Cyclocondensation of 6-Acetyl-4,7-dihydro-5-methyl-7-phenyl[1,2,4]triazolo[1,5-*a*]pyrimidine with Hydroxylamine and Hydrazine

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The cyclocondensation of 6-acetyl-4,7-dihydro-5-methyl-7-phenyl[1,2,4]triazolo[1,5-*a*]pyrimidine (**3**) with hydroxylamine or hydrazine leads to 3a,4,9,9a-tetrahydro-3,9a-dimethyl-4-phenylisoxazolo-[5,4-*d*][1,2,4]triazolo[1,5-*a*]pyrimidine (**4a**) and 3a,4,9,9a-tetrahydro-3,9a-dimethyl-4-phenyl-1*H*-pyrazolo[3,4-*d*][1,2,4]triazolo[1,5-*a*]pyrimidine (**4b**), respectively. In the presence of methanolic hydrogen chloride, **4b** undergoes a cleavage of the pyrimidine ring to yield (5-amino-1,2,4-triazol-1-yl)(3,5-dimethylpyrazol-4-yl)phenylmethane (**5**). The structure determination of the compounds obtained is based on ^1H and ^{13}C nmr spectra including NOE measurements.

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The reactions of acetyl-substituted dihydroazines with binucleophiles represent a convenient synthesis of partially hydrogenated azoloazines [1], compounds with interesting biological and pharmacological properties [2,3].

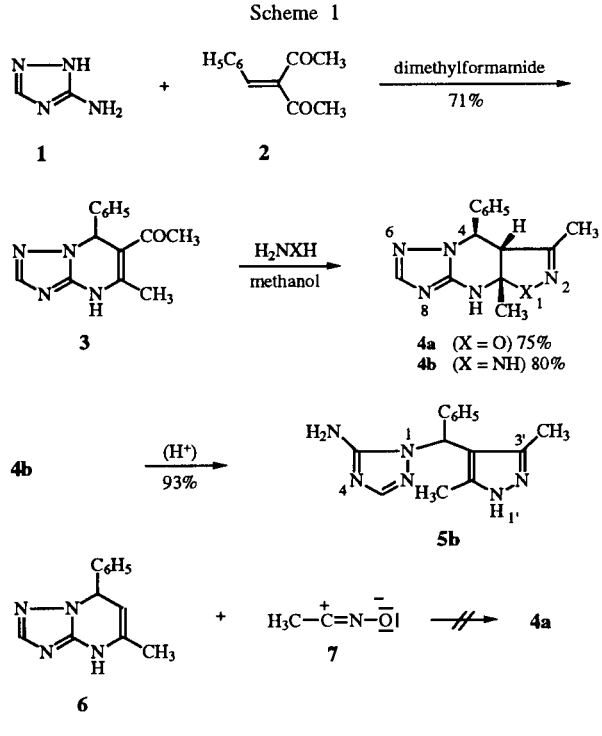
Now we report on the synthesis of new heterocyclic systems, namely substituted isoxazolo[5,4-*d*][1,2,4]triazolo[1,5-*a*]pyrimidine (**4a**) and 1*H*-pyrazolo[3,4-*d*]-[1,2,4]triazolo[1,5-*a*]pyrimidine (**4b**) by the cyclocondensation of 6-acetyl-4,7-dihydro-5-methyl-7-phenyl[1,2,4]triazolo[1,5-*a*]pyrimidine (**3**) with hydroxylamine or hydrazine.

Compound **3** was prepared by the reaction of 3-amino-1,2,4-triazole (**1**) with 2-benzylidenepentane-2,4-dione (**2**). Subsequent refluxing of **3** and hydroxylamine or hydrazine in methanol gave **4a** and **4b**, respectively. Compound **4a** proved to be stable in deuteriochloroform which contained traces of deuterium chloride. In **4b** the central ring was cleaved under these conditions. Product **5b** could be obtained in a preparative scale by treatment of **4b** with methanol/0.01% hydrogen chloride for 24 hours at room temperature.

Attempts to synthesize **4a** by a 1,3-dipolar cycloaddition of acetonitrile oxide **7** and dihydrotriazolopyrimidine **6** under conditions described for dihydropyridine analogues [1] were unsuccessful; compound **6** remained unchanged.

Compounds **4a,b** could principally exist in four diastereomeric pairs of enantiomers. The nmr spectra show a single set of signals. The coupling constants ^3J between 3a-H and 4-H in **4a,b** amount to 2.4 and 3.0 Hz, respectively. This finding is consistent with an axial-equatorial or with an equatorial-equatorial interaction of the two protons. NOE measurements by irradiation into the signal of 3a-H (δ = 3.73 for **4a** and 3.39 for **4b**) confirm the *cis* arrangement of 4-Ph and 3a-H and also the *cis* arrangement of 3a-H and 9a-CH_3. Thus, coupling constants and NOE results reveal the arrangement shown in Scheme 1 for the three stereogenic centers. Force field calculations (MMX, PCMODEL) [4,5] lead to the same stereochemistry - in so far as the axial orientations of 4-Ph and 9a-CH_3 and the equatorial position of 3a-H correspond to the lowest steric energy [6]. Obviously, hydroxylamine (or hydrazine) attack **3** from the side opposite to the phenyl group. Subsequently a *cis* fused 5-membered ring is formed.

Scheme 1



The tricyclic compound **4a** represents a novel heterocyclic system, whereas derivatives of **4b** are known, which have a carbonyl or a thiocarbonyl group in position C-4 [7-10].

EXPERIMENTAL

The melting points, determined on Kofler apparatus, are uncorrected. The ^1H and ^{13}C nmr spectra were obtained on a Bruker AM 400 in deuteriochloroform or dimethyl-d_6 sulfoxide with tetramethylsilane as the internal standard. The mass spectra were recorded on a Finnigan M 95 spectrograph operating at 70 eV.

6-Acetyl-4,7-dihydro-5-methyl-7-phenyl[1,2,4]triazolo-[1,5-*a*]pyrimidine (**3**).

A mixture of 0.84 g (10.0 mmoles) of commercially available 3-amino-1,2,4-triazole (**1**) and 1.88 g (10.0 mmoles) of benzylideneacetylacetone (**2**) in 1 ml dimethylformamide was refluxed for 0.5 hour. The reaction mixture was cooled to 20°, mixed with 20 ml of benzene and the precipitate was filtered and recrystallized from dimethylformamide. Compound **3** (1.8 g, 71%) was isolated which melted at 230°.

The ^1H nmr signals were found in dimethyl-d_6 sulfoxide at δ 2.13 (s, 3H, 5-CH_3), 2.43 (s, 3H, CH_3CO), 6.45 (s, 1H, 7-H), 7.2-7.3 (m, 5H, ArH), 7.65 (s, 1H, 2-H), 10.7 (bs, 1H, NH).

The ^{13}C nmr signals were measured in dimethyl-d_6 sulfoxide at δ 19.4 (5-CH_3), 30.4 (6-CH_3), 59.2 (C-7), 107.4 (C-6), 127.2 (*o*-C_{Ar}), 128.0 (*p*-C_{Ar}), 128.5 (*m*-C_{Ar}), 141.5 (*i*-C_{Ar}), 146.0 (C-2), 146.6 (C-5), 150.0 (C-3a), 194.5 (CO).

The ei mass spectrum had peaks at m/z (%) 254 (45, M^+), 239 (34, M^+ -CH_3), 212 (22), 177 (100, M^+ - C_6H_5).

Anal. Calcd. for $C_{14}H_{14}N_4O$: C, 66.13; H, 5.55; N, 22.03. Found: C, 66.30; H, 5.60; N, 21.92.

3a,4,9,9a-Tetrahydro-3,9a-dimethyl-4-phenylisoxazolo[5,4-*d*]-[1,2,4]triazolo[1,5-*a*]pyrimidine (**4a**).

A solution of 2.54 g (10.0 mmoles) of **3** and 0.70 g (10.0 mmoles) of hydroxylamine hydrochloride was refluxed in 1 ml pyridine and 50 ml methanol for 12 hours. The mixture was evaporated and the residue crystallized from benzene. Compound **4a** (2.0 g, 75%, mp 200-202°) was obtained.

The ^1H nmr spectrum in deuteriochloroform had signals at δ 1.43 (s, 3H, 9a-CH_3), 2.05 (s, 3H, 3-CH_3), 3.73 (d, ^3J = 2.4 Hz, 1H, 3a-H), 5.69 (d, ^3J = 2.4 Hz, 1H, 4-H), 6.9-7.4 (m, 5H, ArH), 7.56 (s, 1H, 7-H), 7.7 (bs, 1H, NH).

The ^{13}C nmr signals were measured in deuteriochloroform at δ 12.0 (9a-CH_3), 26.2 (3-CH_3), 56.1 (C-3a), 60.2 (C-4), 93.3 (C-9a), 125.5 (*o*-C_{Ar}), 128.6 (*p*-C_{Ar}), 129.2 (*m*-C_{Ar}), 136.8 (*i*-C_{Ar}), 149.6 (C-7), 153.6 (C-3), 156.4 (C-8a).

The ei mass spectrum had peaks at m/z (%) 269 (15, M^+), 212 (18, M^+ -CH_3CNO), 197 (10), 186 (43, M^+ -$C_2H_3N_4$), 171 (37), 135 (100).

Anal. Calcd. for $C_{14}H_{15}N_5O$: C, 62.44; H, 5.61; N, 26.01. Found: C, 62.50; H, 5.71; N, 26.21.

3a,4,9,9a-Tetrahydro-3,9a-dimethyl-4-phenyl-1*H*-pyrazolo-[3,4-*d*][1,2,4]triazolo[1,5-*a*]pyrimidine (**4b**).

An analogous procedure led to **4b** from **3** and hydrazine (without pyridine). The product was isolated in a yield of 80% and melted at 149-151°. The ^1H nmr spectrum in deuteriochloroform had signals at δ 1.31 (s, 3H, 9a-CH_3), 1.93 (s, 3H, 3-CH_3), 3.39 (d, ^3J = 3.0 Hz, 1H, 3a-H), 5.65 (d, ^3J = 3.0 Hz, 1H, 4-H), 5.7 (bs, 1H, 1-H), 6.9-7.4 (m, ArH), 7.47 (s 1H, 7-H), 7.8 (bs, 9-H).

The ^{13}C nmr signals were measured in deuteriochloroform at δ 14.7 (9a-CH_3), 26.8 (3-CH_3), 56.8 (C-3a), 59.0 (C-4), 79.0 (C-9a), 126.5 (*o*-C_{Ar}), 128.7 (*p*-C_{Ar}), 129.2 (*m*-C_{Ar}), 138.6 (*i*-C_{Ar}), 149.3 (C-7), 152.4 (C-3), 155.0 (C-8a).

The ei mass spectrum had peaks at m/z (%) 268 (0.4, M^+), 185 (100, M^+ -$C_2H_3N_4$), 171 (28), 135 (100), 108 (17).

Anal. Calcd. for $C_{14}H_{16}N_6$: C, 62.67; H, 6.01; N, 31.32. Found: C, 62.82; H, 6.18; N, 31.09.

(5-Amino-1,2,4-triazol-1-yl)(3,5-dimethylpyrazol-4-yl)phenylmethane (**5b**).

A solution of 0.27 g (1.0 mmole) of **4b** in 5 ml of methanol containing 0.01% hydrogen chloride was allowed to stand for 24 hours at room temperature. The reaction mixture was mixed with 20 ml of water and the precipitate was filtered and recrystallized from benzene. Compound **5b** (0.25 g, 93%) was obtained (mp 191-193°).

The ^1H nmr spectrum in deuteriochloroform had signals at δ 1.91 (s, 6H, 3'-CH_3 and 5'-CH_3), 4.7 (bs, 2H, NH_2), 6.41 (s, 1H, CH), 7.0-7.4 (m, 5H, ArH), 7.50 (s, 1H, 3-H).

The ^{13}C nmr signals were measured in deuteriochloroform at δ 11.3 (3'-CH_3 and 5'-CH_3), 57.3 (CH), 112.3 (C-4'), 127.1 (*o*-C_{Ar}), 128.1 (*p*-C_{Ar}), 128.9 (*m*-C_{Ar}), 137.7 (*i*-C_{Ar}), 143.7 (C-3' and C-5'), 148.4 (C-3), 154.2 (C-5).

The ei mass spectrum had peaks at m/z (%) 268 (0.5, M^+), 185 (100, M^+ -$C_2H_3N_4$).

Anal. Calcd. for $C_{14}H_{16}N_6$: C, 62.67; H, 6.01; N, 31.32. Found: C, 63.12; H, 5.48; N, 31.40.

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