Heterocyclic Transformations by Hydrogenolysis. Pyrimidine Derivatives from 1,2,4-Oxadiazole Derivatives

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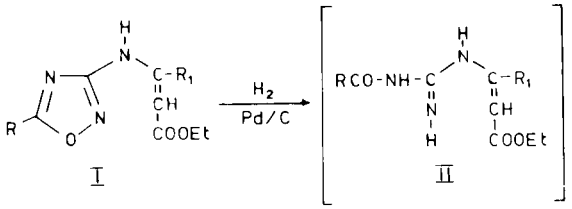
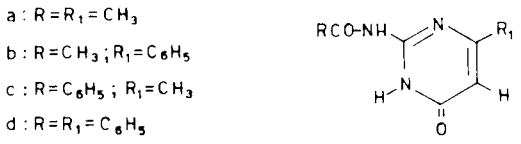
As described in previous communications (1) it is possible to obtain a series of heterocyclic compounds by rearrangement of a suitable substituted 1,2,4-oxadiazole system. Starting from Palazzo and coworkers (2) observation that reductive catalytic hydrogenation of the 1,2,4-oxadiazole ring containing alkyl and aryl groups at position 3 and 5 yielded acylamidines, our attention has now been directed to the use of the 1,2,4-oxadiazole system, containing at position 3 a side-chain able to give ring closure, as a precursor of different heterocyclic systems through the reductive cleavage of N-O bond. In this communication we report a novel synthesis of the pyrimidine ring system as the first example of transformation of 1,2,4-oxadiazole system by hydrogenation.



I II

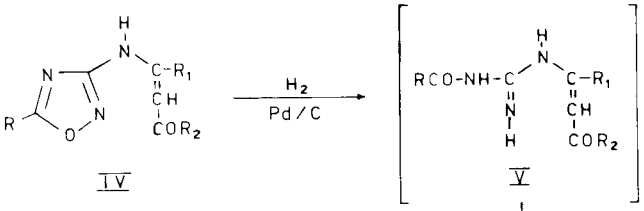


a : R = R$_1$ = CH$_3$
b : R = CH$_3$; R$_1$ = C$_6$H$_5$
c : R = C$_6$H$_5$; R$_1$ = CH$_3$
d : R = R$_1$ = C$_6$H$_5$

III

Hydrogenation of *N*-(1,2,4-oxadiazol-3-yl) β-enamino esters (Ia-d) (3) on Pd/C in ethanol yielded 2-acylaminopyrimidones derivatives (IIIa-d) which must be considered as arising directly from intermediates (IIa-d) resulting from 1,2,4-oxadiazole ring opening.

Under the same experimental condition *N*-(1,2,4-oxadiazol-3-yl) β-enaminoketones (IVa-b) (3,4) yielded directly 2-acetamidopyrimidines derivatives (VIa-b), whereas enaminoketones (IVc-d) (3,4) afforded an oily residue (several spots on tlc), containing probably the intermediates



IV V

VI VII

a : R = R$_1$ = R$_2$ = CH$_3$
b : R = R$_1$ = CH$_3$; R$_2$ = C$_6$H$_5$
c : R = C$_6$H$_5$; R$_1$ = R$_2$ = CH$_3$
d : R = R$_2$ = C$_6$H$_5$; R$_1$ = CH$_3$

(Vc-d), which, without purification, by treatment with aqueous sodium hydroxide gave, beside benzoic acid, 2-aminopyrimidines (VIIc-d).

The structures of compounds IIIa-d, VIa-b and VIIc-d were determined by elemental analyses, spectroscopic evidence (nmr) and, in known cases, by direct comparation with authentic samples.

EXPERIMENTAL

All melting points (Kofler) are uncorrected; nmr (DMSO-d$_6$): Jeol C-60H spectrometer (TMS as internal reference).

Hydrogenation of the *N*-(1,2,4-Oxadiazol-3-yl)-β-enamino Esters (Ia-d) and *N*-(1,2,4-oxadiazol-3-yl)-β-enaminoketones (IVa-d).

General Procedure.

A mixture of 0.01 mole of the compounds (Ia-d) or (IVa-d), 200 ml. of ethanol and 1 g. of 5% Pd/C was hydrogenated in a Parr apparatus at 40 psi for 4 hours at room temperature. Removal of

the catalyst and evaporation of ethanol left the reduced products, yield, *ca.* 50-60%.

(a) Hydrogenation of Ia: 2-Acetamido-6-methylpyrimidin-4-one (IIIa).

The product melted at 222°, (ethanol); lit. (5) m.p. 220-221°; nmr: 2.17 δ (s, 6H, 2 x CH_3), 5.98 δ (s, 1H, C_5-H), 11.68 δ (br. s, 2H, NH) (6).

(b) Hydrogenation of Ib: 2-Acetamido-6-phenylpyrimidin-4-one (IIIb).

The product melted at 254°, (ethanol); lit. (7) m.p. 254-255°; nmr: 2.20 δ (s, 3H, CH_3), 6.66 δ (s, 1H, C_5-H), 7.40-8.20 δ (m, 5H, Ar-H), 11.76 δ (br. s, 2H, NH).

(c) Hydrogenation of Ic: 2-Benzamido-6-methylpyrimidin-4-one (IIIc).

The product melted at 198°, (ethanol); nmr: 2.24 δ (s, 3H, CH_3), 5.98 δ (s, 1H, C_5-H) (6), 7.40-8.40 δ (m, 5H, Ar-H), 12.20 δ (br. s, 2H, NH).

Anal. Calcd. for $C_{12}H_{11}N_3O_2$: C, 62.87; H, 4.84; N, 18.33. Found: C, 62.73; H, 4.79; N, 18.44.

(d) Hydrogenation of Id: 2-Benzamido-6-phenylpyrimidin-4-one (IIId).

The product melted at 230°, (ethanol); nmr: 6.65 δ (s, 1H, C_5-H), 7.35-8.20 δ (m, 10H, Ar-H), 11.90 δ (br. s, 2H, NH).

Anal. Calcd. for $C_{17}H_{13}N_3O_2$: C, 70.09; H, 4.50; N, 14.43. Found: C, 70.24; H, 4.54; N, 14.35.

(e) Hydrogenation of IVa: 2-Acetamido-4,6-dimethylpyrimidine (VIa).

The product melted at 123°, (water); lit. (8) m.p. 124°; nmr: 2.15 δ (s, 3H, CH_3-CO-NH-), 2.30 δ (s, 6H, 2 x CH_3), 6.85 δ (s, 1H, C_5-H), 10.17 δ (s, 1H, NH).

(f) Hydrogenation of IVb: 2-Acetamido-4-methyl-6-phenylpyrimidine (VIb).

The product melted at 148°, (ethanol); lit. (9) m.p. 146°; nmr: 2.32 δ (s, 3H, CH_3-CO-NH-), 2.50 δ (s, 3H, CH_3), 7.58-7.82 δ (m, 4H, *meta* and *para* Ar-H), 8.15-8.50 δ (m, 2H, *ortho* Ar-H), 10.44 δ (s, 1H, NH).

(g) Hydrogenation of IVc: 2-Amino-4,6-dimethylpyrimidine (VIIc).

Removal of the catalyst and evaporation of ethanol left an oil which was refluxed (30 minutes) with 20% aqueous sodium hydroxide (2 ml.) and ethanol (20 ml.). After removing the solvent, water (10 ml.) was added and, after cooling, VIIc was obtained, yield, 50%, m.p. 154°, (water); lit. (10) 152°; nmr: 2.12 δ (s, 6H, 2 x CH_3), 6.28 δ (s, 1H, C_5-H), 6.37 δ (s, 2H, NH_2).

Acidification of the alkaline solution gave benzoic acid.

(h) Hydrogenation of IVd: 2-Amino-4-methyl-6-phenylpyridine (VIId).

As described for the previous sample; m.p. 176°, (ethanol); lit. (9) m.p. 173°; nmr: 2.34 δ (s, 3H, CH_3), 6.66 δ (s, 2H, NH_2), 7.05 δ (s, 1H, C_5-H), 7.45-8.30 δ (m, 5H, Ar-H).

Acidification of the alkaline solution gave benzoic acid.

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