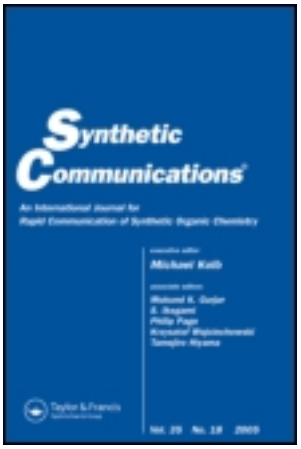

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Utility of α-Oxoketene and α-Cyanoketene Thioacetals in Heterocyclic Syntheses: Synthesis of Some New Benzothiazepine Derivatives

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UTILITY OF α-OXOKETENE AND α-CYANOKETENE THIOACETALS IN HETEROCYCLIC SYNTHESES: SYNTHESIS OF SOME NEW BENZOTHIAZEPINE DERIVATIVES

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Benzo[b][1,5]thiazepines 1a or 1b were prepared via reaction of o-aminothiophenol with 3-(bis(methylthio)methylene)-pentane-2,4-dione or 2-(bis(methylthio)methylene)-3-carbonitrile, respectively. Reaction of compound 1a with malononitrile afforded pyrano[4,3-b][1,5]-benzothiazepine 2a, which underwent cyclization into pyrido[4,3-b][1,5]-benzothiazepine 2b. Also, reaction of compound 1a with ethyl cyanoacetate afforded pyrano[4,3-b][1,5]benzothiazepin-3-one 3. Reaction of compound 1a with hydrazine, phenylhydrazine, or hydroxylamine afforded the corresponding azolobenzothiazepines, 4–6, respectively. Reaction of compound 1a with ethylenediamine afforded 1,5-benzothiazepin-ethanone 7, which underwent cyclization to [1,4]diazepino[5,6-b][1,5]benzothiazepine 8. Also, compound 1b was reacted with acetylacetone or ethyl acetoacetate to afford pyrano[4,3-b][1,5]benzothiazepines 9a or 9b, which reacted with ammonium acetate to give pyrano[4,3-b][1,5]-benzothiazepine 10a or pyrido[4,3-b][1,5]-benzothiazepine 10b, respectively. Compound 1b was allowed to react with hydrazine, phenylhydrazine, or hydroxyl amine to afford pyrazolo or isoxazolo[3,4-b][1,5]benzothiazepines 11, 12, or 13, respectively.

Keywords: Active methylene; benzothiazepines; α-oxoketene dithioacetals; piperidine

INTRODUCTION

Benzothiazepines exhibit antifungal, antibacterial, antifeedant, anti-inflammatory, analgesic, and anticonvulsant properties.[1–4] Compounds possessing a thiophene substructure also find applications as pharmaceuticals,[5,6] precursors for natural products,[7] conjugated polymers,[8] and other materials.[9] Most literature for the synthesis of benzothiazepines depends on the reaction of *o*-aminothiophenol with an α,β-unsaturated carbonyl functionality via [4 + 3]-annulation.[10–13] Recently, new 3-benzyl-1,10-diaryl-4*H*,10*H*-thieno[3,4-c][1,5]benzothiazepines comprising both thiophene and benzothiazepine substructures were synthesized in a one-pot, multistep tandem process from the reaction of 5-aryl-2,4-bis(arylmethylidene)dihydro-3-thiophenones with *o*-aminothiophenol.[14] This prompted us to

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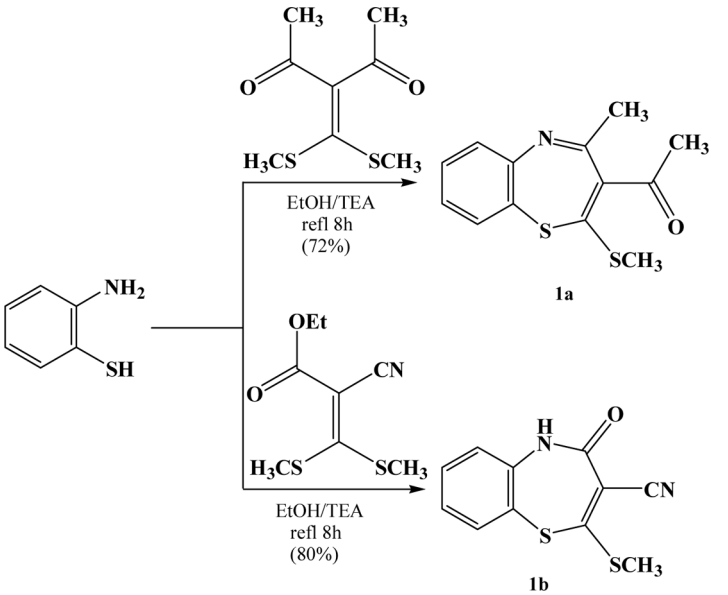
synthesize some fused benzothiazepines derivatives with a variety of nuclei include pyrane, pyridine, and pyrazole oxazole pyrimidinone or 1,4-diazepine as biologically active compounds.

RESULTS AND DISCUSSION

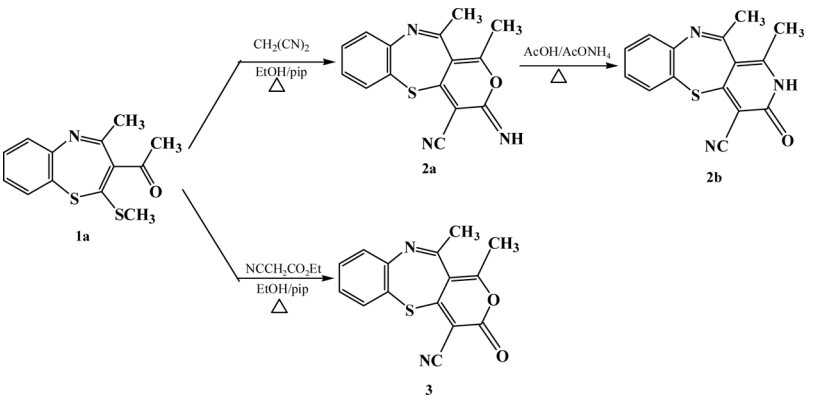
In continuation of our work on the chemistry of α-oxoketene S,S-acetals[15–17] and diazepine derivatives,[18–21] we report here the synthesis of 1-((2*E*,4*Z*)-4-methyl-2-(methylthio)benzo[*b*][1,5]thiazepin-3-yl)ethanone **1a** or (*Z*)-2-(methylthio)-4-oxo-4,5-dihydrobenzo[*b*][1,5]thiazepine-3-carbonitrile **1b** via reaction of 3-(bis(methylthio)methylene)-pentane-2,4-dione or 2-(bis(methylthio)methylene)-3-carbonitrile with *o*-aminothiophenol under reflux in ethanol in the presence of triethylamine (TEA) as a catalyst (cf. Scheme 1).

Reaction of compound **1a** with malononitrile in the presence of piperidine as a base afforded the corresponding 1,11-dimethyl-3-oxo-3*H*-pyrano[4,3-*b*][1,5]-benzothiazepine-4-carbonitrile **2a**, which converted into 1,11-dimethyl-3-oxo-2,3-dihydropyrido[4,3-*b*][1,5]benzothiazepine-4-carbonitrile **2b** after refluxing with ammonium acetate in acetic acid. Also, reaction of compound **1a** with ethyl cyano-acetate afforded 1,4,11-trimethyl-3*H*-pyrano[4,3-*b*][1,5]benzothiazepin-3-one **3** (Scheme 2).

The reaction mechanism was assumed to proceed via a nucleophilic addition of an active methylene at the ethylenic bond of thiazepine ring with eliminatinon of the MeSH molecule followed by enolization and cyclization to the desired pyrano-benzthiazepine derivative.



Scheme 1.



Scheme 2.

Compound **1a** was reacted with hydrazine, phenylhydrazine, or hydroxylamine to afford the corresponding azolobenzothiazepines, namely 3,4-dimethyl-2*H*-pyrazolo[3,4-*b*][1,5]benzothiazepine **4**, 3,4-dimethyl-2-phenyl-2*H*-pyrazolo[3,4-*b*]-[1,5]benzothiazepine **5**, or 3,4-di-methylisoxazolo[3,4-*b*][1,5]benzothiazepine **6**, respectively.

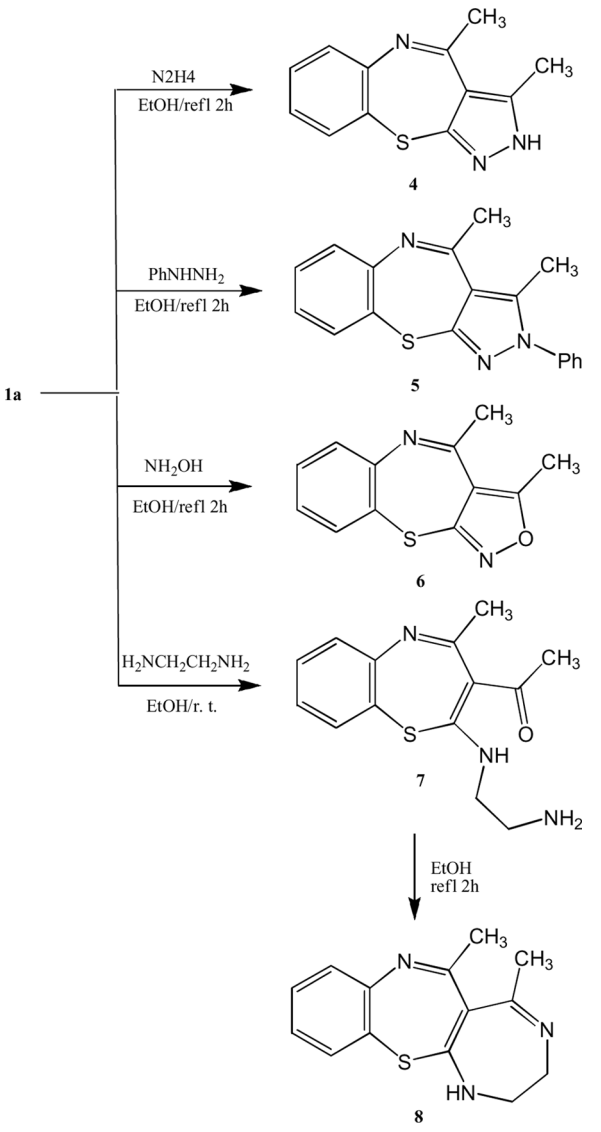
In the same manner, the reaction of compound **1a** with ethylenediamine at room temperature afforded 1-{2-[(2-aminoethyl)amino]-4-methyl-1,5-benzothiazepin-3-yl}ethanone **7**, which underwent cyclization in boiling ethanol to 5,6-dimethyl-2,3-dihydro-1*H*-[1,4]diazepino[5,6-*b*][1,5]-benzothiazepine **8** (Scheme 3). The new products were characterized using infrared (IR) and ^{1}H NMR spectroscopy (Table 1).

On the other hand, compound **1b** was allowed to react with acetylacetone or ethyl acetoacetate to afford the corresponding 4-acetyl-1-imino-3-methyl-1*H*-pyrano[4,3-*b*][1,5]benzothiazepin-11(10*H*)-one **9a** or 4-acetyl-3-methylpyrido[4,3-*b*][1,5]benzothiazepine-1,11(2*H*,10*H*)-dione **9b**, which upon reaction with ammonium acetate gave ethyl 1-imino-3-methyl-11-oxo-10,11-dihydro-1*H*-pyrano[4,3-*b*][1,5]-benzothia-zepine-4-carboxylate **10a** or 3-methyl-1,11-dioxo-1,2,10,11-tetrahydro-pyrido[4,3-*b*][1,5]benzothiazepine-4-carboxylate **10b**, respectively (Scheme 4).

In continuation of the search for the synthesis of a new derivative of benzothiazepine including tricyclic systems, compound **1b** was reacted with hydrazine, phenylhydrazine, or hydroxyl amine in ethanol to afford 3-amino-2*H*-pyrazolo[3,4-*b*][1,5]benzothiazepin-4(5*H*)-one **11,** 3-amino-2-phenyl-2*H*-pyrazolo-[3,4-*b*][1,5]benzothiazepin-4(5*H*)-one **12**, or 3-aminoisoxazolo[3,4-*b*][1,5]-benzothiazepin-4(5*H*)-one **13**, respectively (Scheme 5).

EXPERIMENTAL

All melting points were determined on a Koffler melting-point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker Avance 300-MHz spectrometer using tetramethylsilane (TMS) as internal reference (chemical shifts in δ, ppm), and IR spectra were obtained on a Bruker Fourier transform (FT)–IR ISS 25 spectrophotometer (KBr, ν_{max} in cm^{-1}).



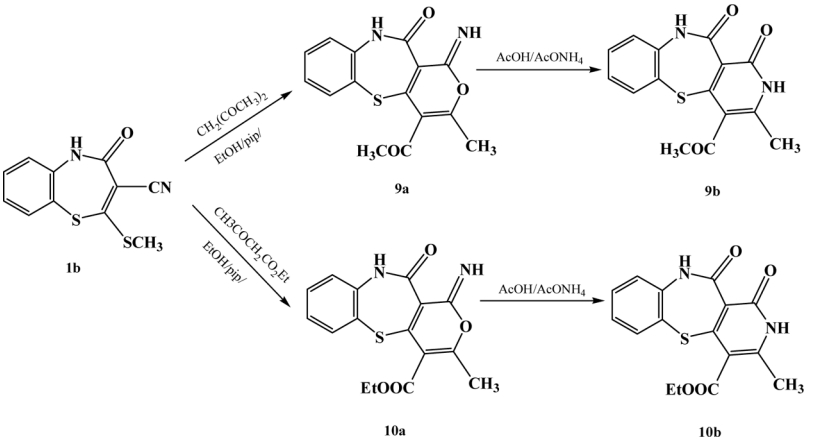
Scheme 3.

Synthesis of 1-[4-Methyl-2-(methylthio)-1,5-benzothiazepin-3-yl]-ethanone (1a)

A mixture of *o*-aminothiophenol (3.13 g, 0.025 mol) and 3-[bis(methylthio)-methylene]pentane-2,4-dione (5.1 g, 0.025 mol) in absolute ethanol (50 mL) was treated with a catalytic amount of TEA, and the reaction mixture was heated under reflux until the evolution of MeSH ceased (8 h). The solvent was evaporated under reduced pressure, and the residual mass was triturated with petroleum ether

Table 1. Analytical and spectral data for the obtained compounds

Compound	Mp (°C)	Molecular formula (weight)	IR (KBr, ν cm^{-1})	^1H NMR (DMSO, δ ppm)
1a	172–174	$C_{13}H_{13}NOS_2$ (263.38)	1675 (CO), 1640 (C=N)	7.88–7.37 (m, 4H, CH-arom.), 2.75 (s, 3H, CH_3), 2.58 (S, 3H, SCH_3), 2.25 (S, 3H, $COCH_3$)
1b	208–210	$C_{11}H_8N_2OS_2$ (248.32)	3266 (NH), 2202 (CN), 1668 (CO)	9.24 (S, 1H, NH), 7.75–7.35 (m, 4H, CH-arom.), 2.60 (S, 3H, SCH_3)
2a	214–216	$C_{15}H_{11}N_3OS$ (281.3)	3308 (NH), 2212 (CN)	11.20 (S, 1H, NH), 7.86–7.44 (m, 4H, CH-arom.), 2.68 (s, 3H, CH_3), 2.20 (S, 3H, CH_3).
2b	195–197	$C_{15}H_{11}N_3OS$ (281.3)	3288 (NH), 2220 (CN), 1692 (CO)	9.34 (s, 1H, NH), 7.80–7.38 (m, 4H, CH-arom.), 2.65 (s, 3H, CH_3), 2.18 (S, 3H, CH_3)
3	243–245	$C_{15}H_{10}N_2O_2S$ (282.3)	2225 (CN), 1748 (CO)	7.78–7.37 (m, 4H, CH-arom.), 2.70 (s, 3H, CH_3), 2.18 (S, 3H, SCH_3)
4	210–212	$C_{12}H_{11}N_2S$ (229.3)	3212 (NH), 1643 (C=N)	10.45 (s, 1H, NH), 7.78–7.43 (m, 4H, CH-arom.), 2.62 (s, 3H, CH_3), 2.32 (s, 3H, CH_3)
5	>300	$C_{18}H_{15}N_3S$ (305.3)	3050 (CH-arom.), 2966 (CH_3)	7.87–7.26 (m, 9H, CH-arom.), 2.66 (s, 3H, CH_3), 2.25 (s, 3H, CH_3)
6	262–264	$C_{12}H_{10}N_2OS$ (230.3)	3036 (CH-arom.), 2945 (CH_3)	7.80–7.43 (m, 4H, CH-arom.), 2.60 (s, 3H, CH_3), 2.22 (s, 3H, CH_3)
7	>300	$C_{14}H_{17}N_3OS$ (275.3)	3396, 3303, 3285 (NH_2, NH), 1676 (CO)	9.87 (s, 1H, NH), 7.75–7.41 (m, 4H, CH-arom.), 2.66 (s, 3H, CH_3), 2.12 (s, 3H, CH_3), 1.85–1.60 (m, 4H, $2CH_2$)
8	230–232	$C_{14}H_{15}N_3S$ (257.3)	3255 (NH)	10.42 (s, 1H, NH), 7.81–7.51 (m, 4H, CH-arom.), 2.61 (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 1.96–1.78 (m, 4H, $2CH_2$)
9a	276–278	$C_{15}H_{12}N_2O_3S$ (300.3)	3302, 3256 (2NH), 1682 (CO), 1666 (CO)	11.22 (s, 1H, NH), 9.87 (s, 1H, NH), 7.77–7.45 (m, 4H, CH-arom.), 2.88 (s, 3H, CH_3), 2.10 (s, 3H, CH_3)
9b	233–235	$C_{15}H_{12}N_2O_3S$ (300.3)	3295, 3267 (2NH), 1683, 1668 (3CO)	10.20 (s, 1H, NH), 9.44 (s, 1H, NH), 7.80–7.48 (m, 4H, CH-arom.), 2.82 (s, 3H, CH_3), 2.10 (s, 3H, CH_3)
10a	250–252	$C_{16}H_{14}N_2O_4S$ (330.3)	3302, 3260 (2NH), 1753 (CO), 1668 (3CO)	10.43 (s, 1H, NH), 9.25 (br, 1H, NH), 7.68–7.35 (m, 4H, CH-arom.), 3.94 (q, 2H, CH_2), 2.64 (s, 3H, CH_3), 1.22 (t, 3H, CH_3)
10b	222–224	$C_{16}H_{14}N_2O_4S$ (330.3)	3287, 3234 (2NH), 1747 (CO), 1684 (CO), 1669 (CO)	9.73 (s, 1H, NH), 9.30 (s, 1H, NH), 7.74–7.46 (m, 4H, CH-arom.), 3.86 (q, 2H, CH_2), 2.60 (s, 3H, CH_3), 1.20 (t, 3H, CH_3)
11	196–198	$C_{10}H_8N_4OS$ (232.3)	3387, 3316, 3265 (NH_2, 2NH), 1676 (CO)	9.67 (s, 1H, NH), 7.70–7.45 (m, 4H, CH-arom.), 5.89 (br, 2H, NH_2)
12	246–248	$C_{16}H_{12}N_4OS$ (308.3)	3387, 3303, 3256 (NH_2, NH), 1676 (CO)	9.32 (s, 1H, NH), 7.86–7.37 (m, 9H, CH-arom.), 5.60 (br, 2H, NH_2)
13	220–222	$C_{10}H_7N_3O_2S$ (233.3)	3404, 3325. 3189 (NH_2, NH), 1670 (CO)	9.87 (s, 1H, NH), 7.77–7.43 (m, 4H, CH-arom.), 5.58 (br, 2H, NH_2)

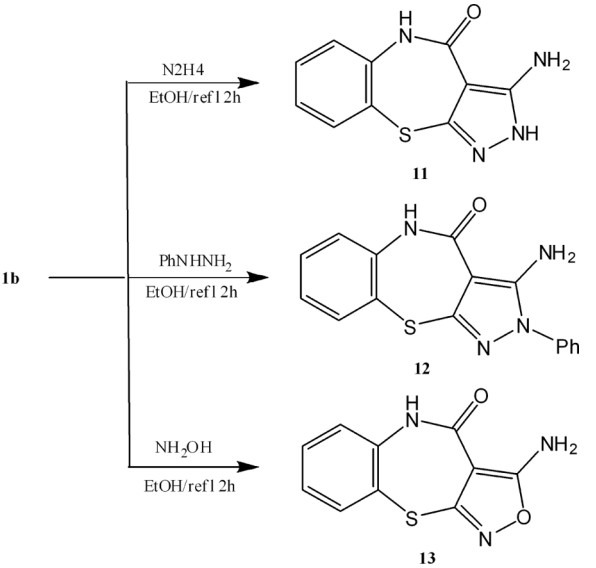


Scheme 4.

(40–60 °C). The formed solid was recrystallized from aq. ethanol into pale yellow needles, mp 172–174 °C.

Synthesis of 2-(Methylthio)-4-oxo-4,5-dihydro-1,5-benzothiazepine-3-carbonitrile (1b)

A mixture of *o*-aminothiophenol (3.13 g, 0.025 mol) and ethyl 2-cyano-3,3-bis(methylthio)acrylate (5.4 g, 0.025 mol) in absolute ethanol (50 mL) was treated with a catalytic amount of TEA, and the reaction mixture was heated under reflux until the evolution of MeSH ceased (6 h). The solvent was evaporated under reduced



Scheme 5.

pressure, and the residual mass was triturated with petroleum ether (40–60 °C). The formed solid was recrystallized from aq. ethanol into pale yellow needles, mp 208–210 °C.

Synthesis of 3-Imino-1,11-dimethyl-3H-pyrano[4,3-b][1,5]benzo-thiazepine-4-carbonitrile 2a

A mixture of compound **1a** (2.63 g, 0.01 mol), malononitrile (0.66 g, 0.01 mol) in absolute ethanol (40 mL) and a catalytic amount of piperidine was heated under reflux for 3 h. The solvent was evaporated, and the formed solid was collected by filtration and recrystallized from MeOH into yellow needles, mp 214–216 °C, yield 72%.

Synthesis of 1,11-Dimethyl-3-oxo-2,3-dihydropyrido[4,3-b][1,5]benzo-thiazepine-4-carbonitrile 2b

Compound **2a** (2.0 g, 0.076 mol) was dissolved in AcOH (25 mL) and then treated with $AcONH_4$ (1.0 g, 0.12 mol). The reaction mixture was heated under reflux for 1 h, solvent was evaporated in vacuo, and then water (50 mL) was added. The formed solid was filtered off and recrystallized from ethanol into white crystals, mp 195–197 °C, yield 65%.

Synthesis of 1,11-Dimethyl-3-oxo-3H-pyrano[4,3-b][1,5]benzo-thiazepine-4-carbonitrile 3

A mixture of compound **1a** (2.63 g, 0.01 mol), ethyl cyanoacetate (1.13 g, 0.01 mol) in absolute ethanol (40 mL), and two drops of piperidine was heated under reflux for 3 h. Solvent was evaporated in vacuo, and the formed solid was collected by filtration and recrystallized from EtOH into pale yellow needles, mp 243–245 °C, yield 78%.

Synthesis of 3,4-Dimethyl-2H-pyrazolo[3,4-b][1,5]benzothiazepine 4, 3,4-Dimethyl-2-phenyl-2H-pyrazolo[3,4-b][1,5]benzothiazepine 5, and, 3,4-Dimethylisoxazolo[3,4-b][1,5]benzothiazepine 6

A mixture of compound **1a** (2.63 g, 0.01 mol) and hydrazine, phenylhydrazine, and/or hydroxylamine (0.012 mol) in absolute EtOH (40 mL) was heated under reflux for 2 h. The solvent was evaporated under reduced pressure, and the formed solid was collected by filtration (yields 85, 81, and 66%, respectively).

Synthesis of 1-{2-[(2-Aminoethyl)imino]-4-methyl-2,3-dihydro-1,5-benzothiazepin-3-yl}ethanone 7

A mixture of compound **1a** (2.63 g, 0.01 mol) and ethylenediamine (0.6 g, 0.01 mol) in ethanol (40 mL) was stirred at room temperature for 3 h. The solvent was evaporated under reduced pressure, water (50 ml) was added, and the mixture was left overnight. The formed solid was filtered off and recrystallized from EtOH into light brown crystals, mp > 300 °C, yield 88%.

Synthesis of 5,6-Dimethyl-2,3-dihydro-1H-[1,4]diazepino[5,6-b][1,5]-benzothiazepine 8

Compound **7** (2 g) was dissolved in ethanol (30 mL) and heated under reflux for 2 h. Solvent was evaporated, and the residual mass was then triturated with petroleum ether (60–80). The formed solid was collected and recrystallized from ethanol into pale yellow needles, mp 230–232 °C, yield 62%.

Synthesis of 4-Acetyl-1-imino-3-methyl-1H-pyrano[4,3-b][1,5]benzothiazepin-11(10H)-one 9a and Ethyl 1-Imino-3-methyl-11-oxo-10,11-dihydro-1H-pyrano[4,3-b][1,5]-benzothiazepine-4-carboxylate 10a

A mixture of compound **1a** (2.63 g, 0.01 mol), acetylacetone or ethyl acetoacetate (0.01 mol) in absolute ethanol (40 mL), and a catalytic amount of piperidine was heated under reflux for 3 h. The solvent was evaporated, and the formed solid was collected by filtration and recrystallized from MeOH into **9a** as a pale yellow solid, mp 276–278 °C, yield 75%, and **10a** as brown crystals, mp 250–252 °C, yield 68%.

Synthesis of 4-Acetyl-3-methylpyrido[4,3-b][1,5]benzothiazepine-1,11(2H,10H)-dione 9b or 3-Methyl-1,11-dioxo-1,2,10,11-tetrahydro-pyrido[4,3-b][1,5]benzothiazepine-4-carboxylate 10b

Compound **9a** or **10a** (0.075 mol) was dissolved in AcOH (25 mL) and then treated with $AcONH_4$ (1.0 g, 0.12 mol). The reaction mixture was heated under reflux for 1 h, solvent was evaporated in vacuo, and then water (50 mL) was added. The residual mass was poored into cold ice water, and the formed solid was filtered off and recrystallized from ethanol into **9b** as white crystals, mp 223–225 °C, yield 66%, and **10b** as pale yellow crystals, mp 222–224 °C, yield 62%.

Synthesis of 3-Amino-2H-pyrazolo[3,4-b][1,5]benzothiazepin-4(5H)-one 11, 3-Amino-2-phenyl-2H-pyrazolo[3,4-b][1,5]benzothiazepin-4(5H)-one 12, or 3-Aminoisoxazolo[3,4-b][1,5]-benzothiazepin-4(5H)-one 13

A mixture of compound **1b** (0.005 mol) and hydrazine, phenylhydrazine, and/or hydroxylamine (0.01 mol) in absolute EtOH (40 mL) was heated under reflux for 2 h. The solvent was evaporated under reduced pressure, and the formed solid was collected by filtration (yields 80, 75, and 65% respectively).

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