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Synthesis of 4-Aminopyrimidines from 1,2,4-Oxadiazoles, III[1]

A Novel Type of Formation of Olefins from Amines

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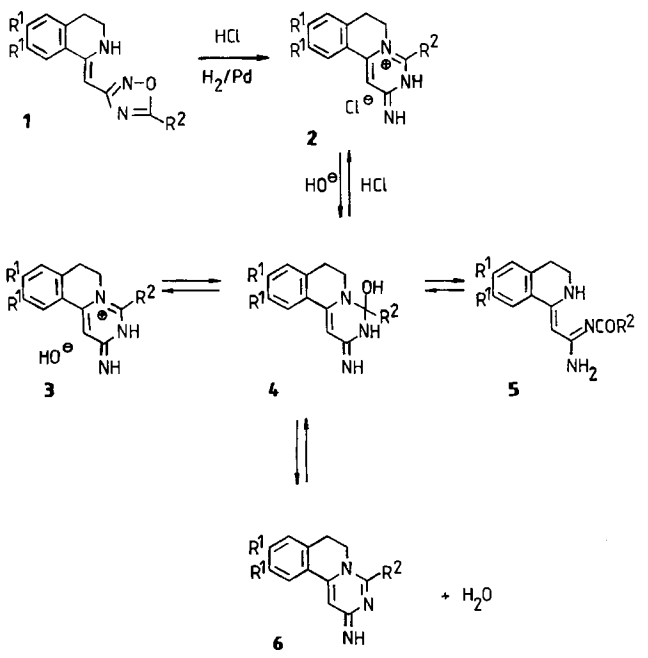
On heating at 100°C, 1,2,3,4-tetrahydro-6,7-dialkoxy-1-[(acylamidino)methylene]isoquinolines (**5**) are transformed into 4-substituted 6,7-dihydro-9,10-dialkoxy-2*H*-pyrimido[6,1-*a*]isoquinoline-2-imines (**6**), while at 140°C they undergo a novel prototropic rearrangement via **6** to give 4-amino-6-(4,5-dialkoxy-2-vinylphenyl)-2-phenylpyrimidines (**7**). The structure of **7a** has been determined by X-ray analysis.

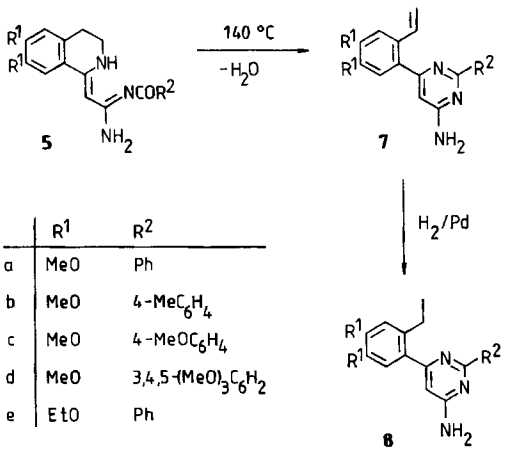
For the formation of olefins from amines containing a mobile hydrogen atom in β position several methods have been described which involve cleavage of the C–N bond, the most widely known being the Hofmann elimination[2]. All of them are accompanied by a fragmentation in which the β hydrogen is eliminated from the resulting olefin. In this paper we report on a novel thermal olefin-forming reaction in which one of the bonds of a tertiary bridgehead nitrogen in a tricyclic molecule is cleaved, but, in contrast to known methods[2], the β hydrogen is not eliminated, rather the molecule undergoes a rearrangement.

Scheme 1



Earlier we have reported that the catalytic hydrogenation of (oxadiazolylmethylene)isoquinolines (**1**) in the presence of hydrochloric acid yields pyrimido[6,1-*a*]isoquinolinium chlorides[1] (**2**). In basic media these salts form an equilibrium system comprising three tautomeric forms of a pseudobase (**3**–**5**) and of an anhydrobase (**6**) derived from them by loss of water or of a proton, respectively. **6** may be isolated in crystalline form if an ethanolic solution of the acylamidine **5** is evaporated at 100°C. In the course of this dehydration water has to be carefully removed since the reaction is reversible, and the pyrimidine ring of **6** is opened even in the presence of only an equimolar amount of water so that **5** is regenerated[3].

Scheme 2



	R^1	R^2
a	MeO	Ph
b	MeO	4-MeC_6H_4
c	MeO	4-$MeOC_6H_4$
d	MeO	3,4,5-$(MeO)_3C_6H_2$
e	EtO	Ph

In order to avoid this disadvantage we have attempted to dehydrate **5** in boiling xylene using a Dean-Stark trap. However, instead of the imines **6** we have obtained the isomeric pyrimidines **7** formed by cleavage of the isoquinoline ring and concurrent formation of a vinyl group. Structures **7** are supported by analytical and spectroscopic data as well by X-ray crystallography of **7a** (Figure 1). The vinyl group is catalytically hydrogenated to give the ethyl derivatives **8** (Scheme 2).

Concerning the mechanism of this interesting isoquinoline-pyrimidine ring transformation combined with dehydration (**5**→**7**)

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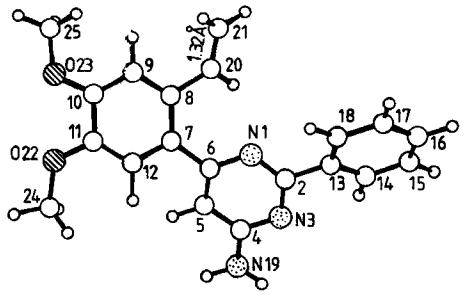
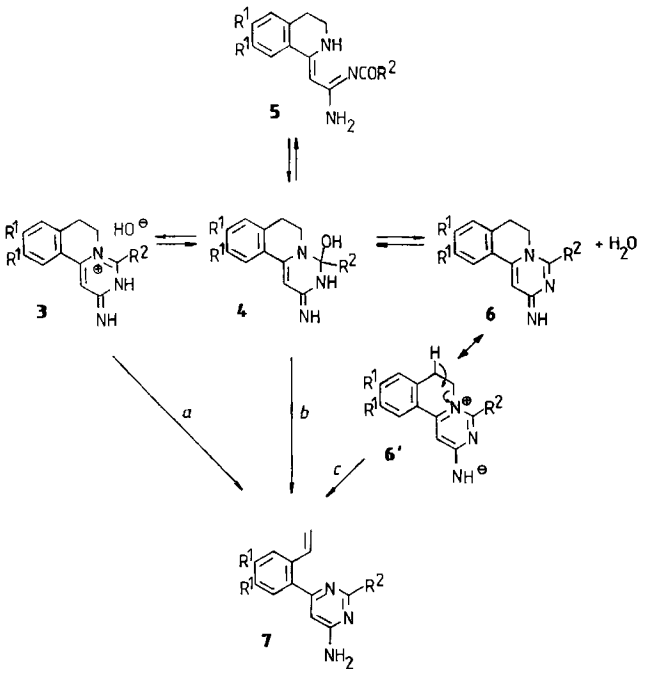


Figure 1. The X-Ray diagram of **7a** with crystallographic atomic numbering. Some characteristic bond lengths and angles: N1–C2 1.333(5), N1–C6 1.372(5), C2–N3 1.359(6), N3–C4 1.333(5), C4–C5 1.395(6), C4–N19 1.377(6), C5–C6 1.371(7), C20–C21 1.323(8) Å, C6–N1–C2 115.7(4), N1–C2–N3 126.4(3), C2–N3–C4 116.7(3), N3–C4–C5 121.2(4), C4–C5–C6 118.4(4), C5–C6–N1 121.5(3), C8–C20–C21 124.4(4)°

several possibilities may be envisaged, all of which involve as the first step formation of the pseudobase **4** as the key intermediate. Doubtlessly, it is the route a which is in closest analogy to the Hofmann elimination, but an ionic mechanism postulating the formation of and attack by a hydroxide anion in an aprotic solvent like xylene is rather improbable.

Scheme 3



A concerted mechanism involving a cyclic transition state (E_i[4]), route b) may be an alternative to a pyrolytic and non-catalyzed olefin-forming elimination in which solvent effects are absent, but with pseudobases **4** a cyclic six-membered transition state is sterically unfavored due to the presence of the condensed ring system.

A further possibility is that on heating of **5** in xylene, subsequent dehydration generates **6** which in its well-established dipolar resonance form **6'** explains the rearrangement to form **7** (route c). Since we have found no example for a similar olefin formation in the literature we were surprised to obtain pyrimidine **7a** in good yield by boiling **6a** in dry xylene. This demonstrates that reaction **5**→**7** may also proceed via imine **6**.

In summary oxadiazoles **1** can be transformed in three simple steps (catalytic hydrogenation in acidic medium, alkalization, and thermal isomerization) to 4-aminopyrimidines **7** representating a novel type of compounds.

This work is a continuation of our research on the transformation of amino amide oximes and amino-1,2,4-oxadiazoles[1,3,5].

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Experimental

IR: Zeiss Specord M 80. – ^{1}H and ^{13}C NMR: Jeol FX-100 (100 and 25 MHz); numbering of atoms according to Figure 1.

4-Amino-6-(4,5-dimethoxy-2-vinylphenyl)-2-phenylpyrimidine (**7a**)

a) A solution of **5a**[3] (3.51 g, 10 mmol) in xylene (50 ml) was boiled for 12 h using a Dean-Stark trap. Evaporation of the solvent and trituration of the residue with ether gave **7a** (2.43 g, 73%), m.p. 188 °C (from methanol).

b) A solution of **6a**[3] (1.66 g, 5.0 mmol) in xylene (15 ml) was boiled for 10 h. Workup as described under a) gave **7a** (1.39 g, 84%), m.p. 188 °C. – IR (KBr): $\tilde{\nu}$ = 3400 cm^{-1}, 3300, 3195, 1642. – ^{1}H NMR ($CDCl_3$): δ = 3.93 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 5.09 (s, 2H, NH_2), 5.21 (dd, *J* = 1 Hz, *cis*, 1H, 21-H), 5.63 (dd, *J* = 1, gem; *J* = 17 Hz, *trans*, 1H, 21-H), 6.41 (s, 1H, 5-H), 7.01 (dd, *J* = 11, *cis*, *J* = 17 Hz, *trans*, 1H, 20-H), 7.12 (s, 1H, 9- or 12-H), 7.18 (s, 1H, 9- or 12-H), 7.3–7.5 (m, 3H, 15,16,17-H), 8.3–8.5 (m, 2H, 14,18-H). – ^{13}C NMR ($CDCl_3$): δ = 56.17 (C-24,25), 103.34 (C-5), 109.05 (C-9), 112.53 (C-12), 113.61 (C-21), 128.27 (C-14,15,17,18), 129.61 (C-8), 130.26 (C-16), 130.93 (C-7), 135.67 (C-20), 138.24 (C-13), 148.92 (C-11), 149.91 (C-10), 163.25 (C-6 or C-2), 164.22 (C-2 or C-6), 165.01 (C-4).

$C_{20}H_{19}N_3O_2$ (333.4) Calcd. C 72.05 H 5.74 N 12.60
Found C 72.01 H 5.70 N 12.65

Crystal Data of **7a**[6]: $C_{20}H_{19}N_3O_2$, *M* = 333.4. Monoclinic, *a* = 25.997(2), *b* = 8.954(1), *c* = 16.141(2) Å, β = 111.4(1)°, space group *C*2/*c*, *Z* = 8, *V* = 3498.2 Å^3, D_c = 1.27 g cm^{-3}. 2579 unique reflections were collected on a Stoe semi-automatic two-circle (Weissenberg) diffractometer, with a crystal mounted along the *b* axis (*h*0*l*-*h*9*l* layers), crystal size 0.1 × 0.5 × 0.2 mm, with Ni-filtered Cu-K_α radiation (λ = 1.5418 Å), 2Θ range 5–136°, scanning speed 1°/min, scan range 2.5°, ω scan, μ(Cu-K_α) = 5.9 cm^{-1}. The structure was solved and refined by the SHELX-76 program[7], *R* = 0.070, R_w = 0.085 for 1794 reflections [$F > 5\sigma(F)$], *R* = 0.079, R_w = 0.119 for 2565 measured reflections (12 strong reflections were left out due to suspected extinction). The weighting scheme was $w = 1/(\sigma^2(F_o) + 0.01\,F_o^2)$, the number of parameters refined: 111, the highest residual electron density was 0.1 e/Å^3.

N–H hydrogen atoms and the critical vinyl hydrogens were taken from difference Fourier map, all other C–H hydrogen positions were generated. Atomic coordinates with e.s.d's are given in Table 1.

4-Amino-6-(4,5-dialkoxy-2-vinylphenyl)-2-substituted Pyrimidines **7b–e**. – General Method: Isoquinolines **5b–e**[3] (10 mmol) were treated as described for **7a** (method a). Yields, m.p.'s, IR spectral data and elementary analyses are compiled in Table 2, characteristic ^{1}H- and ^{13}C-NMR data in Table 3.

Table 1. Atomic coordinates and temperature factors [Å^2] of **7a** with e.s.d's. All atoms given here were refined anisotropically

Atom	x/a	y/b	z/c	B_{eq}
N1	0.1148(1)	0.1433(4)	0.0019(4)	3.91(9)
C2	0.0640(2)	0.1999(5)	-0.0325(5)	3.86(11)
N3	0.0480(1)	0.3385(4)	-0.0172(4)	3.84(9)
C4	0.0871(2)	0.4261(4)	0.0379(4)	3.71(10)
C5	0.1419(2)	0.3790(5)	0.0747(5)	3.99(11)
C6	0.1545(2)	0.2371(4)	0.0566(4)	3.43(10)
C7	0.2119(1)	0.1774(4)	0.0951(4)	3.51(9)
C8	0.2359(2)	0.0863(4)	0.0493(4)	3.49(10)
C9	0.2904(2)	0.0398(5)	0.0914(5)	3.89(11)
C10	0.3207(2)	0.0801(5)	0.1779(5)	3.97(11)
C11	0.2965(2)	0.1738(4)	0.2241(4)	3.68(10)
C12	0.2429(2)	0.2203(4)	0.1828(4)	3.81(10)
C13	0.0207(2)	0.1008(5)	-0.0924(5)	4.12(10)
C14	-0.0262(2)	0.1618(6)	-0.1579(6)	4.99(11)
C15	-0.0667(2)	0.0703(7)	-0.2135(7)	6.07(15)
C16	-0.0609(2)	-0.0856(7)	-0.2028(7)	6.43(18)
C17	-0.0143(2)	-0.1460(6)	-0.1396(6)	6.12(14)
C18	0.0273(2)	-0.0514(5)	-0.0840(5)	5.08(11)
N19	0.0723(2)	0.5667(4)	0.0558(4)	4.62(11)
C20	0.2053(2)	0.0438(5)	-0.0467(5)	4.52(12)
C21	0.2178(3)	-0.0725(7)	-0.0864(7)	6.35(16)
O22	0.3301(1)	0.2105(3)	0.3098(3)	4.34(7)
O23	0.3744(1)	0.0390(4)	0.2251(4)	4.96(9)
C24	0.3136(2)	0.3354(5)	0.3488(5)	5.27(12)
C25	0.4037(2)	-0.0360(8)	0.1798(8)	6.05(19)

Table 2. Yields, melting points, IR spectral, and analytical data of compounds **7b–e**

No.	Yield % (m.p., °C)	$\tilde{\nu}_{max}$ cm^{-1}	Formula (Mol. mass)	Calcd. C	Found H	N
7b	66 (183)	3400, 3300, 3195, 1642	$C_{21}H_{21}N_3O_2$ (347.4)	72.60 72.43	6.09 5.92	12.10 12.28
7c	71 (136)	3350, 3250, 3150, 1640	$C_{21}H_{21}N_3O_3$ (363.4)	69.40 69.31	5.83 5.96	11.56 11.70
7d	79 (160)	3420, 3320, 3220, 1650	$C_{23}H_{25}N_3O_5$ (423.5)	65.23 65.01	5.95 6.05	9.92 9.76
7e	75 (170)	3355, 3260, 3150, 1640	$C_{22}H_{23}N_3O_2$ (361.4)	73.11 72.90	6.41 6.25	11.63 11.72

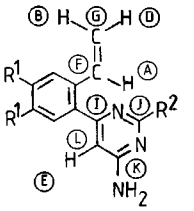
4-Amino-6-(2-ethyl-4,5-dimethoxyphenyl)-2-phenylpyrimidine (**8a**): A solution of **7a** (3.33 g, 10 mmol) in dioxane (60 ml) was hydrogenated over 8% palladium/charcoal (0.2 g). The usual workup and crystallization from benzene gave **8a** (3.22 g, 96%), m.p. 198°C. – IR (KBr): $\tilde{\nu}$ = 3496 cm^{-1}, 3400, 3290, 1670. – ^{1}H NMR ($CDCl_3$): δ = 1.21 (t, *J* = 7.5 Hz, 3H, CH_3, 21-H), 2.82 (q, *J* = 7.5 Hz, 2H, CH_2, 20-H), 3.88 (s, 3H, OCH_3, 25-H), 3.92 (s, 3H, OCH_3, 24-H), 5.07 (bs, 2H, NH_2), 6.38 (s, 1H, 5-H), 6.82 (s, 1H, 9- or 12-H), 6.96 (s, 1H, 12- or 9-H), 7.3–7.5 (m, 3H, 15,16,17-H), 8.3–8.5 (m, 2H, 14,18-H). – ^{13}C NMR ($CDCl_3$): δ = 16.23 (C-21), 25.98 (C-20), 55.99 (C-25), 56.10 (C-24), 102.32 (C-5), 112.53 (C-12), 112.94 (C-9), 128.24 (C-14,15,17,18), 130.20 (C-16), 130.87 (C-7), 135.49 (C-8), 138.30 (C-13), 146.93 (C-11), 149.62 (C-10), 163.46 (C-6), 164.01 (C-2), 166.91 (C-4).

$C_{20}H_{21}N_3O_2$ (335.4) Calcd. C 71.62 H 6.31 N 12.59
Found C 71.62 H 6.21 N 12.38

4-Amino-6-(2-ethyl-4,5-dimethoxyphenyl)-2-(3,4,5-trimethoxyphenyl)pyrimidine (**8d**): Hydrogenation of **7d** (2.12 g, 5.0 mmol) as described for **7a** gave **8d** (2.0 g, 94%), m.p. 180°C (benzene). – IR (KBr): $\tilde{\nu}$ = 3480 cm^{-1}, 3355, 3200, 1630. – NMR data for the ethyl group: ^{1}H NMR ($CDCl_3$): δ = 1.27 (t, *J* = 7.5 Hz, 3H, CH_3), 2.82 (q, *J* = 7.5 Hz, 2H, CH_2). – ^{13}C NMR ($CDCl_3$): δ = 16.56 (CH_3), 26.04 (CH_2).

$C_{23}H_{27}N_3O_5$ (425.5) Calcd. C 64.92 H 6.40 N 9.88
Found C 64.73 H 6.45 N 9.66

Table 3. Characteristic ^{1}H- and ^{13}C-NMR data of compounds **7b–e** (δ values, $CDCl_3$)



No.	^{1}H NMR Ⓐ	Ⓑ	Ⓓ	Ⓔ	^{13}C NMR Ⓕ	Ⓖ	Ⓘ	Ⓙ	Ⓚ	Ⓛ
7b	7.02	5.20	5.63	6.46	135.70	113.52	163.11	164.25	164.86	103.14
7c	7.02	5.20	5.63	6.38	135.70	113.55	163.11	163.90	164.83	102.76
7d	7.05	5.15	5.62	6.44	135.92	112.31	163.24	163.24	164.29	102.74
7e	7.01	5.19	5.60	6.43	135.76	113.41	163.19	164.10	165.01	103.29

CAS Registry Numbers

5a: 124318-06-5 / **5b**: 124318-07-6 / **5c**: 124318-08-7 / **5d**: 124318-09-8 / **5e**: 124318-10-1 / **6a**: 124318-16-7 / **7a**: 128551-27-9 / **7b**: 128551-30-4 / **7c**: 128551-31-5 / **7d**: 128551-32-6 / **7e**: 128551-33-7 / **8a**: 128551-28-0 / **8d**: 128551-29-1

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[6] Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Karlsruhe, Gesellschaft für wissenschaftlich-technische Information mbH, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD-54590, the names of the authors, and the journal citation.

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[160/90]