-1-azabutadienes *via* Friedel-Crafts Cyclization of their Heterocyclic Derivatives.

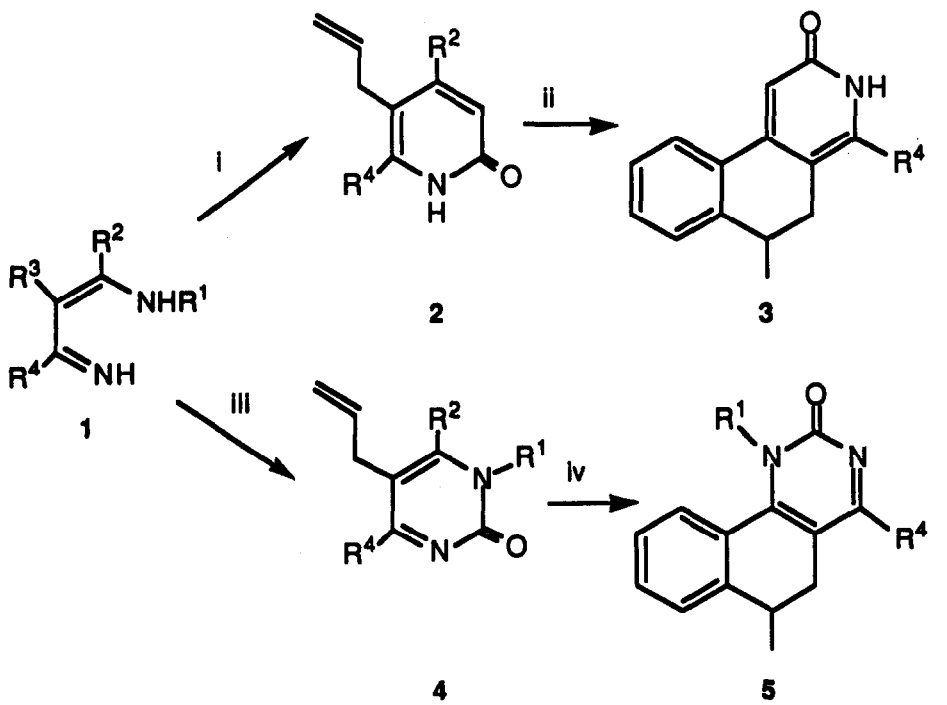
José Barluenga,* Miguel Tomás, Angel Suárez-Sobrino, and Eduardo Rubio.

Departamento de Química Organometálica, Facultad de Química,
Universidad de Oviedo, 33071 Oviedo, Spain.

Summary: Heterocyclic systems bearing an unsaturated carbon chain and aryl groups, readily accesible from 4-amino-1-azabutadienes, undergo cyclization under mild acidic conditions to produce benzo[f]isoquinolines and benzo[h]quinazolines, as well as a new 8,13-diazasteroid derivative.

Recently we have demonstrated the utility of 4-amino-1-azabutadienes **1** in the synthesis of a great variety of nitrogen-containing heterocycles;[1] on the other hand, the availability of these azadienes and the regioselectivity of the cyclizations allowed the preparation of heterocycles with aryl substituent(s) in a specific position. Moreover, it was expected that heterocycles with unsaturated appendages would be easily available by simple C-alkylation of the azabutadiene **1**[2] or N-alkylation of their heterocyclic derivatives. We thought that those heterocycles could undergo intramolecular Friedel-Crafts annulation to provide a versatile procedure for the synthesis of azaphenanthrene systems. In this context, polycyclic azaarenes are currently of great interest, not only in terms of their pharmacological properties,[3] but because of the influence of the presence and position (e.g., near the bay-region) of the heteroatoms on the biological activity[4] of this type of polycycle. Herein, we report our initial findings on the use of **1** for the preparation of tricyclic compounds containing one or two nitrogen atoms (Scheme 1) and a new 8,13-diazasteroid derivative (Scheme 2).

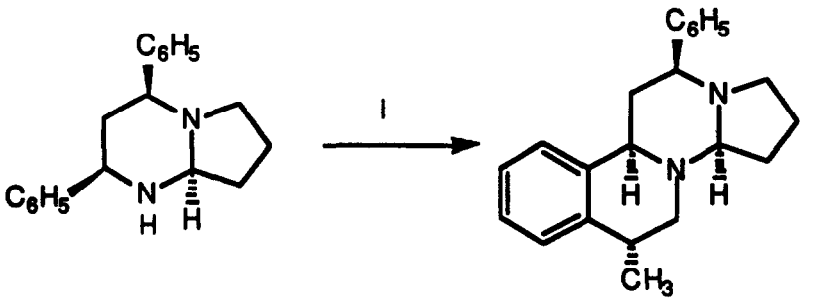
Thus, azadiene **1** (R^3 = H)[5] was treated whith ^{n}BuLi and allyl bromide to give **1** (R^3 = allyl);[2] then acetylation of **1** (R^3 = allyl) followed by LDA-promoted ring closure gave pyridone **2**,[1c] which cleanly afforded a high yield of benzo[f]isoquinoline derivative **3** (85%, m.p. 239-241°C) upon treatment with 85% H_3PO_4 (toluene, 60°C) and aqueous work-up.[6] For the synthesis of polycyclic systems containing two nitrogen atoms, one of them placed in the bay-region, pyrimidinone **4** was first prepared by reaction treatment of **1** (R^3 = allyl) with $ClCO_2Et$, as reported earlier,[7] and heated with 85% H_3PO_4 (toluene, 100°C) to give the benzo[h]quinazoline **5** (85%, m.p. 205-207°C).



R^1 = 4-MeC_6H_4; R^2 = Ph; R^3 = $CH_2CH{=}CH_2$; R^4 = *c* Hex

Scheme 1. ***Reagents and conditions :*** i, see ref. 1c; ii, 85% H_3PO_4, toluene, 60 °C, 12 h; iii, see ref. 7; iv, 85% H_3PO_4, toluene, 100 °C, 12 h.

Finally, owing to the considerable interest in the preparation and biological activity of azasteroids,[8] compound **6**, readily available from **1** [$R^1 = (CH_2)_3CH(OEt)_2$; $R^2 = R^4 = Ph$; $R^3 = H$],[9] was allylated (^{n}BuLi, HMPA, THF; allyl bromide, 94%) and then subjected to intramolecular cyclization (CF_3SO_3H, toluene, 100°C). Stirring overnight led to a 86:14 mixture of diasteroisomers **7a** and **7b** (86% isolated yield), the major isomer being easily isolated by column chromatography (silica gel, hexane-ether, 10:1). Although the actual assignament requires further studies, epimer **7a** is tentatively assigned as the major stereoisomer, since the methyl group would be in an equatorial orientation in the steroid conformation.[10, 11]



6 → **7a** + **7b** (C-5 epimer)

Scheme 2: *Reagents and conditions:* i, (a) ^{n}BuLi, HMPA, THF, -78°C to 10°C; then $BrCH_2CH{=}CH_2$, 20°C, 12 h; (b) CF_3SO_3H, toluene, 100°C, 12 h.

These results demonstrate the potential of using 4-amino-1-azabutadienes for the synthesis of a variety of heteropolycyclic compounds in a simple, high yield, two-step process. Studies directed to broaden the scope of the reaction as well as investigations on the utility of this procedure for the preparation of polycyclic alkaloids are in progress.[12]

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References and notes

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6.- *Spectroscopic data for compound* **3**: δ_H (300 MHz; $CDCl_3$) 1.15 (3H, d, J 6.5 Hz), 1.2-1.9 (10H, m), 2.5 (1H, dd, J 14.6 Hz, J 6.1Hz), 2.65 (1H, dd, J 14.6 Hz, J 4.8 Hz), 2.8 (1H, m), 2.9 (1H, m), 6.9 (1H, s), 7.1-7.4 (3H, m), 7.7 (1H, d, J 7.0 Hz), 10.8 (1H, NH, s, broad) ppm.

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9.- The preparation of compound **6** has not been yet published; for its tetrahydro precursor, see J. Barluenga, M. Tomás, J. Jardón, E. Rubio, and V. Gotor, *Synthesis*, **1989**, 230.

10.- *Spectroscopic data for compound* **7a**: δ_C (75 MHz; $CDCl_3$) 19.0 (q), 19.4(t), 28.7(t), 32.4(d), 40.1(t), 50.3(t), 55.0(t), 63.5(d), 67.7(d), 84.9(d), 124.3(d), 125.2(d), 126.2(d), 126.6(d), 127.1(d), 127.3(d), 128.2(d), 136.8(s), 139.5(s), 143.2(s) ppm.

11.- For ^{13}C n.m.r. data of analogous 8,13-diazasteroids, see: C. Verchère, D. Rouselle, and C. Viel, *Org. Magn. Reson.*, **1978**, *11*, 395.

12.- All new compounds isolated gave satisfactory analytical figures and were characterized by spectroscopic means (i.r., mass, ^1H and ^{13}C n.m.r.).

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