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An efficient *Mannich*-type synthesis of *bis*(pyrido[2,1-*b*][1,3,5]thiadiazin-7-yl)-methanes

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Abstract Morpholinium 3-cyano-4-methyl-6-oxo-1,6-dihydropyridine-2-thiolate upon treatment with primary amines and a formaldehyde excess under mild conditions produces *bis*(pyrido[2,1-*b*][1,3,5]thiadiazin-7-yl)methane derivatives in good yields (67–87%).

Keywords Heterocycles; *Mannich* reaction; *Michael* adducts; Pyridine-2-thiolates; 1,3,5-Thiadiazines.

Introduction

1,3,5-Thiadiazines are known to be the compounds of a great practical interest [1]. Thus, 1,3,5-thiadiazines constitute new classes of insecticides [2]. They exhibit antileukemic [3], antifungal and antimicrobial activity [3, 4], and they are usefully applied as herbicides [5], miticides [6], antibacterial [7], antitumoral [8] and antitubercular agents [9]. Furthermore, these compounds are promising prodrugs for amino acids and similar compounds [10]. Buprofezin (Applaud®, 2-*tret*-butylimino-3-isopropyl-5-phenylperhydro-1,3,5-thiadiazine) is widely known as an insect growth regulator with strong chitin biosynthesis inhibiting effect [11, 12] and suppressor of insect egg-laying [13]. 2-Thioxotetrahydro-1,3,5-thiadiazines (''carbothialdines'') also posess antidermatophytic [14], hypolipidemic [15], anti-leishmanial, parasiticidal [16], and antihelmintic [17] types of activity. 3,5-Dimethyl-2-thioxotetrahydro-1,3,5-thiadizine (*DTTT*, carbothialdine, Dazomet, Basamid®, in former USSR known under the name ''thiazon'') is highly effective soil fungicide and slimicide [18] and produces a total ovicidal effect on the helminth eggs in soil [19]. *DTTT* also behaves as a monodentate ligand towards some metal carbonyls [20].

One of the most concise and effective approaches to the ring-fused 1,3,5-thiadiazines based on the double *Mannich*-type condensation of 2-mercaptoazole or -azine derivatives with primary amines and a formaldehyde excess. In fact, the related syntheses of *s*-triazolo[3,4-*b*][1,3,5]thiadiazines [21], thiazolo-[3′,4′:1,5][1,2,4]triazolo[3,4-*b*][1,3,5]thiadiazines [22], 1,3,5-thiadiazino[3,2-*a*]benzimidazoles [23], imidazo[2,1-*b*][1,3,5]thiadiazines [24], 1,2,4-triazino-[3,2-*b*][1,3,5]thiadiazines [25], pyrido[2,1-*b*][1,3,5]-thiadiazines [26], and pyrimido[6,1-*b*][1,3,5]thiadiazines [27] have been reported in literature to date.

In continuation of our efforts on the application of 3-cyanopyridine-2(1*H*)-chalcogenones in heterocyclic synthesis [28], and to develop the above *Mannich*-type method for 1,3,5-thiadiazine ring construction, studies have been taken up on the aminomethylation

† Deceased
‡ This paper is dedicated to the blessed memory of our colleague, Prof. *Victor Petrovich Litvinov* (December 24, 1932–February 26, 2007)
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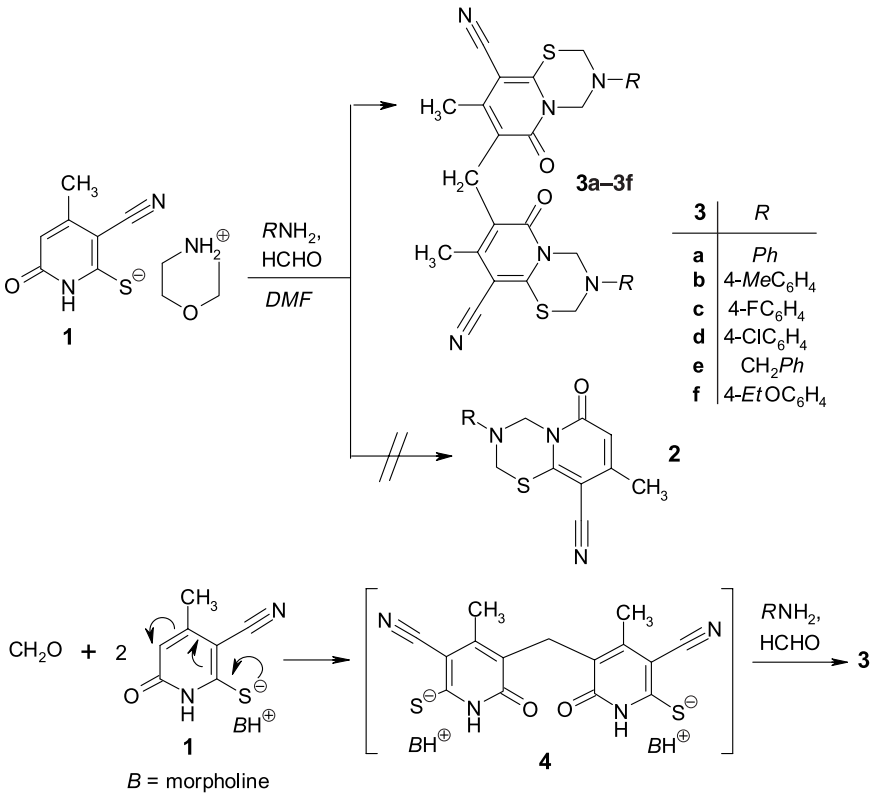
of accessible morpholinium 3-cyano-4-methyl-6-oxo-1,6-dihydropyridine-2-thiolate (**1**). The latter can be easily obtained by reaction of ethyl 3-morpholinocrotonate with cyanothioacetamide [29, 30], or by the ternary condensation of cyanothioacetamide, acetoacetic ester and morpholine [31]. Due to the presence of various functional groups thiolate **1** is expected to be a good starting point for the synthesis of pyrido[2,1-*b*][1,3,5]thiadiazine derivatives under double *Mannich*-type reaction conditions.

Results and discussion

We have found that thiolate **1** readily reacts with primary amines and a formaldehyde excess under short-time heating in *DMF* to form *Mannich*-type condensation products. The latter were supposed first to have a pyrido[2,1-*b*][1,3,5]thiadiazine structure **2**. Surprisingly, the ^{1}H NMR spectra of all the obtained compounds lacked the characteristic peaks at $\delta = 5.36$–6.51 ppm corresponding to C(5)H pyridine protons [29–31]. Instead of it, the broadened singlets with total integral values of 1H in ratio to the values of aromatic or H_3C-protons appeared in the stronger field at $\delta = 3.66$–3.76 ppm. It seems reasonable to accept the assumption that these peaks must be assigned to the H_2C-protons of 7,7′-methylene bridge of dipyridylmethane structure **3**, while other resonances in the spectra fit the two sets of magnetically equal protons. The plausible assumption that the peaks at $\delta = 3.66$–3.76 ppm were that of the H_2C-bridge protons resonances agreed well with chemical shifts (generally in the range $\delta = 3.5$–5.0 ppm) reported for related dihetarylmethane species (for instance, see [32, 33]). There have been a number of tandem *Knoevenagel-Michael*-type reactions with aldehydes to form 3,3′-dipyridylmethane species reported for a variety of C(3)-nucleophilic 2-pyridones [32–36]. So, both a survey of literature and our interpretation of ^{1}H NMR data were consistent with the structure for products **3a**–**3f** given in the Scheme 1.

It is strongly supposed that the reaction procced through the formation of non-isolable intermediate **4**. Presumably, the former resulted from the condensation of formaldehyde with pyridine-2-thiolate **1** occurred at C(5) atom followed by the *Michael* addition. Adduct **4**, in turn, undergo *S*,*N*-*bis*-amino-



Scheme 1

methylation to afford *bis*(pyrido[2,1-*b*][1,3,5]thiadiazin-7-yl)methanes **3** in high yields (67–87%). Both aliphatic and aromatic primary amines reacted under these conditions, but the synthesis is not so variable since sterically unhindered primary amines should be employed only. For instance, we failed to carry out the reaction with 2,6-dimethylaniline, *o*-phenetidine, *tert*-butylamine, or 2-ethyl-6-methylaniline. All efforts to use amines with strong electron-accepting substituents such as *o*-nitroaniline also gave unsatisfactory results.

All the obtained **3a–3f** are fine colorless crystals, readily soluble in *DMSO* or hot *DMF*, but insoluble in alcohols, dioxane, or acetone. The structures of **3a–3f** were confirmed by IR- and ^{1}H NMR-spectra, as well as elemental analysis data. The ^{1}H NMR spectra revealed the signals of C(8)CH_3 protons as singlets at $\delta = 2.09$–2.30 ppm and broadened singlets at $\delta = 3.66$–3.76 ppm corresponding to methylene bridge protons. The protons of SCH_2NCH_2N system appeared as two broadened singlets in the lower field ($\delta = 4.85$–5.67 ppm) that agreed well with the values of $\delta = 4.50$–5.32 ppm as we reported prior for related compounds [24, 26]. The IR spectra of **3a–3f** showed typical lactam C=O band absorption ($\bar{\nu} = 1630$–$1650\ cm^{-1}$) and the peaks at $\bar{\nu} = 2205$–$2216\ cm^{-1}$ attributed to conjugated cyano group, but revealed a lack of any NH group stretching bands.

Finally, it should be noted that 3,3′-dipyridomethanes, being a relatively rare class of compounds, are of practical interest due to their inhibitory effects on the growth of a wide range of cancer cell lines [34, 36]. In this paper, we proposed an effective approach for synthesis of previously unknown dipyridomethanes containing a biologically active 1,3,5-thiadiazine fragment, that may therefore be expected to have a biological role needs to be examined.

Experimental

Melting points were measured on a *Kofler* hot stage apparatus. Elemental analyses for C, H, and N were conducted using a Perkin-Elmer C, H, and N Analyzer; their results were found to be in good agreement with the calculated values (±0.2%). IR spectra were recorded on an IKS-29 spectrophotometer in Nujol mulls. The ^{1}H NMR spectra were performed on Varian Mercury VX-200 (199.97 MHz) spectrometer on *DMSO*-d_6 solutions with Me_4Si as the internal standard. The purity of all obtained compounds was checked by TLC on Silufol® UV 254 plates (sorbent – Silpearl, large-pore silicagel after *Pitra* with luminiscent indicator for UV 254 on the aluminium foil, binder – starch) in the acetone–heptane (1:1) system; spots were visualized with iodine vapors and UV light. The starting thiolate **1** was prepared according to the general method reported in Refs. [29, 30].

*Bis(3-R-9-cyano-8-methyl-6-oxo-3,4-dihydro-2H,6H-pyrido[2,1-b][1,3,5]thiadiazin-7-yl)methanes (**3a–3f**). General procedure*

To the solution of thiolate **1** (1.0 g, 4 mmol) in 5–6 cm^3 *DMF*, corresponding primary amine (4 mmol) and an excess of 37% aqueous formaldehyde solution (4 cm^3, 53 mmol) were added. The mixture was refluxed for 1–2 min, cooled, filtered through a paper filter and left to stand for 24 h at ambient temperature. The colorless crystals of **3a–3f** were filtered off, washed twice with hot *Et*OH and recrystallized from an appropriate solvent.

Bis(9-cyano-8-methyl-6-oxo-3-phenyl-3,4-dihydro-2H,6H-pyrido[2,1-b][1,3,5]thiadiazin-7-yl)methane

(**3a**, $C_{31}H_{26}N_6O_2S_2$)

Yield 67%; mp 247–250°C (dec, from acetone:*DMF* = 1:1); ^{1}H NMR (200 MHz, *DMSO*-d_6): $\delta = 2.12$ (br s, 2C(8)CH_3), 3.67 (s, CH_2), 5.53, 5.67 (both br s, each 4H, 2SCH_2NCH_2), 6.96–7.26 (m, 2*Ph*) ppm; IR (nujol): $\bar{\nu} = 2205$ (2C≡N), 1650 (2C=O) cm^{-1}.

Bis{9-cyano-8-methyl-3-(4-methylphenyl)-6-oxo-3,4-dihydro-2H,6H-pyrido[2,1-b][1,3,5]thiadiazin-7-yl}methane

(**3b**, $C_{33}H_{30}N_6O_2S_2$)

Yield 84%; mp 265°C (dec, from *Et*OH:*DMSO* = 1:1); ^{1}H NMR (200 MHz, *DMSO*-d_6): $\delta = 2.08$ (br s, 2*Ar*–CH_3), 2.19 (br s, 2C(8)CH_3), 3.70 (s, CH_2), 5.47, 5.64 (both br s, each 4H, 2SCH_2NCH_2), 6.98 (q, $^3J = 8.2$ Hz, 2C$_6H_4$CH$_3$) ppm; IR (nujol): $\bar{\nu} = 2216$ (2C≡N), 1647 (2C=O) cm^{-1}.

Bis{9-cyano-3-(4-fluorophenyl)-8-methyl-6-oxo-3,4-dihydro-2H,6H-pyrido[2,1-b][1,3,5]thiadiazin-7-yl}methane

(**3c**, $C_{31}H_{24}F_2N_6O_2S_2$)

Yield 70%; mp 270–272°C (dec, from *DMF*); ^{1}H NMR (200 MHz, *DMSO*-d_6): $\delta = 2.14$ (br s, 2C(8)CH_3), 3.66 (s, CH_2), 5.49, 5.64 (both br s, each 4H, 2SCH_2NCH_2), 7.01–7.20 (m, 2C$_6H_4$F) ppm; IR (nujol): $\bar{\nu} = 2205$ (2C≡N), 1642 (2C=O) cm^{-1}.

Bis{3-(4-chlorophenyl)-9-cyano-8-methyl-6-oxo-3,4-dihydro-2H,6H-pyrido[2,1-b][1,3,5]thiadiazin-7-yl}methane

(**3d**, $C_{31}H_{24}Cl_2N_6O_2S_2$)

Yield 87%; mp 272–275°C (dec, from *DMF*); ^{1}H NMR (200 MHz, *DMSO*-d_6): $\delta = 2.13$ (br s, 2C(8)CH_3), 3.66 (s, CH_2), 5.50, 5.67 (both br s, each 4H, 2SCH_2NCH_2), 7.18 (q, $^3J = 8.6$ Hz, 2C$_6H_4$CH$_3$) ppm; IR (nujol): $\bar{\nu} = 2205$ (2C≡N), 1650 (2C=O) cm^{-1}.

Bis(3-benzyl-9-cyano-8-methyl-6-oxo-3,4-dihydro-2H,6H-pyrido[2,1-b][1,3,5]thiadiazin-7-yl)methane

(**3e**, $C_{33}H_{30}N_6O_2S_2$)

Yield 84%; mp 220–222°C (dec, from *DMF*:*Et*OH = 2:1); ^{1}H NMR (200 MHz, *DMSO*-d_6): $\delta = 2.30$ (br s, 2C(8)CH_3), 3.61

(s, CH_2), 3.76 (br s, CH_2C$_6$H$_5$), 4.85, 4.96 (both br s, each 4H, 2SCH_2NCH_2), 7.20–7.28 (m, 2*Ph*) ppm; IR (nujol): $\bar{\nu} = 2203$ (2C≡N), 1630 (2C=O) cm^{-1}.

Bis{9-cyano-3-(4-ethoxyphenyl)-8-methyl-6-oxo-3,4-dihydro-2H,6H-pyrido[2,1-b][1,3,5]thiadiazin-7-yl}methane (**3f**, $C_{35}H_{34}N_6O_4S_2$)

Yield 68%; mp 250–253°C (dec, from *DMF*:*Et*OH = 1:1); ^{1}H NMR (200 MHz, *DMSO*-d$_6$): $\delta = 1.25$ (t, $^3J = 7.0$ Hz, OCH$_2$CH_3), 2.09 (br s, 2C(8)CH_3), 3.67 (s, CH_2), 3.91 (q, $^3J = 7.0$ Hz, OCH_2CH$_3$), 5.45, 5.60 (both br s, each 4H, 2SCH_2NCH_2), 6.88 (q, $^3J = 8.9$ Hz, 2*Ar*) ppm; IR (nujol): $\bar{\nu} = 2211$ (2C≡N), 1648 (2C=O) cm^{-1}.

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