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Synthesis of pyrano[3,4-*c*]thieno[3,2-*e*][1,2,4]triazolo[4,3-*a*]pyridines, representatives of a new fused heterocyclic system

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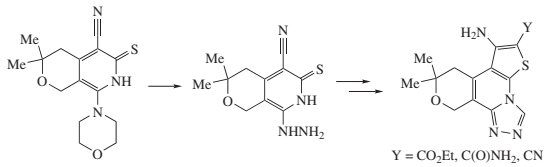
New effective synthesis of functionalized pyrano[3,4-*c*]thieno-[3,2-*e*][1,2,4]triazolo[4,3-*a*]pyridines comprises nucleophilic substitution in 8-morpholino-6-thioxopyrano[3,4-*c*]pyridine-5-carbonitrile with hydrazine hydrate followed by sequential heterocyclization with formic acid and chloroacetic acid derivatives.

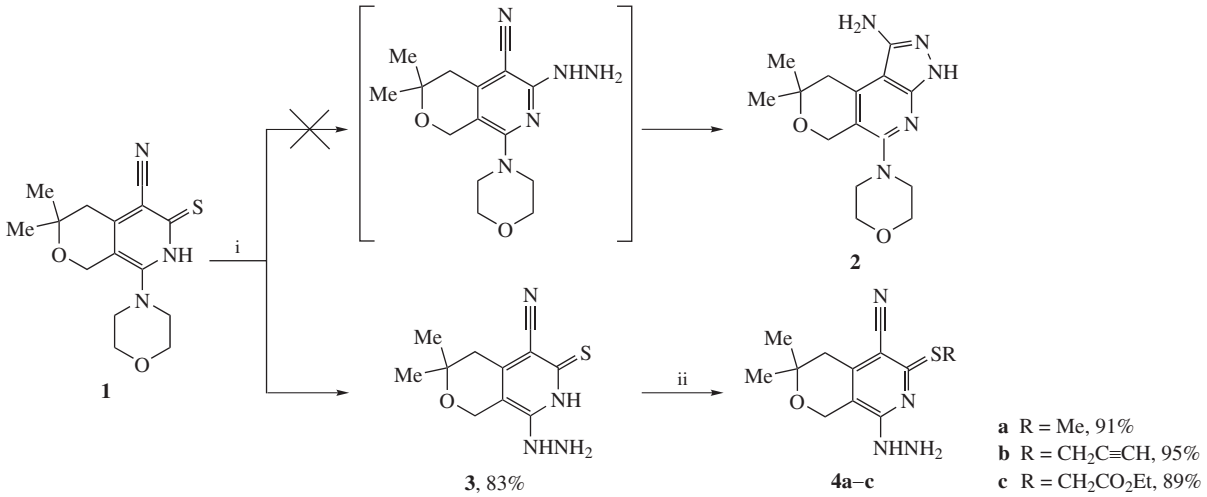


Keywords: pyrano[3,4-*c*]pyridines, triazolo[4,3-*a*]pyridines, pyrano[3,4-*c*]thieno[3,2-*e*][1,2,4]triazolo[4,3-*a*]pyridines, hydrazines, thiones, heterocyclization, alkylation.

Nitrogen heterocyclic compounds play an important role in the drug discovery.[1] Among them, bicyclic fused compounds containing pyridine ring such as pyranopyridines,[2,3] triazolo-[4,3-*a*]pyridines,[4,5] and thieno[2,3-*b*]pyridines[6,7] possess a broad spectrum of biological activity. In recent years, synthetic methods to obtain pyrano[3,4-*c*]pyridines,[8–11] triazolo[4,3-*a*]pyridines[12,13] and thieno[2,3-*b*]pyridines[14–16] have been developed. Previously, we synthesized tricyclic pyrano[3,4-*c*][1,2,4]triazolo[4,3-*a*]pyridines employing pyridine ring rearrangement[17] and accessed pyrano-[4,3-*d*]thieno[2,3-*b*]pyridines.[18] Tetracyclic pyrano[3,4-*c*]thieno-[3,2-*e*][1,2,4]triazolo[4,3-*a*]pyridines have not been reported so far.

Herein, we synthesized new functional derivatives of pyrano-[3,4-*c*][1,2,4]triazolo[4,3-*a*]pyridines and accomplished their heterocyclization into novel pyrano[3,4-*c*]thieno[3,2-*e*][1,2,4]-triazolo[4,3-*a*]pyridines. The starting compound was known[19] 8-morpholino-6-thioxopyrano[3,4-*c*]pyridine-5-carbonitrile derivative **1** (Scheme 1). It was previously converted into 5-alkyl(aryl)-pyrazolo[3,4-*b*]pyrano[4,3-*d*]pyridines possessing pronounced anti-convulsant activity.[20] In view of this, we emloyed compound **1** in the reaction to react highly nucleophilic hydrazine hydrate anticipating to obtain 5-morpholinopyrazolo[3,4-*b*]pyrano[4,3-*d*]pyridine derivative **2**. However, the transamination occurred to displace morpholine and to afford 8-hydrazino analogue **3**† (see Scheme 1) whose structure was elucidated from ^{1}H NMR spectum which revealed the appearance of broad singlet for $NHNH_2$ moiety at 6.96 ppm and disappearance of signals for the morpholine ring.

Alkylation of compound **3** with alkyl halides in the presence of sodium carbonate occurred at thione group and produced sulfides



Scheme 1 *Reagents and conditions*: i, $N_2H_4 \cdot H_2O$, EtOH, reflux, 2 h; ii, RCH_2Hal, $Na_2CO_3/H_2O/EtOH$, room temperature, 10 h.

† *8-Hydrazino-3,3-dimethyl-6-thioxo-3,4,6,7-tetrahydro-1*H*-pyrano-[3,4-c]pyridine-5-carbonitrile* **3**. Compound **1** (3.05 g, 10 mmol) and hydrazine hydrate (4 ml, 80 mmol) were heated for 1 h, then ethanol (15 ml) was added, and reflux was continued for additional 1 h. The precipitate formed was filtered off and recrystallized from dioxane to afford yellow solid. Yield 83%, mp 278–279 °C. IR (ν/cm^{-1}): 3212–3259 (NH, NH_2), 2202 (CN), 1270 (C=S). ^{1}H NMR (300 MHz, DMSO-d_6/CCl_4, 1 : 3) δ: 1.20 (s, 6H, CMe_2), 2.50 (s, 2H, CH_2), 4.25 (s, 2H, CH_2), 6.96 (br. s, 3H, $NHNH_2$), 9.49 (br. s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6/CCl_4, 1 : 3) δ: 25.8, 37.6, 57.1, 69.5, 98.6, 102.3, 117.6, 148.4, 149.4, 171.7 (CS). Found (%): C, 52.93; H, 5.47; N, 22.56; S, 12.94. Calc. for $C_{11}H_{14}N_4OS$ (%): C, 52.78; H, 5.64; N, 22.38; S, 12.81.

4a–c.‡ Their IR spectra contained absorption bands at 3211–3347 cm^{-1} assigned to the NH, NH_2 groups, and strong absorption at 2203–2205 cm^{-1} for the C≡N one. In their ^1H NMR spectra, singlets at 3.93–4.02 ppm (SCH_2, **4b**,**c**) or at 2.60 ppm (SCH_3, **4a**) were detected. The regioselectivity of this reaction is explained by the greater polarizability of the sulfur atom as compared to the nitrogen one.

The heterocyclization of hydrazino derivative **3** with formic acid afforded triazolo[4,3-*a*]pyridine **5** (Scheme 2).§ Compound **5** exists as a thione tautomer. In its IR spectrum, the absorption bands characteristic of the C=S and NH groups appear at 1257 and 3113 cm^{-1}, respectively, and its ^{13}C NMR spectrum contains the C=S signal at 163.6 ppm. Alkylation of compound **5** occurs at the sulfur atom and comprises its thiol tautomer. In fact, alkylation with chloroacetic acid derivatives involves further heterocyclization between active methylene and nitrile groups to produce thiophene ring. As a result, compounds **6a–c** of novel pyrano[3,4-*c*]thieno-[3,2-*e*][1,2,4]triazolo[4,3-*a*]pyridine fused heterocyclic system were obtained in a one-pot procedure.¶ Their IR spectra contain bands characteristic of NH_2 groups at 3172–3431 cm^{-1}, while their ^1H NMR spectra manifest signals of NH_2 groups at 6.88–7.24 ppm.

In conclusion, we have developed an efficient synthesis of 8-hydrazino-6-thioxopyrano[3,4-*c*]pyridine derivative whose heterocyclizations with formic acid and chloroacetic acid derivatives open an access to novel promising pyrano[3,4-*c*]thieno[3,2-*e*]-[1,2,4]triazolo[4,3-*a*]pyridines.

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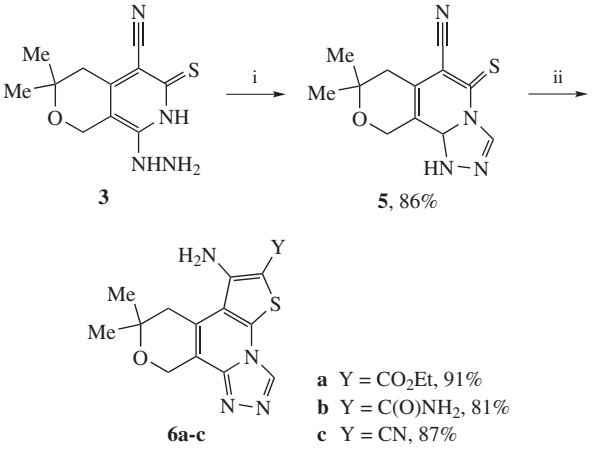

Scheme 2 *Reagents and conditions*: i, HCOOH, reflux, 0.5 h; ii, YCH_2Hal, AcONa, EtOH, reflux, 4 h.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2020.03.017.

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‡ *Compounds* **4a–c** *(general procedure)*. Thione **3** (5.0 g, 20 mmol) was added to a solution of sodium carbonate (2.12 g, 20 mmol) in a mixture of water (5 ml) and ethanol (50 ml). After full dissolution, the appropriate alkyl halide (20 mmol) was added with cooling, and the mixture was stirred at room temperature for 10 h. The obtained crystals were filtered off, washed with water, dried, and recrystallized from a 1 : 2 ethanol–dioxane mixture.

*8-Hydrazino-3,3-dimethyl-6-methylthio-3,4-dihydro-1*H*-pyrano[3,4-*c*]-pyridine-5-carbonitrile* **4a**. A white solid, yield 91%, mp 226–227 °C. IR (ν/cm^{-1}): 3211–3289 (NH, NH_2), 2203 (CN). ^1H NMR (300 MHz, DMSO-d_6/CCl_4, 1 : 3) δ: 1.24 (s, 6H, CMe_2), 2.54 (s, 2H, CH_2), 2.60 (s, 3H, SMe), 4.27 (br. s, 2H, NH_2), 4.32 (s, 2H, CH_2), 8.07 (br. s, 1H, NH). ^{13}C NMR (300 MHz, DMSO-d_6/CCl_4, 1 : 3) δ: 12.2, 25.7, 37.0, 57.6, 68.9, 93.1, 107.9, 115.4, 143.0, 154.8, 159.7. Found (%): C, 54.41; H, 6.27; N, 21.03; S, 12.25. Calc. for $C_{12}H_{16}N_4OS$ (%): C, 54.52; H, 6.10; N, 21.19; S, 12.13.

§ *8,8-Dimethyl-5-thioxo-1,7,8,10-tetrahydro-5*H*-pyrano[3,4-*c*][1,2,4]triazolo[4,3-*a*]pyridine-6-carbonitrile* **5**. A mixture of compound **3** (6.3 g, 25 mmol) and formic acid (60 ml) was refluxed for 0.5 h. The solid formed was filtered off, washed with water, dried, and recrystallized (chloroform–ethanol, 2 : 1) to afford yellow solid. Yield 86%, mp 274–275 °C. IR (ν/cm^{-1}): 3113 (NH), 2221 (CN), 1257 (C=S). ^1H NMR (300 MHz, DMSO-d_6) δ: 1.29 (s, 6H, CMe_2), 2.69 (s, 2H, CH_2), 4.70 (s, 2H, CH_2), 9.56 (s, 1H, CH), 11.73 (br. s, 1H, NH). ^{13}C NMR (300 MHz, DMSO) δ: 25.9, 37.2, 57.3, 70.4, 102.5, 103.0, 117.4, 137.3, 141.3, 142.1, 163.6 (CS). Found (%): C, 55.25; H, 4.78; N, 21.39; S, 12.18. Calc. for $C_{12}H_{12}N_4OS$ (%): C, 55.37; H, 4.65; N, 21.52; S, 12.32.

¶ *Compounds* **6a–c** *(general procedure)*. A mixture of thioxo nitrile **5** (0.52 g, 2 mmol) and appropriate chloroacetic acid derivative (2 mmol) was refluxed in ethanol (15 ml) in the presence of anhydrous NaOAc (0.66 g, 8 mmol) for 4 h. The precipitate formed was filtered off, washed with water, dried, and recrystallized (ethanol–chloroform, 1 : 3).

*Ethyl 7-amino-9,9-dimethyl-8,11-dihydro-9*H*-pyrano[3,4-*c*]thieno-[3,2-*e*][1,2,4]triazolo[4,3-*a*]pyridine-6-carboxylate* **6a**. A white solid, yield 91%, mp 299–300 °C. IR (ν/cm^{-1}): 3325, 3431 (NH_2), 1664 (C=O). ^1H NMR (300 MHz, DMSO-d_6/CCl_4, 1 : 3) δ: 1.35 (s, 6H, CMe_2), 1.38 (t, 3H, OCH_2Me, J 7.1 Hz), 3.09 (s, 2H, CH_2), 4.30 (q, 2H, OCH_2Me, J 7.1 Hz), 4.95 (s, 2H, CH_2), 6.72 (s, 2H, NH_2), 9.24 (s, 1H, CH). ^{13}C NMR (300 MHz, DMSO-d_6/CCl_4, 1 : 3) δ: 14.1, 26.0, 35.4, 58.3, 59.5, 69.3, 92.0, 115.9, 117.7, 129.2, 134.3, 145.4, 151.0, 163.6. Found (%): C, 55.34; H, 5.36; N, 16.02; S, 9.13. Calc. for $C_{16}H_{18}N_4O_3S$ (%): C, 55.48; H, 5.24; N, 16.17; S, 9.26.