Synthesis of Pyrano[4,3-d]pyrimidine Derivative and Its Behaviour towards Nitrogen Nucleophiles and Active Methylenes

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Pyrano[4,3-d]pyrimidine derivative **3** was prepared by reaction of chlorocarbonyl isocyanate **1** with enaminonitrile **2**.

Compound **3** reacted with nitrogen nucleophiles **4a-f** to afford 2-substituted pyrido[4,3d]pyrimidine **5-8**, pyrimido[i]1,5a-diaza-9-oxafluorene **9** and pyrimido[i]5a-aza-9-thiafluorene **10** derivatives. Also, compound **3** reacted with active methylene compounds **4j** to yield pyrimidine derivatives **14-16** which on reaction with EtONa **4k** afforded 1,5,7-triaza-10-oxaphenanthrene derivatives **17-19**.

Keywords: Enaminonitrile; Pyrano[4,3-d]pyrimidine; Pyrido[4,3-d]pyrimidine; 1,5,7-triaza-10-oxaphenanthrene derivatives.

INTRODUCTION

The derivatives of pyrano[4,3-d]pyrimidines have been reported to display biological activities, especially antipyretic, anti-inflammatory and gastroprotective.[1]

Synthesis of pyrano[4,3-d]pyrimidine[1-3] and pyrido-[4,3-d]pyrimidine[4-8] derivatives have been reported.

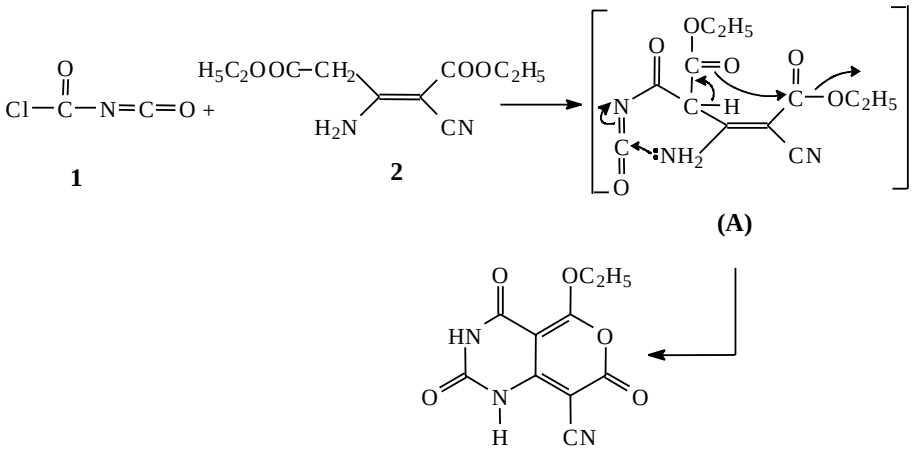
Chlorocarbonyl isocyanate **1** was used in the synthesis of new types of heterocyclic compounds.[9,10] The dimer of ethylcyanoactate **2** reacted with nitrile imines to yield pyranopyrazole derivatives.[11]

RESULTS AND DISCUSSION

Chlorocarbonyl isocyanate **1** reacted with the dimer of ethylcyanoacetate **2** to yield 1-ethoxy-4-cyano-3,6,8-trioxo-pyrano[4,3-d]pyrimidine **3** through cyclization of the intermediate **A**.

A similar mechanism has been recently suggested for the reaction of chlorocarbonyl isocyanate with active methylene nitriles.[10] The IR spectrum of the cyclization product **3** in which its structure is in agreement with its spectral data (Scheme I, cf experimental) still exhibits a characteristic

Scheme I



1 **2** **3**

prominent nitrile absorption at 2215 cm^{-1}, therefore ruling out cyclization with the nitrile.

The behaviour of compound **3** towards N-nucleophiles **4a-f** was studied. Thus, compound **3** reacted with hydroxylamine hydrochloride **4a** in boiling pyridine affording 2-substituted pyrido[4,3-d]pyrimidine derivative **5** through hetero ring opening followed by ring closure (intermediate **B**).

Similarly, compound **3** reacted with formamide **4b** resulted in the ring transformation to afford pyrido[4,3-d]pyrimidine derivative **6**. Compound **3** reacted with semicarbazide **4c** in boiling pyridine affording 2-substituted pyrido-[4,3-d]pyrimidine **7** which on reaction with diethylmalonate **4g** resulted in the formation of 2,4,6-trioxopyrimidinyl-[1′:2]pyrido[4,3-d]pyrimidine derevative **11**. While on reaction of 3 with hydrazine hydrate afforded 2-amino pyrido-[4,3-d]pyrimidine **8** which reacted with benzaldehyde **4h** in ethanol to afford compound **12** which in its turn cyclized with thioglycolic acid **4i** resulted in the formation of 2-thiazolo-[3′:2]pyrido[4,3-d]pyrimidine derivative **13**.

Compound **3** reacted with 2-hydroxy 3-amino pyridine **4e** in the presence of sodium acetate and glacial acetic acid to afford pyrimido[i]1,5a-diaza-9-oxafluorene derivative **9** through ring opening and ring closure followed by elimination of water (intermediate **C**).

Similarly, compound **3** reacted with 0-aminothiophenole **4f** to afford pyrimido[i]5a-aza-9-thiafluorene derivative **10**. The prepared compounds are in agreement with their spectral data (Scheme II, cf experimental).

On the other hand compound **3** was subjected to react with active methylene reagents **4j** to yield pyrimidine derivatives **14-16** in their enolic form without further cyclization under the reaction conditions which cyclized when refluxed in ethanol/benzene containing sodium ethoxide **4k** to afford 1,5,7-triaza-10 oxaphenanthrene derivatives **17-19**. The IR spectrum of the cyclization products **17**, **18** proved the absence of nitrile absorption, therefore, ruling in cyclization with nitrile. The ^{1}H NMR spectra of cyclization products **17-19** revealed an enol hydrogen at 13.63 ppm as a broad signal (Scheme III, cf experimental). The purity of the prepared compounds were measured using thin layer chromatography TLC.

EXPERIMENTAL

Preparation of 1-ethoxy-4-cyano-3,6,8-trioxopyrano-[4,3-d]pyrimidine 3

To a stirred solution of the dimer of ethylcyanoacetate (0.01 mole) **2** in methylene chloride (50 mL) containing three drops of triethylamine at 0 °C was added Chlorocarbonyl isocyanate **1** (0.01 mole). The reaction mixture was stirred for 1 h at room temperature. The solution was left to stand overnight at room temperature. The solid was collected by filtration and crystallized from ethanol.

3: 2.21 g (89%); m.p. > 300; IP (KBr) ν_{max}/cm^{-1}: 1720 (CO), 2215 (CN), 3350 (NH); ^{1}H NMR (200 MHz, DMSO-d_6) δ/ppm: 8.3 (br, s, H, NH) D_2O exchangeable, 1.2 (t, 3H, *J* = 8, CH_3), 4.3 (q, 2H, *J* = 6, CH_2); MS *m/z*: 249 (M^+, 77%).

Anal. Calcd. for $C_{10}H_7N_3O_5$ (M_r = 249.1813): C, 48.20; H, 2.83; N, 16.86%, found: C, 48.14; H, 2.77; N, 16.78%.

Preparation of 2-substituted-2,3,5,8-tetraoxo-7-cyano-pyrido[4,3-d]pyrimidine 5-8, pyrimidino[i]1,5a-diaza-9-oxafluorene 9 and pyrimido[i]5a-aza-9-thiafluorene 10; general procedures

A mixture of **3** (0.01 mole) and N-nucleophile **4a-f** (0.01 mole) was refluxed in (pyridine for **5-7**, ethanol for **8**, freshly fused sodium acetate 0.49 g in glacial acetic acid 40 mL for **9**, **10**) for 3 h. the reaction mixture was cooled and the solid product was collected by filtration and crystallized from ethanol.

5: 1.959 g (83%); m.p. 320; IR (KBr) ν_{max}/cm^{-1}: 1725 (CO), 2215 (CN), 3350 (NH); ^{1}H NMR (200 MHz, DMSO-d_6) δ/ppm: 8.3 (br, s, H, NH) D_2O exchangeable, 6.7 (s, 1H, OH), 9.2 (s, 1H, 8a-H); MS *m/z*: 236 (M^+, 44%).

Anal. Calc. for $C_8H_4N_4O_5$ (M_r = 236.1426): C, 40.69; H, 1.70; N, 23.72%, found: C, 40.61; H, 1.63; N, 23.65%.

6: 1.69 g (77%); m.p > 300; IR (KB_r) ν_{max}/cm^{-1}: 1725 (CO), 2215 (CN), 3350 (NH); ^{1}H NMR (200 MHz, DMSO-d_6) δ/ppm: 8.3 (br, s, H, NH), 9.2 (s, 1H, 8a-H); MS *m/z*: 220 (M^+, 38%).

Anal. Calc. for $C_8H_4N_4O_4$ (M_r = 220.1436): C, 43.64; H, 1.83; N, 25.45%, found: C, 43.56; H, 1.85; N, 25.38%.

7: 2.19 g (79%); m.p. 315; IR (KBr) ν_{max}/cm^{-1}: 1728 (CO), 2215 (CN), 3350 (NH), 3245 (NH_2); ^{1}H NMR (200 MHz, DMSO-d_6) δ/ppm: 8.3 (br, s, H, NH), 9.2 (s, 1H, 8a-H), 6.3 (s, 2H, NH_2); MS *m/z*: 278 (M^+, 47%).

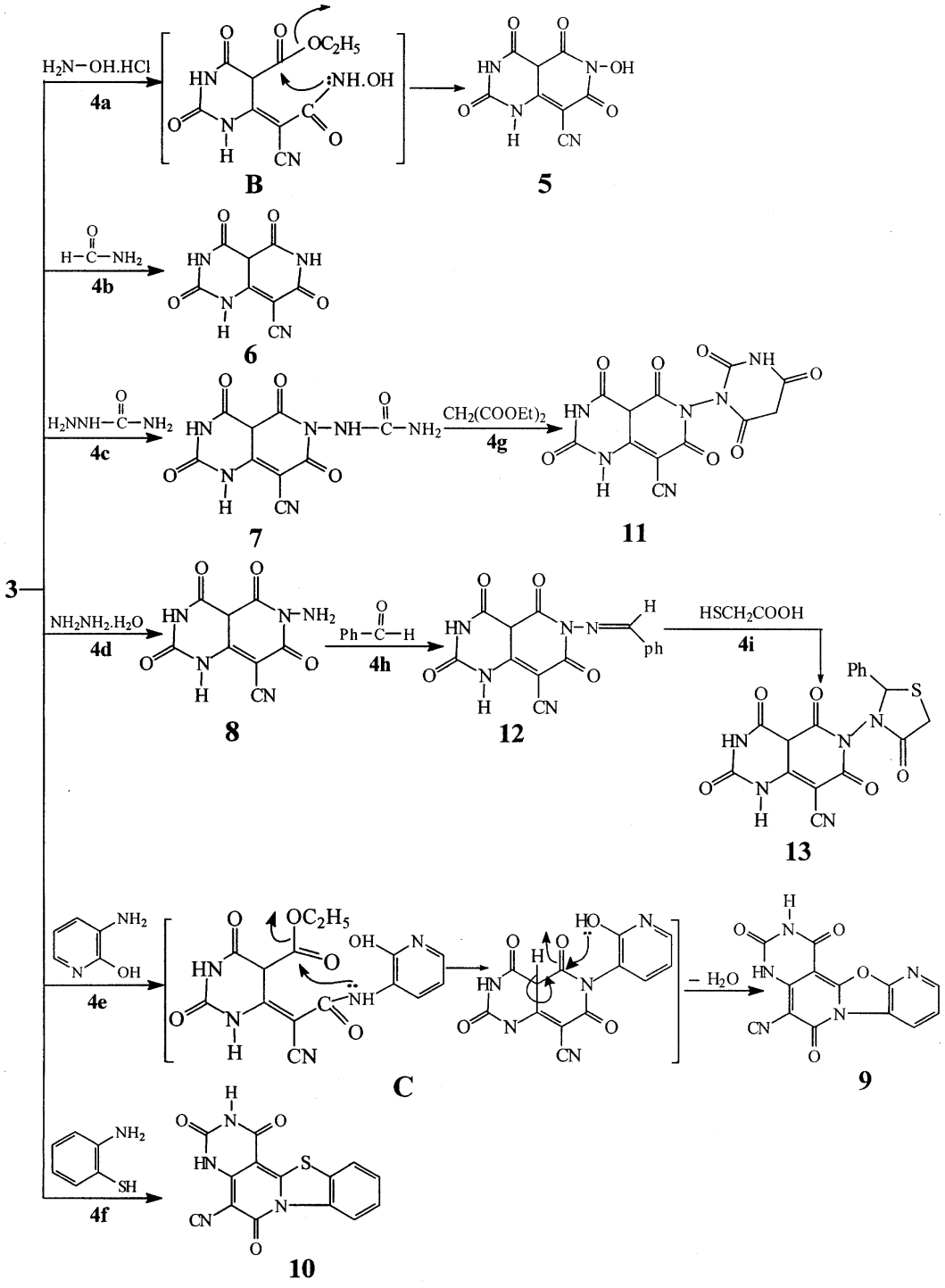
Anal. Calc. for $C_9H_6N_6O_5$ (M_r = 278.1834): C, 38.85; H, 2.17; N, 30.21%, found: C, 38.78; H, 2.09; N, 30.14%.

8: 1.78 g (76%); m.p. > 300; IR (KBr) ν_{max}/cm^{-1}: 1725 (CO), 2215 (CN), 3240 (NH_2), 3350 (NH); ^{1}H NMR (200 MHz, DMSO-d_6) δ/ppm: 8.3 (br, s, H, NH), 5.4 (s, 2H, NH_2), 9.2 (s, 1H, 8a-H); MS *m/z*: 235 (M^+, 22%).

Anal. Calc. for $C_8H_5N_5O_4$ (M_r = 235.1585): C, 40.86; H, 2.14; N, 29.78%, found: C, 40.81; H, 2.07; N, 29.69%.

9: 2.15 g (73%); m.p. 276; IR (KBr) ν_{max}/cm^{-1}: 1720 (CO), 2215 (CN), 3350 (NH), ^{1}H NMR (200 MHz, DMSO-

Scheme II

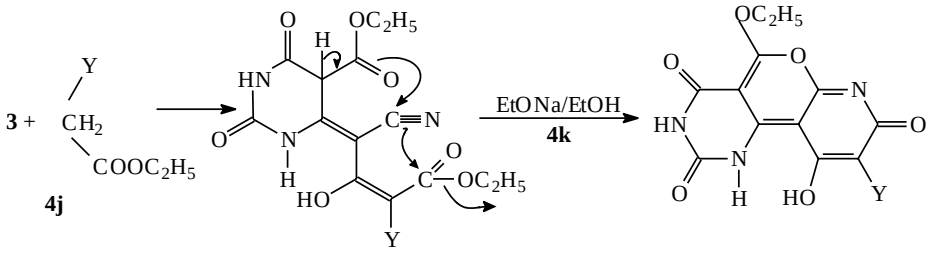


d_6) δ/ppm: 8.3 (br, s, H, NH); 8.36 (d, *J* = 8.2, 1H, H-2), 7.25 (t, *J* = 7.2 , 1H, H-3), 8.15 (d, *J* = 7.70, 1H, H-4); MS *m/z*: 295 (M^+, 64%).

Anal. Calc. for $C_{13}H_5N_5O_4$ (M_r = 295.2135): C, 52.89; H, 1.70; N, 23.72%, found: C, 52.82; H, 1.63; N, 23.64%.

10: 2.109 g (68%); m.p. 261; IR (KBr) ν_{max}/cm^{-1}: 1720 (CO), 2215 (CN), 3350 (NH), ^{1}H NMR (200 MHz, DMSO-d_6) δ/ppm: 8.3 (br, s, H, NH); 7.40 (d, *J* = 7.6, 1H, H-1), 7.42 (t, *J* = 7.40, 1H, H-2), 7.64 (t, *J* = 7.55, 1H, H-3), 7.95 (d, *J* = 7.75, 1H, H-4); MS *m/z*: 310 (M^+, 44%).

Scheme III



14, y = $COOC_2H_5$
15, y = $COCH_3$
16, y = CN

17, y = $COOC_2H_5$
18, y = $COCH_3$
19, y = CN

Anal. Calc. for $C_{14}H_6N_4O_3S$ (M_r = 310.2924): C, 54.19; H, 1.94; N, 18.05%, found: C, 54.11; H, 1.87; N, 18.00%.

Preparation of 2-substituted-2,3,5,8-tetraoxo-7-cyano-pyrido[4,3-d]pyrimidine 11

Compound **7** (0.01 mole) and diethylmalonate **4g** (0.01 mole) were refluxed in ethanol/piperidine solution (2:1) for 3 h. The mixture was cooled, was 100 mL water poured in, then it was filtered, washed and crystallized from ethanol.

11: 2.80 g (81%); m.p. > 300; IR (KBr) ν_{max}/cm^{-1}: 1730 (CO), 2215 (CN), 3350 (NH); ^{1}H NMR (200 MHz, DMSO-d_6) δ/ppm: 8.3 (br, s, H, NH), 9.2 (s, 1H, 8a-H), 11.4 (s, 2H, CH_2); MS *m/z*: 346 (M^+, 29%).

Anal. Calc. for $C_{12}H_6N_6O_7$ (M_r = 346.2144): C, 41.63; H, 1.74; N, 24.27%, found: C, 41.56; H, 1.67; N, 24.19%.

Preparation of 2-substituted-2,3,5,8-tetraoxo-7-cyano-pyrido[4,3-d]pyrimidine 12

Compound **8** (0.01 mole) and benzaldehyde **4h** (0.01 mole) were refluxed in ethanol 50 (mL) for 3 h. The mixture was cooled, filtered and crystallized from ethanol.

12: 1.77 g (55 %); m.p. 293; IR (KBr) ν_{max}/cm^{-1}: 1725 (CO), 2215 (CN), 3350 (NH), 1610 (C=N), 1650 (Ph), ^{1}H NMR (200 MHz, DMSO-d_6) δ/ppm: 8.3 (br, s, H, NH); 9.2 (s, 1H, 8a-H), 8.4 (s, 1H, methine-H), 7.96-8.15 (m, 5H, Ph); MS *m/z*: 323 (M^+, 57%).

Anal. Calc. for $C_{15}H_9N_5O_4$ (M_r = 323.2671): C, 55.73; H, 2.80; N, 21.66%, found: C, 55.66; H, 2.73; N, 21.57%.

Preparation of 2-substituted-2,3,5,8-tetraoxo-7-cyano-pyrido[4,3-d]pyrimidine 13

Compound **12** (0.01 mole) and thioglycolic acid **4i** (0.01 mole) were refluxed in benzene (70 mL) for 3 h. The mixture was cooled, filtered and crystallized from ethanol.

13: 2.62 g (66%); m.p. 284; IR (KBr) ν_{max}/cm^{-1}: 1730 (CO), 2215 (CN), 3350 (NH), ^{1}H NMR (200 MHz, DMSO-d_6) δ/ppm: 9.2 (s, 1H, 8a-H,), 3.35 (s, 2H, CH_2), 4.75 (s, 1H, CHPh), 8.02-8.23 (m, 5H, ph), 8.3 (br, s, H, NH); MS *m/z*: 397 (M^+, 32%).

Anal. Calc. for $C_{17}H_{11}N_5O_5S$ (M_r = 397.3699): C, 51.38; H, 2.79; N, 17.62%, found: C, 51.31; H, 2.68; N, 17.54%.

Preparation of pyrimidine derivatives 14-16; general procedure[12]

Potassium *tert*-butoxide (2.24 g, 0.02 mol) was stirred in *tert* butyl alcohol (100 mL) at room temperature for 20 min. after which the active methylene compound **4j** was added dropwise to the mixture. Stirring was continued for 1 h after which compound **3** (0.01 mol) was added to the mixture and stirring continued at room temperature for 1 h. Water and diethyl ether were added to the reaction mixture and the aqueous layer was separated and acidified with 10% hydrochloric acid. The solid product was filtered off, washed with water and crystallized from ethanol.

14: 2.36 g (58%); m.p. 195; IR (KBr) ν_{max}/cm^{-1}: 1725, 1710 (CO-ester, ketoform), 3350 (NH), 2215 (CN), 1605 (C=C); ^{1}H NMR (200 MHz, DMSO-d_6) δ/ppm: 8.3 (br, s, H, NH); 13.63 (br, 1H, OH), 9.4 (s, 1H, H-5), 4.48 (q, 2H, J = 8, CH_2CH_3), 1.24 (t, 3H, J = 6, CH_2CH_3); MS *m/z*: 408 (M^+, 16%).

Anal. Calc. for $C_{17}H_{18}N_3O_9$ (M_r = 408.3412): C, 50.00; H, 4.44; N, 10.29%, found: C, 49.92; H, 4.33; N, 10.21%.

15: 2.57 g (68%); m.p. 223; IR (KBr) ν_{max}/cm^{-1}: 1725, 1710 (CO-ester, ketoform), 3350 (NH), 2215 (CN), 1605 (C=C); ^{1}H NMR (200 MHz, DMSO-d_6) δ/ppm: 2.76 (s, 3H, $COCH_3$), 8.3 (br, s, H, NH); 13.63 (br, 1H, OH), 9.4 (s, 1H, H-5), 4.48 (q, 2H, J = 8, CH_2CH_3), 1.24 (t, 3H, J = 6, CH_2CH_3); MS *m/z*: 378 (M^+, 46%).

Anal. Calc. for $C_{16}H_{16}N_3O_8$ (M_r = 378.3154): C, 50.79;

H, 4.26; N, 11.10%, found: C, 50.70; H, 4.19; N, 11.02%.

16: 2.74 g (76%); m.p. 241; IR (KBr) ν_{max}/cm^{-1}: 1725, 1710 (CO-ester, ketoform), 3350 (NH), 2225 (CN), 1605 (C=C); ^{1}H NMR (200 MH_2, DMSO-d_6) δ/ppm: 8.3 (br, s, H, NH); 13.63 (br, 1H, OH), 9.4 (s, 1H, H5), 4.48 (q, 2H, *J* = 8, CH_2CH_3), 1.24 (t, 3H, *J* = 6, CH_2CH_3); MS *m/z*: 361 (M^+, 27%).

Anal. Calc. for $C_{15}H_{13}N_4O_7$ (M_r = 361.2887): C, 49.86; H, 3.62; N, 15.50%, found: C, 49.79; H, 3.55; N, 15.43%.

Preparation of 1,5,7-triaza-10-oxaphenanthrene derivatives 17-19; general procedure

Compound **14-16** was refluxed in ethanol/benzene containing sodium ethoxide (2 equiv.) for 3 h. The solid product was filtered, washed with water and crystallized from ethanol.

17: 2.90 g (80%); m.p. 215; IR (KBr) ν_{max}/cm^{-1}: 1720 (CO), 3350 (NH), 1725, 1710 (CO ester, ketoform); ^{1}H NMR (200 MHz, DMSO-d_6) δ/ppm: 8.2 (br, s, H, NH); 13.63 (br, 1H, OH), 4.48 (q, 2H, *J* = 8, $COOCH_2CH_3$), 1.24 (t, 3H, *J* = 6, $COOCH_2CH_3$), 4.3 (q, *J* = 6, 2H, OCH_2CH_3), 1.2 (t, *J* = 8, 3H, OCH_2CH_3); MS *m/z*: 363 (M^+, 49%).

Anal. Calc. for $C_{15}H_{13}N_3O_8$ (M_r = 363.2807): C, 49.59; H, 3.60; N, 11.56%, found: C, 49.48; H, 3.51; N, 11.47%.

18: 2.56 g (77%); m.p. 236; IR (KBr) ν_{max}/cm^{-1}: 1720 (CO), 3350 (NH), 1710 (ketoform); ^{1}H NMR (200 MHz, DMSO-d_6) δ/ppm: 8.2 (br, s, H, NH); 13.63 (br, 1H, OH), 4.3 (q, *J* = 6, 2H, OCH_2CH_3), 2.76 (s, 3H, $COCH_3$), 1.2 (t, *J* = 8, 3H, OCH_2CH_3); MS *m/z*: 333 (M^+, 56%).

Anal. Calc. for $C_{14}H_{11}N_3O_7$ (M_r = 333.2549): C, 50.45; H, 3.32; N, 12.60%, found: C, 50.39; H, 3.24; N, 12.54%.

19: 2.62 g (83%); m.p. 247; IR (KBr) ν_{max}/cm^{-1}: 1720 (CO), 3350 (NH), 2215 (CN), 1710 (ketoform); ^{1}H NMR (200 MHz, DMSO-d_6) δ/ppm: 8.2 (br, s, H, NH); 13.63 (br, 1H, OH), 4.3 (q, *J* = 6, 2H, OCH_2CH_3), 1.2 (t, *J* = 8, 3H, OCH_2CH_3); MS *m/z*: 316 (M^+, 56%).

Anal. Calc. for $C_{13}H_8N_4O_6$ (M_r = 316.4802): C, 49.33; H, 2.54; N, 17.70%, found: C, 49.25; H, 2.48; N, 17.62%.

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