THERMOLYSIS OF 4-AZIDOPYRIMIDINES AND 4-AZIDOQUINAZOLINES

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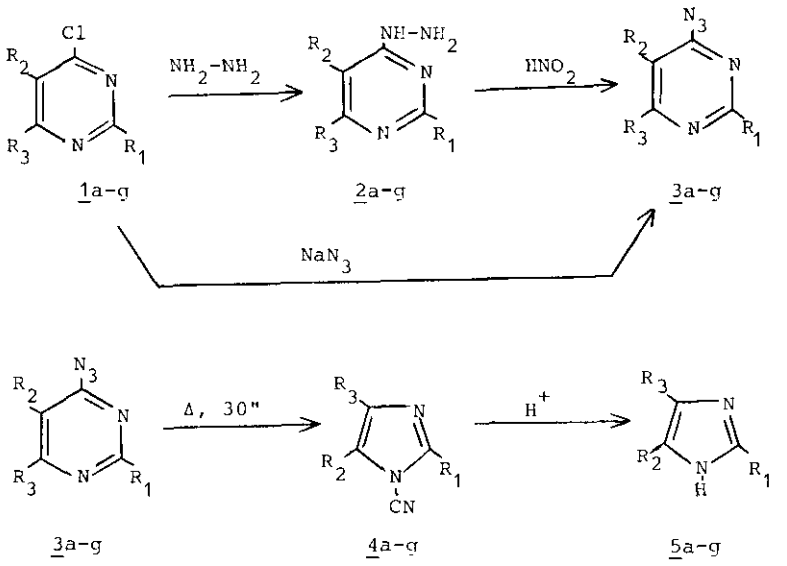
Abstract- A facile thermolysis of 4-azidopyrimidines and 4-azidoquinazolines leading, by ring contraction, in excellent yields to 1-cyanoimidazoles and benzimidazoles is reported.

The pyrolysis of substituted phenylazides gave, inter alia, the ring contraction products cyanocyclopentadienes through the nitrene intermediate. Since the composition of the cyanocyclopentadiene mixture showed to be independent of the nature of the substituent, it was proposed that the reaction was due to sigmatropic shifts of the cyano group.[1]

Extension of this kind of isomerization into the heterocyclic field generalized the reaction and also clarified the mechanism. In fact nitrenoazines and -diazines, generated by gas-phase pyrolysis of the triazolo-azines and -diazines, gave the carbonitrile derivatives of the corresponding five membered heterocycles.[2] Both heteroaromatic and aromatic nitrene showed a ring expansion-ring contraction dichotomy.[3,4] Energy calculation and labelling experiments on nitrenoazines and -diazines led to the theory that both ring contraction and ring expansion can be regarded as concerted processes which are governed mainly by the energy differences between the reacting species and the products.[4]

Now we report a facile thermal rearrangement of the 4-azidopyrimidines and -quinazolines 3a-g which, by ring contraction, give in very high yield, 89-100%, 1-carbonitrileimidazoles and -benzimidazoles 4a-g.

The compounds 3a-g were prepared from the chloro derivatives 1a-g either by reac-



1a-g 2a-g 3a-g

3a-g 4a-g 5a-g

a $R_1=R_2=R_3=C_6H_5$; b $R_1=R_3=C_6H_5, R_2=H$; c $R_1=C_6H_5, R_2=H, R_3=CH_3$; d $R_1=C_6H_5, R_2=R_3=CH_3$; e $R_1=C_6H_5, R_2=C_2H_5, R_3=CH_3$; f[5] $R_1=C_6H_5, R_2-R_3$=benzo; g[5] R_1=pyridin-3-yl, R_2-R_3=benzo

tion with sodium azide or by action of hydrazine and subsequent nitrosation of the compounds 2a-g. The azides 3a-g, when heated in oil bath at 5°C above their melting points for a few seconds, violently develop nitrogen and solidify to give a solid which was identified as the carbonitrile derivatives 4a-g. Hydrolysis of the compounds 4a-g in acidic medium gave the corresponding imidazoles and benzimidazoles 5a-g.

The formazion of the carbonitrile derivatives 4 under these reaction conditions seems to be interesting considering that this kind of ring contraction was always observed under much more vigorous conditions and the carbonitrile derivatives were typical products of violent pyrolysis,[6] whereas the same rearrangement under milder conditions, thermolysis in organic solvent, was observed to small extent and together with other side reactions.[7]

EXPERIMENTAL

All melting points were taken on a Büchi-Tottoli capillary melting point apparatus and are uncorrected; ir spectra were determined in nujol mull with a Perkin-Elmer 299 spectrophotometer; nmr spectra were obtained with a Varian FT 80 spectrometer (TMS as internal reference). Mass spectra were run on a JEOL JMS-01 SG-2 double focusing mass spectrometer operating with an electron beam energy of 75 eV and 10 KV accelerating voltage.

Preparation of 2-phenyl-5-ethyl-6-methyl-4-chloropyrimidine(1e) and 2-(pyridin-3-yl)-4-chloroquinazoline(1g).

These compounds were prepared according to the procedure described previously.[8]

The compound 1e(R_1=C_6H_5,R_2=C_2H_5,R_3=CH_3) was recrystallized from ethanol(yield 80%), mp 67°C; ms: M^+= 232; Anal. Calcd. for $C_{13}H_{12}N_2Cl$: C, 67.09; H, 5.63; N, 12.04. Found: C, 66.88; H, 5.43; N, 12.00.

The compound 1g(R_1=pyridin-3-yl,R_2--R_3=benzo) was recrystallized from cyclohexane(yield 92%), mp 179-180°C; ms: M^+= 241; Anal. Calcd for $C_{13}H_8N_3Cl$: C, 64.60, H, 3.34; N, 17.39. Found: C, 64.48, H, 3.31; N, 17.23.

Preparation of 2,5,6-trisubstituted 4-hydrazinopyrimidines(2c,e) and 2-(pyridin-3-yl)-4-hydrazinoquinazoline(2g).

A mixture of the chloro derivatives 1a[9],b[8],c[10],d[11],e,f[12],g (10 mmoles) and anhydrous hydrazine (10 mmoles) in absolute ethanol (100 ml) was refluxed for 4 h. The mixture was poured onto crushed ice, the solid precipitated was filtered off, and shaked in aqueous hydrochloric acid(1N). The solid insoluble in acid solution was filtered off and the solution was made basic with aqueous ammonia (2N) and the solid was dried and recrystallized.

The compound 2c(R_1=C_6H_5,R_2=H,R_3=CH_3) was recrystallized from ethanol(yield 80%), mp 94°C; ir: 3300 and 3240(NH_2), 3200 (NH)cm^{-1}; ms: M^+= 200; Anal. Calcd. for $C_{11}H_{12}N_4$: C, 65.98; H, 6.04; N, 27.98. Found: C, 65.97; H, 6.29; N, 28.23.

The compound 2e(R_1=C_6H_5,R =C_2H_5,R_3=CH_3) was recrystallized from ethanol(yield80%) mp 104-105°C; ir: 3290 and 3250 (NH_2), 3190 (NH) cm^{-1}; ms: M^+= 228; Anal. Calcd. for $C_{13}H_{16}N_4$: C, 68.39; H, 7.06; N, 24.54. Found: C, 68.31; H, 7.25; N, 24.91.

The compound 2g(R_1=pyridin-3-yl,R_2—R_3=benzo) was recrystallized from ethanol (yield 84%), mp 234-235°C; ir: 3280 and 3240 (NH_2), 3100 (NH) cm^{-1}; ms: M^+= 237; Anal. Calcd. for $C_{13}H_{11}N_5$: C, 65.81; H, 4.67; N, 29.52. Found: C, 65.79; H, 4.91; N, 29.87.

Preparation of 4-azido-2,5,6-trisubstituted pyrimidines(3c-e) and 4-azido-2-(pyridin-3-yl)quinazoline(3g).

Method A: A mixture of 4-chloro derivatives 1a-g (10 mmoles) and sodium azide (10 mmoles) in anhydrous DMF (100 ml) was refluxed for 10 min. After cooling the reaction mixture was poured onto crushed ice. The solid was collected, dried and recrystallized.

The compound 3c(R_1=C_6H_5,R_2=H,R_3=CH_3) was recrystallized from ethanol(yield 94%), mp 50°C; ir: 2120 (N_3) cm^{-1}; nmr($CDCl_3$)δ: 2.51(3H,s,CH_3), 6.51-8.45(6H,m,C_6H_5 and C_4N_2H); ms: M^+= 211; Anal. Calcd. for $C_{11}H_9N_5$: C, 62.55; H, 4.30; N, 33.16. Found: C, 62.49; H, 4.56; N, 33.51.

The compound 3d(R_1=C_6H_5,R_2=R_3=CH_3) was recrystallized from ethanol(yield 96%), mp 82°C; ir: 2110 (N_3) cm^{-1}; nmr($CDCl_3$)δ: 2.08(3H,s,CH_3), 2.48 (3H,s,CH_3), 7.38-8.47 (5H,m,C_6H_5); ms: M^+= 225; Anal. Calcd. for $C_{12}H_{11}N_5$: C, 63.98; H, 4.92; N, 31.09. Found: C, 63.85; H, 5.08; N, 31.36.

The compound 3e(R_1=C_6H_5,R_2=C_2H_5,R_3=CH_3) was recrystallized from ethanol(yield 92%), mp 51°C; ir: 2120 (N_3) cm^{-1}; nmr($CDCl_3$)δ: 1.10 (3H,t,CH_2-$\underline{CH_3}$), 2.51 (3H,s,CH_3), 2.60 (2H,q,CH_2), 7.38-8.63 (5H,m,C_6H_5); ms: M^+= 239; Anal. Calcd. for $C_{13}H_{13}N_5$: C, 65.25; H, 5.48; N, 29.27. Found: C, 65.18; H, 5.76; N, 29.49.

The compound 3g(R_1=pyridin-3-yl,R_2—R_3=benzo) was recrystallized from ethanol (yield 98%), mp 184°C; ms: M^+= 248; Anal. Calcd. for $C_{13}H_8N_6$: C, 62.89; H, 3.25; N, 33.86. Found: C, 62.81; H, 3.52; N, 33.99.

Method B: To a solution of the compounds 2a[9],b[13],c,d[11],e,f[14],g (10 mmoles) in acetic acid (50 ml), sodium nitrite (10 mmoles) in water (5 ml) was added dropwise with stirring and cooling. The reaction mixture was, then, poured onto crushed ice. The solid precipitated was collected, air dried and recrystallized. The compounds 3 were obtained with the following yields: c,93%; d,90%; e,90%; g,86%.

Thermolysis of azides 3a-g: 2,4,5-trisubstituted 1-carbonitrileimidazoles (4a-e) and 2-substituted 1-carbonitrilebenzimidazoles (4f-g).

2 m mol of 3a[13],b[13],c-e,f[15],g were heated in an oil bath at 5°C above their melting points. As soon as the compound melted a violently development of nitrogen was observed. The reactants were kept at the same temperature for 30 sec, cooled down and triturated with hot ethanol to give the carbonitrile derivatives 4a-g.

The compound 4a(R_1=R_2=R_3=C_6H_5) was recrystallized from ethanol (yield 96%), mp 210°C; ir: 2260 (CN) cm^{-1}; ms: M^+= 321; Anal. Calcd. for $C_{22}H_{15}N_3$: C, 88.22; H, 4.71; N, 13.08. Found: C, 82.13; H, 4.66; N, 12.98.

The compound 4b(R_1=R_2=C_6H_5,R_2=H) was recrystallized from ethanol (yield 94%), mp 114°C; ir: 2260 (CN) cm^{-1}; ms: M^+= 245; Anal. Calcd. for $C_{16}H_{11}N_3$: C, 78.35; H, 4.52; N, 17.13. Found: C, 78.28; H, 4.39; N, 17.13.

The compound 4c(R_1=C_6H_5,R_2=H,R_3=CH_3) was recrystallized from cyclohexane (yield 92%), mp 173°C; ir: 2240 (CN) cm^{-1}; nmr($CDCl_3$)δ: 2.27 (3H,s,CH_3), 6.80-7.85 (5H, m,C_6H_5); ms: M^+= 183; Anal. Calcd. for $C_{11}H_9N_3$: C,72.11; H, 4.95; N, 22.94. Found: C, 72.01; H, 5.16; N, 23.18.

The compound 4d(R_1=C_6H_5,R_2=R_3=CH_3) was recrystallized from cyclohexane (yield 94%), mp 64°C; ir: 2230 (CN) cm^{-1}; nmr($CDCl_3$)δ: 2.16 (3H,s,CH_3), 2.30 (3H,s,CH_3), 7.40-7.92 (5H,m,C_6H_5); ms: M^+= 197; Anal. Calcd. for $C_{12}H_{11}N_3$: C, 73.07; H, 5.62; N, 21.31; H, 5.62. Found: C, 72.96; H, 5.79; N, 21.62.

The compound 4e(R_1=C_6H_5,R_2=C_2H_5,R_3=CH_3) was isolated as uncrystallizable oil (yield 94%), ir 2260 (CN) cm^{-1}; nmr($CDCl_3$)δ: 1.25 (3H,t,CH_3), 2.18 (3H,s,CH_3), 2.62 (2H, q,CH_2), 7.39-8.31 (5H,m,C_6H_5); ms: M^+= 211; Anal. Calcd. for $C_{13}H_{13}N_3$: C,73.90; H, 6.20; N, 19.89. Found: C, 73.79; H, 6.42; N, 20.22.

The compound 4f(R_1=C_6H_5,R_2—R_3=benzo) was recrystallized from ethanol (yield 100%), mp 110-112°C (lit.[15], mp 110°C); ir: 2250 (CN) cm^{-1}; Anal. Calcd. for $C_{14}H_9N_3$: C, 76.69; H, 4.14; N, 19.17. Found: C, 76.76; H, 4.08; N, 18.96.

The compound 4g(R_1=pyridin-3-yl,R_2—R_3=benzo) was recrystallized from cyclohexane (yield 92%), mp 106°C; ir: 2250 (CN) cm^{-1}; Anal. Calcd. for $C_{13}H_8N_4$: C,70.89; H, 3.66; N, 25.44. Found: C, 70.81; H, 3.90; N, 25.79.

Hydrolysis of the compounds 4a-g: 2,4,5-trisubstituted imidazoles 5a-e and 2-substituted benzimidazoles 5f-g.

A mixture of 4a-g (10 mmoles), H_2SO_4 (10%, 16 ml) and ethanol (100 ml) was refluxed for 20 h. After cooling, the mixture was poured into cold water and made basic with ammonia (32%). The solid precipitated was collected and recrystallized to give derivatives 5a-g whose analytical and spectroscopical data were in agreement with those reported in literature.

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