HETEROCYCLES, Vol. 71, No. 11, 2007, pp. 2449 - 2456. © The Japan Institute of Heterocyclic Chemistry
Received, 17th June, 2007, Accepted, 25th July, 2007, Published online, 3rd August, 2007. COM-07-11142

SYNTHESIS OF *AZA*-ANALOG OF *N*-METHYLATED ACYCLOFORMYCIN A [1]

Mariusz Mojzych* and Andrzej Rykowski

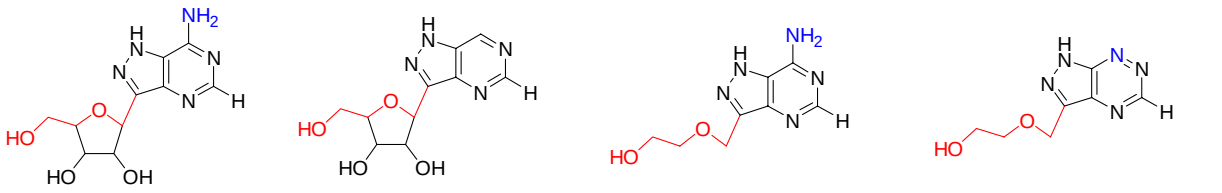
Department of Chemistry, University of Podlasie, 08-110 Siedlce, Poland

*corresponding author, e-mail: mmojzych@yahoo.com

Abstract – Starting from 3-methyl-5-methylsulfanyl-1*H*-pyrazolo[4,3-*e*][1,2,4]-triazine (**1**) by reaction with methyl iodide, subsequent oxidation, *ipso*-substitution with hydrazine and reaction with yellow mercury (II) oxide 1,3-dimethyl-1*H*-pyrazolo[4,3-*e*][1,2,4]triazine (**14**) is prepared. Further radical bromination and treatment with ethylene glycol in the presence of potassium carbonate afforded 3-(2-hydroxy-ethoxymethyl)-1-methyl-1*H*-pyrazolo[4,3-*e*]-[1,2,4]triazine (**16**) as *aza*-analog of *N*-methylated acycloformycin A.

The naturally occurring *C*-nucleoside formycin A exhibits antitumour, antiviral, and antibacterial activities.[2,3] Its analogues (Figure 1) in which either modified base is linked to the D-ribose, or the sugar itself is altered, are interesting synthetic targets in view of their possible biological activity.[4-7] For example, deaminoformycin A (Figure 1) is a good herbicide and its corresponding 5'-monophosphate is a strong inhibitor of adenosine 5'-monophosphate deaminase (AMPDA).[8]

Figure 1

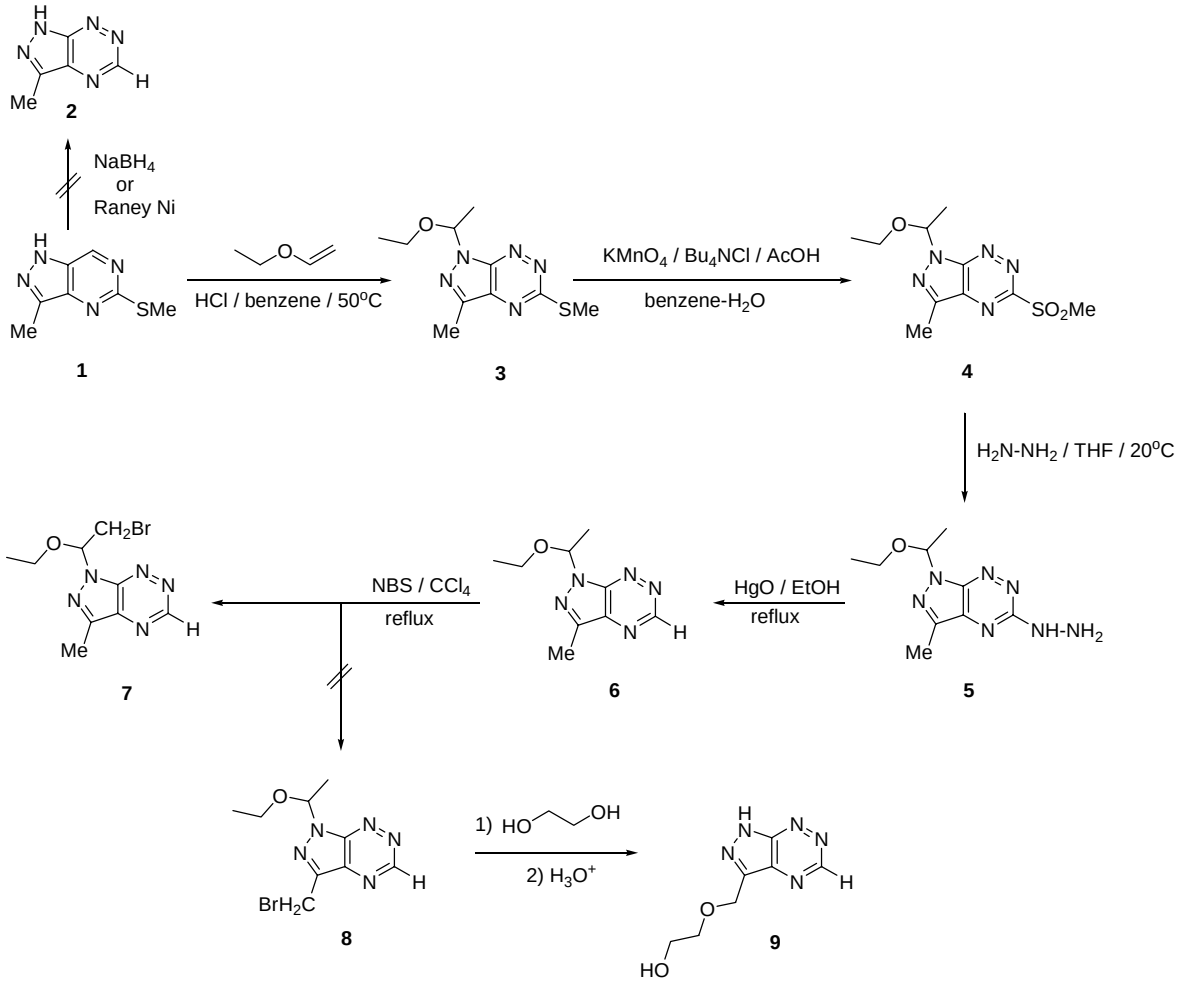


formycin A deaminoformycin A acycloformycin A *aza*-analog of acycloformycin A

In an effort to produce more strongly inhibiting *C*-nucleosides we have now synthesized a

new *aza*-analog of acycloformycin A (Figure 1). This system, *e.g*. pyrazolo[4,3-*e*][1,2,4]triazine is structurally related to acycloformycin A aglycone, in which amino group in the pyrimidine part is replaced by ring nitrogen. Earlier, we reported the synthesis of 1*H*-pyrazolo[4,3-*e*][1,2,4]triazines by one-pot reaction between 5-acyl-1,2,4-triazines and various hydrazine derivatives under acidic conditions.[9-12] Based on our previous results we have elaborated a route to *aza*-analog of acycloformycin. A key feature of this strategy is outlined in Scheme 1.

Scheme 1



The common intermediate, 3-methyl-5-methylsulfanyl-1*H*-pyrazolo[4,3-*e*][1,2,4]triazine (**1**) has been readily prepared using literature procedure from easily available 5-acetyl-3-methylsulfanyl-1,2,4-triazine and hydrazine hydrochloride, followed by acid-promoted ring closure of the resulting intermediate.[13,14] Desulfurization of sulfide **1** with sodium borohydride or Raney nickel to give the parent heterocycle **2**, failed. With the failure of reductive desulfurization we turned to the hydrazine-oxidation method which has been used in the removal of methylsulfanyl group from 1,2,4-triazine.[10] However, N^1-

unsubstituted pyrazolotriazine (**1**) appeared to be unreactive and attempts to perform nucleophilic displacement of methylsulfanyl group with hydrazine afforded only unreactive starting material. In searching for more effective nucleofugal group, the protected sulfide **3** was converted into its sulfone **4**. Reaction of 1*H*-pyrazolo[4,3-*e*][1,2,4]triazine **1** with ethyl vinyl ether (a new protecting group for *NH*-pyrazoles[15,16]) in benzene at 40 °C in the presence of catalytic amount of concentrated hydrochloric acid gave the protected intermediate **3** in excellent yield. The latter was isolated by chromatography and treated with potassium permanganate (VII) under phase transfer catalytic conditions at rt for 1 h to give sulfone **4** almost quantitatively. Compound **4** was next reacted with anhydrous hydrazine in THF to provide the corresponding hydrazine derivative **5** in 90% yield. Oxidation of hydrazine **5** with yellow mercury (II) oxide in refluxing ethanol gave the 3-unsubstituted pyrazolotriazine **6** as yellow oil. Reaction of the protected intermediate **6** with *N*-bromosuccinimide in carbon tetrachloride under reflux furnished unwanted derivative **7** instead of expected compound **8**, as is outlined in Scheme 1.

The correct structure of the isolated pyrazolotriazine **7** was supported by high-resolution mass spectroscopy and nmr spectroscopic data. In the ^{1}H nmr spectra of compound **7** the singlet signal corresponding to the pyrazole methyl group was present at δ = 2.73. Also, the ^{1}H nmr spectra of **7** showed that proton at tertiary carbon appeared as a multiplet at δ = 6.33-6.40, while the same proton in **6** was observed as a quartet. This evidence establishes the reaction route **6** → **7**, and rules out the formation of compound **8** as expected precursor of **9**.

The results described above and the failure in the synthesis of **9** as *aza*-analog of acycloformycin A clearly showed that the bromination of methyl group adjacent to the pyrazole ring is possible in the presence of relevant protecting group for *NH*-pyrazole fragment; it could be achieved only when protecting group is resistant to bromination.

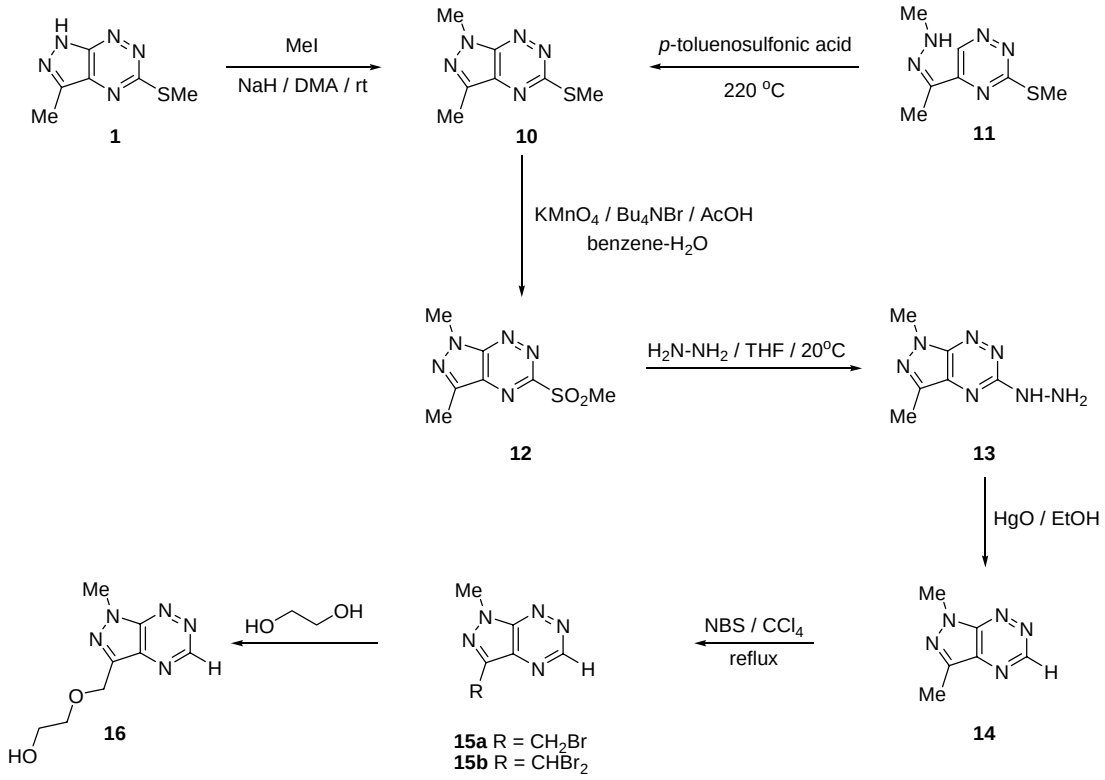
Continuing our study on the intended synthesis of the *aza*-analog of acycloformycin A and bearing in mind that last time we proposed easy approach to the synthesis of *N*-alkyl derivatives of *1H*-pyrazolo[4,3-*e*][1,2,4]triazine ring system,[14] we decided to exploit N_1-methyl derivative (**10**) of this system to realize our target (Scheme 2). Thus, unsubstituted pyrazolotriazine (**1**) was smoothly converted into the corresponding structure **10** upon the reaction with methyl iodide in the presence of sodium hydride in DMA at rt. Additionally, compound **10** can be also prepared, by the second way, by heating the methylhydrazone of 5-acetyl-1,2,4-triazine (**11)** over its melting point (220 °C) in

the presence of *p*-toluenosulfonic acid, according to previously published procedure.[12,14]

Based on described above method for replacement of thiomethyl group by hydrogen using (i) phase transfer catalytic oxidation, (ii) *ipso*-substitution of methylsulfonyl group with hydrazine and (iii) reaction with yellow mercury (II) oxide, 5-unsubstituted pyrazolotriazine **14** was obtained in good yield. Further reaction of **14** with NBS in the presence of catalytic amount of dibenzoylperoxide in carbon tetrachloride under reflux gave the bromomethyl compound **15a** (25% yield) and dibrominated derivative **15b** (20% yield). The conversion of **15a** into the N_1-methylated *aza*-analog of acyclopurine nucleoside **16** could be achieved by reaction with ethylene glycol in acetone in the presence of potassium iodide and potassium carbonate, as illustrated in Scheme 2.

Structures of compounds **15a**,**b** and **16** were confirmed by analytical and spectral data (See experimental).

Scheme 2



In summary, we have obtained *aza*-analog of *N*-methylated acycloformycin A where nitrogen atom N-1 of the triazine ring plays a role amino group being a structural fragment of formycin A. Further studies on *O*-phosphitylation of this formycin analog are in progress.[17]

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. ^{1}H nmr spectra were recorded on a Varian Gemini 200MHz spectrometer using tetramethylsilane as the internal standard. The ir spectra were measured with a Magna IR-760 spectrophotometer in KBr pellets. Mass spectra were measured on AMD 604 spectrometer (electron impact, 70eV). Elemental analyses were obtained on Perkin-Elmer 2400-CHN analyzer and the results for the indicated elements were within 0.3 % of the calculated values. Compounds **1**, **10** and **11** were synthesized according to literature procedure.[14]

Synthesis of 1-(1-ethoxyethyl)-3-methyl-5-methylsulfanyl-1*H*-pyrazolo[4,3-*e*][1,2,4]triazine (3)

To a solution of **1** (1.81 g, 10 mmol) in benzene (140 mL) 2-ethoxyethene (2 mL, 20 mmol) and concentrated HCl (0.2 mL) were added and the resulting reaction mixture was stirred at 40 ^{o}C for 8 h. Then a saturated aqueous solution of $NaHCO_3$ was added to the reaction mixture. The benzene layer was separated, dried over $MgSO_4$, filtered through celite, and concentrated in *vacuo*. The final product **3** was purified by column chromatography using silica gel and $CHCl_3$ as eluent to afford 2.27 g (9 mmol, 90%) of the title compound. mp 51 ^{o}C; ^{1}H nmr ($CDCl_3$) δ: 1.14 (t, 3H, *J* = 7.0 Hz), 1.92 (d, 3H, *J* = 6.0 Hz), 2.65 (s, 3H), 2.74 (s, 3H), 3.19-3.34 (m, 1H), 3.49-3.64 (m, 1H), 6.30 (q, 1H, *J* = 6.0 Hz); HRMS (*m/z*) for $C_{10}H_{15}N_5OSNa$: 276.0910 [M^+Na]; Calcd. 276.0890. *Anal*. Calcd for $C_{18}H_{15}N_5$: C, 71.76; H, 5.02; N, 23.25. Found: C, 71.87; H, 4.98; N, 23.11.

1-(1-Ethoxyethyl)-3-methyl-5-methylsulfonyl-1*H*-pyrazolo[4,3-*e*][1,2,4]triazine (4)

To a solution of **3** (253 mg, 1 mmol) in benzene (20 mL) water (30 mL), potassium manganate (VII) (44 mg, 3 mmol), catalitic amounts of tetrabuthylammonium bromide (65 mg, 0.2 mmol) and AcOH (1.5 mL) were added. The reaction mixture was stirred at rt for 1h. A saturated solution of $Na_2S_2O_5$ in water was then added to the mixture until the purple color disappeared. The organic layer was separated and the aqueos phase was extracted with benzene (3x10 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromathography on silica gel (eluent : $CHCl_3$) to afford 270 mg (95%) of **4** as a yellowish oil. ^{1}H nmr ($CDCl_3$) δ: 1.17 (t, 3H, *J* = 7.0 Hz), 1.98 (d, 3H, *J* = 6.0 Hz), 2.79 (s, 3H), 3.20-3.35 (m, 1H), 3.52-3.68 (m, 1H), 3.58 (s, 3H), 6.43 (q, 1H, *J* = 6.0 Hz); IR (KBr) cm^{-1}: 2980, 1330, 1140; HRMS (*m/z*) for $C_{10}H_{15}N_5O_3SNa$: 308.0780 [M^+Na]; Calcd. 308.0788.

1-(1-Ethoxyethyl)-3-methyl-5-hydrazino-1*H*-pyrazolo[4,3-*e*][1,2,4]triazine (5)

To the solution of **4** (285 mg, 1 mmol) in dry THF (10 mL) cooled to 0-5 ^{o}C, anhydrous hydrazine (0.1 mL, 3 mmol) was added. The reaction mixture was stirred at 0-5 ^{o}C for 30 min and an additional 5h at rt. After that time the solvent was evaporated *in vacuo* and the crude product was recrystallized from EtOH to give 213 mg (90%) of **5** as an orange solid. mp 120-123 ^{o}C; ^{1}H nmr ($CDCl_3$) δ: 1.14 (t, 3H, *J* = 7.0 Hz), 1.91 (d, 3H, *J* = 6.0 Hz), 2.55 (s, 3H), 3.21-3.36 (m, 1H), 3.48-3.63 (m, 1H), 6.22 (q, 1H, *J* = 6.0 Hz), 6.84 (s, 1H); HRMS (*m/z*) for $C_9H_{15}N_7ONa$: 260.1226 [M^+Na]; Calcd. 260.1230.

1-(1-Ethoxyethyl)-3-methyl-1*H*-pyrazolo[4,3-*e*][1,2,4]triazine (6)

To the solution of compound **5** (237 mg, 1mmol) in dry EtOH (20 mL) yellow mercury oxide (II) (1.08 g, 5 mmol) was added and the mixture was heated at 40 ^{o}C for 0.5 h. After that time the reaction mixture was filtered off and the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (silica gel, eluent: $CHCl_3$) to give 124 mg (60%) of **6** as a yellow oil. ^{1}H nmr ($CDCl_3$) δ: 1.14 (t, 3H, *J* = 7.0 Hz), 1.93 (d, 3H, *J* = 6.0 Hz), 2.72 (s, 3H), 3.19-3.34 (m, 1H), 3.51-3.66 (m, 1H), 6.38 (q, 1H, *J* = 6.0 Hz), 9.76 (s, 1H);IR (KBr) cm^{-1}: 2980, 1130; HRMS (*m/z*) for $C_9H_{13}N_5ONa$: 230.1030 [M^+Na]; Calcd. 230.1012.

1-(2-Bromo-1-ethoxyethyl)-3-methyl-1H-pyrazolo[4,3-*e*][1,2,4]triazine (7)

A mixture of NBS (534 mg, 3 mmol) and dibenzoyl peroxide (48 mg, 0.2 mmol) was added to a solution of **6** (207 mg, 1 mmol) in CCl_4 (5 mL). The mixture was refluxed for 21 h. After cooling, the succinimide formed was filtered off and the solvent was removed *in vacuo*. The residue was purified on column chromatography (silica gel, $CHCl_3$) to provide 114 mg (0.4 mmol, 40%) of **7**. mp 107 ^{o}C; ^{1}H nmr ($CDCl_3$) δ: 1.18 (t, 3H, *J* = 7 Hz), 2.73 (s, 3H), 3.37-3.52 (m, 1H), 3.61-3.76 (m, 1H), 3.95-4.02 (m, 1H), 4.17-4.27 (m, 1H), 6.33-6.40 (m, 1H), 9.80 (s, 1H); ms (*m*/*z*, %): 285 (5) [M^+], 162 (100), 125 (56), 123 (58); HRMS (*m/z*) for $C_9H_{12}N_5O^{79}Br$: 285.02207 [M^+]; Calcd. 285.02252. ***Anal.*** Calcd for $C_9H_{12}N_5O^{79}Br$: C, 37.76; H, 4.23; N, 24.48. Found: C, 37.84; H, 4.28; N, 24.29.

1,3-Dimethyl-5-methylsulfonyl-1*H*-prazolo[4,3-*e*][1,2,4]triazine (12)

The compound was prepared according to the procedure described for derivative **4** in a 93% yield; mp 171 ^{o}C; ^{1}H nmr ($CDCl_3$) δ: 2.77 (s, 3H), 3.57 (s, 3H), 4.39 (s, 3H); IR (KBr) cm^{-1}: 2920, 1330, 1120; ms (*m*/*z*, %): 227 (8) [M^+], 199 (32), 120 (21), 95 (51), 79 (94), 67 (28), 52 (100); ***Anal.*** Calcd for $C_{17}H_{13}N_5S$: C, 37.00; H, 3.96; N, 30.83. Found: C, 37.10; H, 3.85; N, 30.76.

5-Hydrazino-1,3-dimethyl-1*H*-pyrazolo[4,3-*e*][1,2,4]triazine (13)

The compound was prepared according to the procedure described for derivative **5** in a 90% yield; mp 197-198 °C; ^{1}H nmr ($CDCl_3$) δ: 2.56 (s, 3H), 3.49 (s, 2H, NH_2), 4.19 (s, 3H), 6.86 (s, 1H, NH); IR (KBr) cm^{-1}: 3300 (NH); MS (*m*/*z*, %): 179 (55) [M^+], 164 (25), 136 (72), 121 (56), 67 (88), 53 (100); *Anal*. Calcd for $C_6H_9N_7$: C, 40.22; H, 5.02; N, 54.74. Found: C, 40.63; H, 4.89; N, 54.75.

1,3-Dimethyl-1*H*-pyrazolo[4,3-*e*][1,2,4]triazine (14)

The compound was prepared according to the procedure described for derivative **6** in a 70% yield; mp 120 °C; ^{1}H nmr ($CDCl_3$) δ: 2.70 (s, 3H), 4.31 (s, 3H), 9.73 (s, 1H); MS (*m*/*z*, %): 149 (24) [M^+], 121 (26), 80 (100), 53 (50); *Anal*. Calcd for $C_6H_7N_5$: C, 48.32; H, 4.69; N, 46.97. Found: C, 48.37; H, 4.47; N, 47.15.

3-Bromomethyl-1methyl-1*H*-pyrazolo[4,3-*e*][1,2,4]triazine (15a) and 3-dibromomethyl-1-methyl-1*H*-pyrazolo[4,3-*e*][1,2,4]triazine (15b)

A mixture of NBS (5.34 g, 30 mmol) and dibenzoylperoxide (484 mg, 2 mmol) was added to a solution of **14** (1.49 mg, 10 mmol) in CCl_4 (70 mL). The mixture was refluxed for 6 h. After cooling, the succinimide formed was filtered off and the solvent was removed *in vacuo*. The residue was purified on column chromatography (silica gel, $CHCl_3$) to provide the mixture of compounds **15a** and **15b**.

15a: Yield 25%; mp 112 °C; ^{1}H nmr ($CDCl_3$) δ: 4.38 (s, 3H), 4.89 (s, 2H), 9.84 (s, 1H);
MS (EI, 70 eV, *m*/*z*, %): 229 (14) [M^+], 227 (14), 201 (38), 199 (39), 148 (89), 120 (100) 80 (74), 79 (84) 52 (50); HRMS (*m*/*z*) for $C_6H_7N_5{}^{79}Br$ [M^+H]: 227.9890; Calcd. 227.9879.

15b: Yield 20%; mp 202 °C; ^{1}H-NMR ($CDCl_3$) δ: 4.48 (s, 3H), 7.26 (s, 1H), 10.00 (s, 1H); MS (*m*/*z*, %): 308 (48), 306 (100) [M^+], 304 (50), 237 (10), 122 (15), 120 (16), 91 (23).

3-(2-Hydroxyethoxymetyl)-1-methyl-1*H*-pyrazolo[4,3-*e*][1,2,4]triazine (16)

To a solution of **15a** (200 mg, 0.87 mmola) in anhydrous acetone (6 ml), KI (36 mg, 0.2 mmol), K_2CO_3 (121 mg, 0.87 mmol) and ethylene glycol (2 mL) were added. The reaction mixture was stirred at rt for 48 h. After removal of acetone *in vacuo*, the residue was taken up in 10 mL of water and extracted 5 times with 5 mL of $CHCl_3$. The combined organic layers were dried over Na_2SO_4 and taken to dryness. After column chromatography (silica gel, $CHCl_3$/EtOH 20:1) 89 mg (0.42 mmol, 49%) of **16** was obtained. mp 54 °C; ^{1}H nmr (CD_3OD) δ: 4.36 (s, 2H), 4.38 (s, 3H), 5.03 (s, 2H), 5,06 (s, 2H), 9.81 (s, 1H); MS (*m*/*z*, %): 179 (9), 165 (14), 149 (100), 148 (53), 106 (26), 80 (55), 79 (58); HRMS (*m*/*z*) for $C_8H_{11}N_5O_2Na$ [M^+Na]: 232.0794; Calcd. 232.0805.

REFERENCES AND NOTES

1. Part 38 in a series "1,2,4-Triazines in Organic Synthesis". For Part 37, see M. Mojzych and A.

Rykowski, *J. Heterocycl. Chem*., 2007, **44**, (in print).

2. R. J. Suhadolnik, *Nucleosides as Biological Probes*, Wiley, New York, 1979, p. 172.
3. D. A. Carson and K.-P. Chang, *Biochem. Biophys. Res. Commun*., 1981, **100**, 1377.
4. G. J. Ellames, I. M. Newington, and A. J. Stobie, *J. Chem. Soc., Perkin Trans. 1*, 1985, 2087.
5. J.-C. Graciet, P. Faury, M. Camplo, A.-S. Charvet, N. Mourier, C. Trabaud, V. Niddam, V. Simon, and J.-L. Kraus, *Nucleos. Nucleot*., 1995, **4**, 1379.
6. E. S. H. El Ashry and Y. El Kilany, *Adv. Heterocycl. Chem*., 1997, **68**, 1.
7. E. S. H. El Ashry and Y. El Kilany, *Adv. Heterocycl. Chem*., 1998, **69**, 129.
8. S. D. Lindell, B. A. Moloney, B. D. Hewitt, Ch. G. Earnshaw, P. J. Dudfield, and J. E. Dancer, *Bioorg. Med. Chem. Lett*., 1999, **9**, 1985
9. A. Rykowski, M. Mojzych, and Z. Karczmarzyk, *Heterocycles*, 2000, **53**, 2175.
10. M. Mojzych and A. Rykowski, *Heterocycles*, 2004, **63**, 1829.
11. M. Mojzych and A. Rykowski, *Heterocyclic Commun.,* 2006, **12**, 191.
12. M. Mojzych and A. Rykowski, *J. Heterocycl. Chem*., 2007, **44**, (in print).
13. A. Rykowski and T. Lipinska, *Synth. Commun*., 1996, **26**, 4409.
14. M. Mojzych and A. Rykowski, *Polish J. Chem*., 2003, **77**, 1797.
15. S. F. Vasilevsky, S. V. Klyatskaya, E. V. Tretyakov, and J. Elquero, *Heterocycles*, 2003, **60**, 879.
16. M. Mojzych, A. Rykowski, and J. Wierzchowski, *Molecules*, 2005, **10**, 1298.
17. W. Dabkowski, A. Ozarek, and I. Tworowska, *New J. Chem*., 2005, **29**, 1396.