SYNTHESIS OF HETEROCYCLIC KETENE *N,S*-ACETALS AND THEIR REACTIONS WITH α,β-UNSATURATED NITRILES

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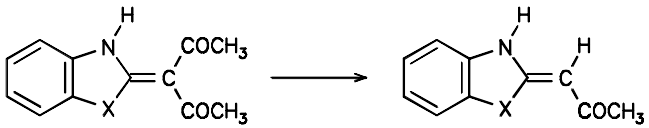
In an extention of our recent studies[1–4] on the application of ketoketene or cyanoketene *S,S*-acetals in heterocyclic synthesis we report here a simple procedure for the synthesis of 1-amino-4-acetyl- 2-cyano-3-phenyl-3*H*-pyrido[2,1-*b*][1,3]benzothiazole (*Va*) or benzoxazole derivative *Vb* from 2-(1-acetyl-2-oxopropylidene)benzothiazole[5] *IIIa* or benzoxazole derivative[4] *IIIb* and benzylidenemalononitrile (cf. Scheme 1).

The reaction mechanism was assumed to follow a preliminary hydrolysis of one of the acetyl groups followed by a nucleophilic addition of the ethylenic −CH hydrogen atom at the ethylenic double bond of the benzylidenemalononitrile with subsequent cyclization. This proposed mechanism was confirmed by a separate two-step reaction where compound *IIIa* and *IIIb* were hydrolyzed by boiling either in ethanol in presence of piperidine or in methanol in presence of sodium methoxide into the intermediate product 2-(2-oxopropylidene)benzothiazole (*IVa*) or benzoxazole derivative[4] *IVb* which was reacted with benzylidenemalononitrile in boiling ethanol in the presence of a catalytic amount of piperidine to afford compounds *Va* and *Vb*.

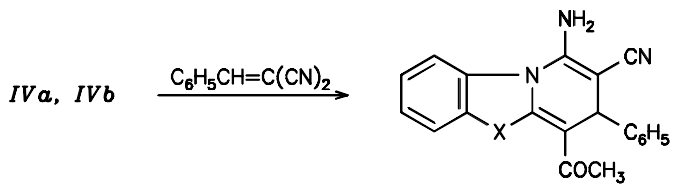
Compound *IIIa* was also allowed to react with a variety of α,β-unsaturated nitriles including arylidenemalononitrile, arylidene ethylcyanoacetate, arylidenecyano-acetamide and arylidenephenylacetonitrile in refluxing ethanol containing piperidine base where in each case a preliminary hydrolysis of one of the two acetyl groups was affected followed by a nucleophilic addition of the formed carbanion at the arylidene double bond and cyclization into the desired 3*H*-pyrido-[2,1-*b*][1,3]benzothiazole derivatives *VIa–VIi*, cf. Scheme 1.

EXPERIMENTAL

Melting points are uncorrected. IR spectra were obtained (KBr disc) on a Nicolet 710 FT-IR spectrometer, wavenumbers are given in cm^{-1}. ^1H NMR spectra were measured on a Varian EM 360A instrument (60 MHz) in CD_3SOCD_3 or $CDCl_3$ with tetramethylsilane as internal standard. Chemical shifts are given in ppm (δ-scale), coupling constants (*J*) in Hz.

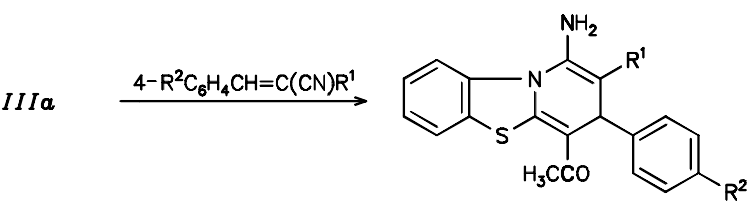


IIIa, IIIb *IVa, IVb*



Va, Vb

In formulae *III* – *V*:
a, X = S; *b*, X = O



VIa–VIi

In formula *VI* :

	R^1	R^2
a	$COOC_2H_5$	H
b	$CONH_2$	H
c	CN	OCH_3
d	$COOC_2H_5$	OCH_3
e	$CONH_2$	OCH_3

	R^1	R^2
f	CN	NO_2
g	$COOC_2H_5$	NO_2
h	$CONH_2$	NO_2
i	C_6H_5	NO_2

SCHEME 1

2-(1-Acetyl-2-oxopropylidene)benzothiazole (*IIIa*)

A solution of 2-[di(methylthio)methylene]pentan-2,4-dione[4] (817 mg, 4.0 mmol) and 2-aminothiophenol (513 mg, 4.1 mmol) in absolute ethanol (25 ml) was refluxed for 24 h. After cooling the precipitate was filtered off and recrystallized from ethanol. Yield 886 mg (95%) of *IIIa*, m.p. 155 °C. IR spectrum: 3 430 (NH); 1 660 (C=O); 1 540 (C=C). ^{1}H NMR spectrum ($CDCl_3$): 10.70 br, 1 H (NH); 7.90–7.40 m, 4 H (H-arom.); 2.30 s, 3 H (CH_3); 2.15 s, 3 H (CH_3). For $C_{12}H_{11}NO_2S$ (233.3) calculated: 61.78% C, 4.75% H, 6.00% N, 13.74% S; found: 61.64% C, 4.68% H, 6.13% N, 13.71% S.

2-(2-Oxopropylidene)benzothiazole (*IVa*)

A) Compound *IIIa* (2.33 g, 10 mmol) was added to the solution of sodium (1 g) in methanol (30 ml) and the mixture was refluxed for 4 h. Water (20 ml) was then added and the mixture was extracted with chloroform (3 × 50 ml). The collected extracts were dried over anhydrous sodium sulfate, the solvent was evaporated and the solid precipitate was recrystallized from ethanol. Yield 2.12 g (91%), m.p. 110 °C. IR spectrum: 3 450 (NH); 1 650 (C=O). ^{1}H NMR spectrum ($CDCl_3$): 11.70 br, 1 H (NH); 8.70–8.20 m, 4 H (H-arom.); 5.40 s, 1 H (=CH–); 3.10 s, 3 H ($COCH_3$). For $C_{10}H_9NOS$ (191.3) calculated: 62.80% C, 4.70% H, 7.32% N, 16.77% S; found: 62.64% C, 4.81% H, 7.55% N, 16.87% S.

B) A mixture of compound *IIIa* (2.33 g, 10 mmol) and piperidine (1 ml) in ethanol (30 ml) refluxed for 1 h, the reaction mixture was then concentrated to its half volume. After cooling, the precipitate solid was filtered off and recrystallized from ethanol. Yield 1.98 g (85%) of compound *IVa* identical with sample prepared by procedure *A*.

2-(2-Oxopropylidene)benzoxazole (*IVb*)

A) Compound *IVb* was prepared from compound *IIIb* (2.17 g, 10 mmol) according the above mentioned procedure *A*. Yield 2.07 g (89%) of *IVb*, m.p. 70 °C, literature[4] gives m.p. 70 °C.

B) Compound *IVb* was prepared from compound *IIIb* (2.17 g, 10 mmol) according the above mentioned procedure *B*. Yield 1.96 g (84%) of *IVb* identical with sample prepared by procedure *A*.

4-Acetyl-1-amino-2-cyano-3-phenyl-3*H*-pyrido[2,1-*b*][1,3]benzothiazole (*Va*)

A) A mixture of compound *IVa* (1.91 g, 10 mmol) and benzylidenemalononitrile (1.54 g, 10 mmol) in ethanol (30 ml) was refluxed for 30 min in presence of a catalytic amount of piperidine. On cooling the solid precipitate was filtered off and recrystallized from ethanol into yellow crystals. Yield 3.28 g (95%) of *Va*, m.p. 269 °C. IR spectrum: 3 400, 3 302 (NH_2); 2 180 (CN); 1 654 (C=O). ^{1}H NMR spectrum (CD_3SOCD_3): 7.90–7.10 br, 9 H (H-arom.); 6.30–6.10 br, 2 H (NH_2); 4.70 s, 1 H (CH-Ph); 2.00 s, 3 H (CH_3). For $C_{20}H_{15}N_3OS$ (345.4) calculated: 69.55% C, 4.38% H, 12.17% N, 9.28% S; found: 69.32% C, 4.63% H, 11.87% N, 9.54% S.

B) Compound *IIIa* (2.33 g, 10 mmol) and piperidine (1 ml) are added to a stirred suspension of benzylidenemalononitrile (1.54 g, 10 mmol) in ethanol (30 ml). The reaction mixture was refluxed for 2 h, and then was left to cool. The precipitated solid was filtered off and recrystallized from ethanol into yellow crystals. Yield 3.10 g (90%) of compound *Va* identical with sample prepared by procedure *A*.

4-Acetyl-1-amino-2-cyano-3-phenyl-3*H*-pyrido[2,1-*b*][1,3]benzoxazole (*Vb*)

A) A mixture of compound *IVb* (1.75 g, 10 mmol) and benzylidenemalononitrile (1.54 g, 10 mmol) in ethanol (30 ml) was heated at reflux temperature for 30 min in presence of a catalytic amount of

piperidine. The solid product was filtered off and recrystallized from ethanol into orange crystals. Yield 2.83 g (86%) of compound *Vb*, m.p. 200 °C. IR spectrum: 3 400, 3 320 (NH_2); 2 184 (CN); 1 677 (C=O). ^{1}H NMR (CD_3SOCD_3): 7.90 – 7.20 br, 9 H (H-arom.); 4.90 s, 1 H (CH-Ph); 4.70 s, 2 H (NH_2). For $C_{20}H_{15}N_3O_2$ (329.4) calculated: 72.93% C, 4.59% H, 12.76% N; found: 72.65% C, 4.76% H, 12.89% N.

B) Compound *IIIb* (2.17 g, 10 mmol) and piperidine (1 ml) are added to a stirred suspension of benzylidenemalononitrile (1.54 g, 10 mmol) in ethanol (30 ml). The reaction mixture was refluxed for 2 h and then was left to cool. The precipitated solid was filtered off and recrystallized from ethanol into orange crystals. Yield 2.63 g (80%) of compound *Vb* identical with sample prepared by procedure *A*.

General Procedure for Preparation of 3*H*-Pyrido[2,1-*b*][1,3]benzothiazole Derivatives *VIa – VIi*

Compound *IIIa* (2.33 g, 10 mmol) and piperidine (1 ml) was added to a stirred suspension of the appropriate α,β-unsaturated nitrile (10 mmol) in ethanol (50 ml). The reaction mixture was refluxed over different periods of time and then allowed to cool, the product was filtered off and recrystallized from methanol (compounds *VIc*, *VIf–VIh*) or ethanol (compounds *VIa*, *VIb*, *VIe*, *VIi*).

4-Acetyl-1-amino-2-ethoxycarbonyl-3-phenyl-3H-pyrido[2,1b][1,3]benzothiazole (VIa). Reaction time 3 h, yield 3.18 g (81%), m.p. 318 °C. IR spectrum: 3 436, 3 351 (NH_2); 1 738 (C=O). ^{1}H NMR spectrum (CD_3SOCD_3): 7.70–7.20 m, 9 H (H-arom.); 6.30 s, 2 H (NH_2); 4.25 q, 2 H, J = 7 (OCH_2); 2.30 s, 3 H ($COCH_3$); 1.30 t, 3 H, J = 7 (CH_3). For $C_{22}H_{20}N_2O_3S$ (392.5) calculated: 67.33% C, 5.14% H, 7.14% N, 8.17% S; found: 67.76% C, 5.09% H, 7.28% N, 8.34% S.

4-Acetyl-1-amino-2-carbamoyl-3-phenyl-3H-pyrido[2,1-b][1,3]benzothiazole (VIb). Reaction time 4 h, yield 2.58 g (71%), m.p. 217 °C. IR spectrum: 3 370, 3 260 (NH_2); 1 632 (C=O). ^{1}H NMR (CD_3SOCD_3): 7.90–7.30 m, 9 H (H-arom.); 6.40–6.10 br, 2 H (NH_2); 4.80 s, 1 H (CH-Ar); 4.30–4.00 br, 2 H ($CONH_2$); 2,60 s, 3 H (CH_3). For $C_{20}H_{17}N_3O_2S$ (363.4) calculated: 66.10% C, 4.71% H, 11.56% N, 8.82% S; found: 66.34% C, 4.53% H, 11.34% N, 8.54% S.

4-Acetyl-1-amino-2-cyano-3-(4-methoxyphenyl)-3H-pyrido[2,1-b][1,3]benzothiazole (VIc). Reaction time 2.5 h, yield 3.08 g (82%), m.p. 262 °C. IR spectrum: 3 471, 3 372 (NH_2); 2 182 (CN); 1 647 (C=O). ^{1}H NMR (CD_3SOCD_3): 8.20–6.80 m, 8 H (H-arom.); 6.30–5.90 br, 2 H (NH_2); 4.60 s, 1 H (CH-Ar); 3.70 s, 3 H (OCH_3); 2.20 s, 3 H ($COCH_3$). For $C_{21}H_{17}N_3O_2S$ (375.4) calculated: 67.19% C, 4.56% H, 11.19% N, 8.54% S; found: 67.54% C, 4.33% H, 11.56% N, 8.63% S.

4-Acetyl-1-amino-2-ethoxycarbonyl-3-(4-methoxyphenyl)-3H-pyrido[2,1-b][1,3]benzothiazole (VId). Reaction time 3 h, yield 3.17 g (75%), m.p. 230 °C. IR spectrum: 3 408, 3 351 (NH_2); 1 698 (C=O). ^{1}H NMR (CD_3SOCD_3): 8.00–7.20 m, 8 H (H-arom.); 5.80 s, 2 H (NH_2); 5.20 s, 1 H (CH-Ar); 4.25 q, 2 H, J = 7 (OCH_2); 3.30 s, 3 H (OCH_3); 2.20 s, 3 H ($COCH_3$); 1.35 t, 3 H, J = 7 (CH_3). For $C_{23}H_{22}N_2O_4S$ (422.5) calculated: 65.39% C, 5.25% H, 6.63% N, 7.59% S; found: 65.55% C, 5.60% H, 6.33% N, 7.19% S.

4-Acetyl-1-amino-2-carbamoyl-3-(4-methoxyphenyl)-3H-pyrido[2,1-b]-[1,3]benzothiazole (VIe). Reaction time 6 h, yield 2.56 g (65%), m.p. 266 °C. IR spectrum: 3 400, 3 307, 3 290 (NH_2, $CONH_2$); 1 630 (C=O). ^{1}H NMR ($CDCl_3$): 7.90–7.10 m, 8 H (H-arom.); 6.70 s, 2 H (NH_2); 5.20 s, 1 H (CH-Ar); 4.40–3.90 br, 2 H ($CONH_2$); 3.40 s, 3 H (OCH_3); 2.20 s, 3 H ($COCH_3$). For $C_{21}H_{19}N_3O_3S$ (393.5) calculated: 64.10% C, 4.86% H, 10.68% N, 8.15% S; found: 64.46% C, 4.44% H, 10.98% N, 8.09% S.

4-Acetyl-1-amino-2-cyano-3-(4-nitrophenyl)-3H-pyrido[2,1-b][1,3]benzothiazole (VIf). Reaction time 3 h, yield 3.24 g (83%), m.p. 257 °C. IR spectrum: 3 470, 3 370 (NH_2); 1 665 (C=O). ^{1}H NMR (CD_3SOCD_3): 8.80–7.80 m, 8 H (H-arom.); 7.20 s, 2 H (NH_2); 5.60 s, 1 H (CH-Ar); 2.60 s, 3 H ($COCH_3$). For $C_{20}H_{14}N_4O_3S$ (390.4) calculated: 61.53% C, 3.61% H, 14.35% N, 8.21% S; found: 61.21% C, 3.43% H, 14.86% N, 8.08% S.

4-Acetyl-1-amino-2-ethoxycarboxycarbonyl-3-(4-nitrophenyl)-3H-pyrido[2,1-b][1,3]-benzothiazole (VIg). Reaction time 3 h, yield 3.37 g (77%), m.p. 259 °C. IR spectrum: 3 422, 3 330 (NH_2); 1 724 (C=O). ^{1}H NMR (CD_3SOCD_3): 8.10–7.70 m, 8 H (H-arom.); 6.80 s, 2 H (NH_2); 5.40 s, 1 H (CH-Ar); 4.00 q, 2 H, J = 7 (OCH_2); 2.60 s, 3 H ($COCH_3$); 1.55 t, 3 H, J = 7 (CH_3). For $C_{22}H_{19}N_3O_5S$ (437.5) calculated: 60.40% C, 4.38% H, 9.61% N, 7.33% S; found: 60.89% C, 4.76% H, 9.27% N, 7.64% S.

4-Acetyl-1-amino-2-carbamoyl-3-(4-nitrophenyl)-3H-pyrido[2,1-b][1,3]benzothiazole (VIh). Reaction time 5 h, yield 2.74 g (67%), m.p. 247 °C. IR spectrum: 3 400, 3 300, 3 280 (NH_2, $CONH_2$); 1 650 (C=O). ^{1}H NMR (CD_3SOCD_3): 8.00–7.10 m, 8 H (H-arom.); 6.80 s, 2 H (NH_2); 5.40 s, 1 H (CH-Ar); 4.40–4.00 br, 2 H ($CONH_2$); 2.30 s, 3 H ($COCH_3$). For $C_{20}H_{16}N_4O_4S$ (408.4) calculated: 58.82% C, 3.95% H, 13.72% N, 7.85% S; found: 58.64% C, 3.91% H, 13.66% N, 7.53% S.

4-Acetyl-1-amino-2-phenyl-3-(4-nitrophenyl)-3H-pyrido[2,1-b][1,3]benzothiazole (VIi). Reaction time 3 h, yield 2.46 g (62%), m.p. 130 °C. IR spectrum: 3 480, 3 400 (NH_2), 1 703 (C=O). ^{1}H NMR (CD_3SOCD_3): 9.00–7.90 m, 13 H (H-arom.); 7.10 s, 2 H (NH_2); 5.40 s, 1 H (CH-Ar); 2.50 s, 3 H ($COCH_3$). For $C_{25}H_{20}N_2OS$ (396.5) calculated: 75.73% C, 5.08% H, 7.07% N, 8.09% S; found: 75.35% C, 5.32% H, 7.41% N, 8.33% S.

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