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An Efficient *Mannich*-Type One-Pot Synthesis of 3,5,7,11-Tetraazatricyclo [7.3.1.0^{2,7}]tridec-2-ene Derivatives Starting from Functionalized 1,4-Dihydropyridines

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Summary. 3,5,7,11-Tetraazatricyclo[7.3.1.0^{2,7}]tridec-2-ene derivatives were prepared in one-pot manner from *N*-methylmorpholinium 6-amino-3,5-dicyano-4-spiro(1′-cycloalkane)-1,4-dihydropyridine-2-thiolates, primary amines, and formaldehyde in 70–88% yields. The structure of 5,11-dibenzyl-13-spiro(1′-cyclopentane)-8-thioxo-3,5,7,11-tetraazatricyclo[7.3.1.0^{2,7}]tridec-2-ene-1,9-dicarbonitrile was determined by X-ray diffraction analysis.

Keywords. Heterocycles; Cyclizations; *Mannich* reaction; 1,4-Dihydropyridine-2-thiolates; X-Ray structure determination.

Introduction

Since the first report in 1912 the *Mannich* reaction has been widely studied and received considerable attention as a valuable synthetic method [1]. Apart from recent advances in this field, such as developments in metal- and non-metal-catalyzed asymmetric *Mannich*-type syntheses [2] or successful introduction of *Lewis* [3] or *Brønsted* [4] acid promoters for condensation of trialkylsilyl enolates with electrophiles, the *Mannich* reaction has emerged as an efficient method for the construction of a variety of heterocyclic systems. In fact, recently *Mannich*-type reactions were successfully applied in the synthesis of substituted nicotinonitriles [5], 7,12a-epiiminopyrido[4,3-*b*][1,5]benzoxazocine derivatives [6], 1,3-oxazines

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and oxazolidines [7], 1,4λ^5-azaphosphorinane and 1,4-thiazine derivatives [8], 1,3,5-oxadiazines and 1,3,5-triazines [9], 1,3,5-dithiazine and 1,3,5-dioxazine derivatives [10], and 9-thia-3,7-diazabicyclo[3.3.1]nonanes [11].

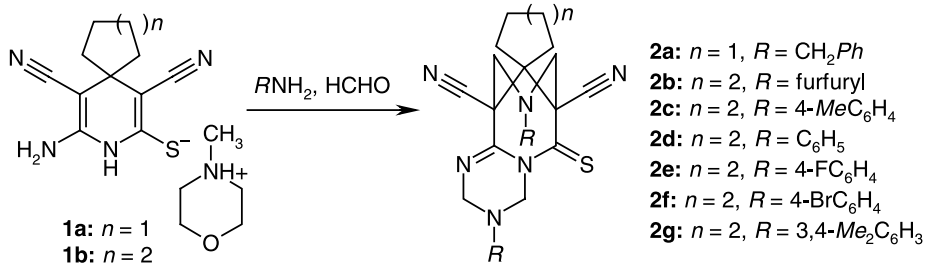
Our continuous interest in the synthetic capabilities of pyridine-2(1*H*)-thiones and related thiolates [12] prompted us to investigate the *Mannich* reaction of spiro-conjugated 1,4-dihydropyridine-2-thiolates **1** towards primary amines and HCHO. The starting thiolates **1** could be easily prepared *via* an improved method [13] based on the three-component *Hantzsch*-type condensation of cycloalkanones, malononitrile, and cyanothioacetamide, reported for the first time by *Abdel-Latif* [14]. Generally, double *Mannich*-type condensation of 2-mercaptoazole or -azine derivatives with primary amines and formaldehyde excess is the method of choice for construction of the ring-fused 1,3,5-thiadiazine moiety [15]. In this way, the syntheses of *s*-triazolo[3,4-*b*][1,3,5]thiadiazines [16], thiazolo[3′,4′:1,5][1,2,4] triazolo[3,4-*b*][1,3,5]thiadiazines [17], 1,3,5-thiadiazino[3,2-*a*]benzimidazoles [18], imidazo[2,1-*b*][1,3,5]thiadiazines, and 1,2,4-triazino[3,2-*b*][1,3,5]thiadiazines [19] developed following this approach have been reported hitherto. Recently, we have demonstrated the efficient one-pot synthesis of pyrido[2,1-*b*][1,3,5]thiadiazine derivatives *via* a three-component condensation of 4-aryl-5-cyano-2-oxo-1,2,3,4-tetrahydropyridine-6-thiolates with primary amines and formaldehyde [20]. Thus, as we expected, partially hydrogenated pyridine-2-thiolates such as **1** should act as *S*,*N*-binucleophiles in the *Mannich* reaction.

On the other hand, it is well known that piperidin-4-ones and other 3,5-binucleophilic pyridine species react with formaldehyde and primary amines under mild conditions at both C-3 and C-5 to yield 3,7-diazabicyclo[3.3.1]nonane (bispidine) derivatives [21]. The latter are of considerable practical interest both from specific complexation properties towards transition metals [22] and due to their remarkable biological activities [23]. In contrast, stereoselective aminomethylation of the *Hantzsch*-type 1,4-dihydropyridines under the *Mannich* conditions occurred at N-1, C-3, and exocyclic methyl group to give 1,6-naphthyridine and pyrimido[5,6, 1-*ij*][1,6]naphthyridine derivatives [24]. Hence, our parent 1,4-dihydropyridine-2-thiolates **1** have at least four nucleophilic centers, namely, C-3, C-5, N-1, and the sulfur atom, which could be involved in the consequent *Mannich* aminomethylation.

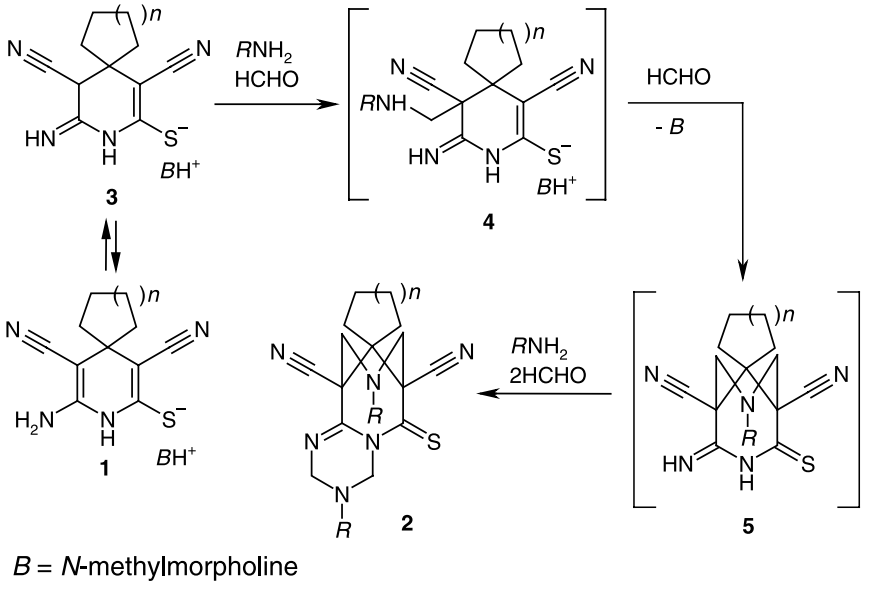
Results and Discussion

We found that the reaction of pyridine-2-thiolates **1** with 1 equivalent of the corresponding amine in the presence of an excess of 37% formaldehyde solution gave neither 1,3,5-thiadiazine derivatives nor bispidine analogs at all. Surprisingly, tetraazatricyclo[7.3.1.0^{2,7}]tridec-2-enes **2** were formed as sole products in low yields (25–40%, calculated for **1**) (Scheme 1). Series of experiments were conducted in which the reaction conditions were varied in an attempt to improve the yield of the desired products. It was found that the yields were increased up to 70–88% when thiolates **1** and the corresponding amines were taken in the optimum molar 1:2 ratio, in presence of not less than a ten-fold formaldehyde excess.

A possible reaction mechanism for the formation of **2** is suggested in Scheme 2. Presumably, the above cascade reaction proceeds as an aminomethylation occurring at the C-3 atom of the tautomeric iminopyridines **3** followed by a consecutive



Scheme 1



Scheme 2

condensation with formaldehyde to form the bispidine-type intermediates **4**. It should be noted that the tautomeric equilibrium between **1** and **3** is well documented both in the case of thiolate **1** and its derivatives [13]. Subsequently, or at the same time as the above process, a highly active amidine moiety reacted with a second mole amine and 2 equivalents of HCHO to close the tetrahydro-1,3,5-triazine ring and complete the cascade process. Both aliphatic and aromatic amines reacted under these conditions. However, all attempts to prepare tricyclotridecenes **2** from certain sterically hindered amines, such as *t*-butylamine, 2,6-dimethylaniline, or 2-ethyl-6-methylaniline, failed. The obtained tricyclotridecenes **2** are stable, mostly yellow or yellowish crystalline solids, soluble in hot acetone, *DMF*, or *DMSO* and insoluble in alcohols.

The structures of the obtained compounds were confirmed by means of elemental analysis, as well as IR and ^{1}H NMR data. Thus, IR spectra of **2** showed the absence of conjugated C≡N groups. Instead, the very weak absorption bands stretching at $\bar{\nu} = 2250–2248\,\mathrm{cm}^{-1}$ corresponding to non-conjugated C≡N groups, were observed. The intensive bands at $\bar{\nu} = 1654–1640\,\mathrm{cm}^{-1}$ were assigned to the C=N group stretches. The ^{1}H NMR spectra revealed peaks at $\delta = 6.30–7.30$ and

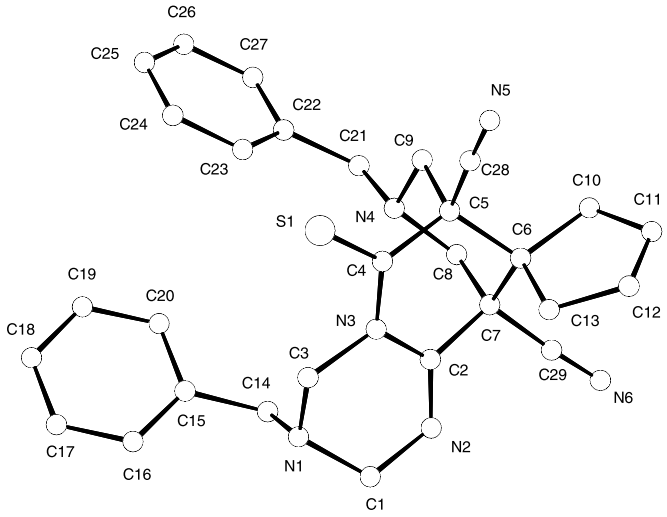


Fig. 1. A perspective view and labelling scheme for **2a**; selected bond lengths (Å): S(1)–C(2) 1.669(4), N(1)–C(1) 1.455(4), N(1)–C(3) 1.425(4), N(2)–C(1) 1.463(4), N(2)–C(2) 1.264(3), N(3)–C(2) 1.418(3), N(3)–C(3) 1.506(3), N(3)–C(4) 1.357(3), N(4)–C(8) 1.468(3), N(4)–C(9) 1.459(3)

1.56–2.24 ppm which are characteristic of aromatic and $(CH_2)_n$ protons. The $C(10)H_2$ and $C(12)H_2$ protons appeared as two doublets of doublets or as complex multiplets due to overlapping. Two doublets of doublets at weaker field ($\delta =$ 4.46–5.10 ppm, $^2J = 16.4$–17.3 Hz, and $\delta = 5.11$–5.71 ppm, $^2J = 12.7$–13.5 Hz) correspond to the $C(4)H_2$ and $C(6)H_2$ protons.

For additional and unambiguous evidence the structure of **2a** was established by a single crystal X-ray diffraction analysis. The perspective view of **2a** and selected geometrical parameters are given in Fig. 1. The N(4)C(5–9) six-membered heterocycle has a *chair* conformation, the conformation of both N(1–3)C(1–3) and N(3)C(2)C(4–7) heterocycles is *half-chair*. Both the N(1) and N(4) atoms have a pyramidal bond configuration (sum of the bond angles 335.0(8) and 333.5(6)°), whereas the N(3) atom is trigonal-planar (sum of the bond angles 359.9(6)°). Due to the $n_{N(3)}$-$\pi_{S(1)=C(4)}$ conjugation the N(3)–C(4) bond of 1.357(3) Å is significantly shortened in comparison with the standard value for N(sp^2)–C(sp^2) single bonds of 1.45 Å [25, 26].

In conclusion, the present one-pot method provides a quick and efficient access to 3,5,7,11-tetraazatricyclo[7.3.1.$0^{2,7}$]tridec-2-ene derivatives under *Mannich* conditions from easily available starting materials.

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, 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 a Varian Gemini 200 (200 MHz) spectrometer in *DMSO*-d_6 solution with Me_4Si as the internal standard. The purity of all obtained compounds was checked by TLC on Silufol UV 254 plates in the acetone:heptane (1:1) system; spots

were visualized with iodine vapors and UV light. The starting thiolates **1a**–**1b** were prepared according to Ref. [13].

Spiro-conjugated tetraazatricyclo[7.3.1.0^{2,7}]tridec-2-enes (**2**)
To the suspension of corresponding thiolate **1a** or **1b** (1.5 mol) in 8–10 cm^3 *Et*OH primary amine (3.1 mol) and an excess of 37% aqueous formaldehyde solution (2–3 cm^3) were added. The mixture was refluxed for 3–5 min, cooled, and left to stand overnight. The crystals formed were filtered off and recrystallized from an appropriate solvent to afford **2a**–**2g**.

5,11-Dibenzyl-8-thioxo-13-spiro-1′-cyclopentane-3,5,7,11-tetraazatricyclo[7.3.1.0^{2,7}]tridec-2-ene-1,9-dicarbonitrile (**2a**, $C_{29}H_{30}N_6S$)
Yield 80%; yellow crystals, mp 175–177°C (*Et*OH:acetone = 1:1); ^{1}H NMR (200 MHz, *DMSO*-d$_6$): $\delta = 1.90$–2.03 (m, $(CH_2)_4$), 2.84–3.24 (2dd, 4H, C(10)H_2 and C(12)H_2 overlapped), 3.65 (m, 2H, CH_2Ph), 3.77 (dd, 2H, $^2J = 13.1$ Hz, CH_2Ph), 4.46 (dd, 2H, $^2J = 16.7$ Hz, C(6)H_2 or C(4)H_2), 5.13 (dd, 2H, $^2J = 13.0$ Hz, C(4)H_2 or C(6)H_2), 7.13–7.31 (m, 10H, C*H*-arom) ppm; IR (nujol): $\bar{\nu} = 2248$ (C≡N), 1645 (C=N) cm^{-1}.

5,11-Difurfuryl-8-thioxo-13-spiro-1′-cyclohexane-3,5,7,11-tetraazatricyclo[7.3.1.0^{2,7}]tridec-2-ene-1,9-dicarbonitrile (**2b**, $C_{26}H_{28}N_6O_2S$)
Yield 76%; pale yellow crystals, mp 161–163°C (*Et*OH:acetone = 1:1); ^{1}H NMR (200 MHz, *DMSO*-d$_6$): $\delta = 1.56$–2.03 (m, $(CH_2)_5$), 3.09–3.23 (2dd, 4H, C(10)H_2 and C(12)H_2 overlapped), 3.72 (m, 2 CH_2-furyl overlapped), 4. 47 (dd, 2H, $^2J = 16.9$ Hz, C(6)H_2 or C(4)H_2), 5.11 (dd, 1H, $^2J = 12.7$ Hz, C(4)H_2 or C(6)H_2), 6.18–6.30 (m, 4H, 2 C(3)*H*-furyl and 2 C(4)*H*-furyl), 7.34–7.43 (m, 2H, 2 C(5)*H*-furyl) ppm; IR (nujol): $\bar{\nu} = 2250$ (C≡N), 1640 (C=N) cm^{-1}.

5,11-Di(4-methylphenyl)-8-thioxo-13-spiro-1′-cyclohexane-3,5,7,11-tetraazatricyclo[7.3.1.0^{2,7}] tridec-2-ene-1,9-dicarbonitrile (**2c**, $C_{30}H_{32}N_6S$)
Yield 88%; yellowish crystals, mp 170–172°C (*Et*OH:acetone = 2:1); ^{1}H NMR (200 MHz, *DMSO*-d$_6$): $\delta = 1.60$–2.00 (m, $(CH_2)_5$), 2.10 and 2.26 (2s, 2H_3C–Ar), 3.48–3.79 (2dd, 4H, C(10)H_2 and C(12)H_2 overlapped), 5.05 (dd, 2H, $^2J = 16.7$ Hz, C(6)H_2 or C(4)H_2), 5.63 (dd, 2H, $^2J = 13.4$ Hz, C(4)H_2 or C(6)H_2), 6.54 (d, 2H, $^3J = 8.2$ Hz, C(3)*H*-arom and C(5)*H*-arom), 6.66 (m, 4H, 4-$H_3CC_6H_4$), 6.93 (d, 2H, $^3J = 8.2$ Hz, C(2)*H*-arom and C(6)*H*-arom) ppm; IR (nujol): $\bar{\nu} = 2249$ (C≡N), 1653 (C=N) cm^{-1}.

5,11-Diphenyl-8-thioxo-13-spiro-1′-cyclohexane-3,5,7,11-tetraazatricyclo[7.3.1.0^{2,7}]tridec-2-ene-1,9-dicarbonitrile (**2d**, $C_{28}H_{28}N_6S$)
Yield 87%; pale yellow crystals, mp 169–171°C (*Et*OH:acetone = 3:1); ^{1}H NMR (200 MHz, *DMSO*-d$_6$): $\delta = 1.72$–1.99 (m, $(CH_2)_5$), 3.55–3.82 (2dd, 4H, C(10)H_2 and C(12)H_2 overlapped), 5.10 (dd, 2H, $^2J = 16.4$ Hz, C(6)H_2 or C(4)H_2), 5.65 (m, 2H, C(4)H_2 or C(6)H_2), 6.73–7.16 (m, 10H, 2C_6H_5) ppm; IR (nujol): $\bar{\nu} = 2250$ (C≡N), 1642 (C=N) cm^{-1}.

5,11-Di(4-fluorophenyl)-8-thioxo-13-spiro-1′-cyclohexane-3,5,7,11-tetraazatricyclo[7.3.1.0^{2,7}] tridec-2-ene-1,9-dicarbonitrile (**2e**, $C_{28}H_{26}F_2N_6O_2S$)
Yield 83%; yellowish crystals, mp 206–208°C (acetone); ^{1}H NMR (200 MHz, *DMSO*-d$_6$): $\delta = 1.56$–2.24 (m, $(CH_2)_5$), 3.61 (dd, 2H, $^2J = 12.2$ Hz, C(10)H_2 or C(12)H_2), 3.72 (dd, 2H, $^2J = 12.1$ Hz, C(12)H_2 or C(10)H_2), 5.08 (dd, 2H, $^2J = 17.3$ Hz, C(6)H_2 or C(4)H_2), 5.71 (dd, 2H, $^2J = 13.4$ Hz, C(4)H_2 or C(6)H_2), 6.57–6.93 (m, 8H, C*H*-arom) ppm; IR (nujol): $\bar{\nu} = 2250$ (C≡N), 1650 (C=N) cm^{-1}.

5,11-Di(4-bromophenyl)-8-thioxo-13-spiro-1′-cyclohexane-3,5,7,11-tetraazatricyclo[7.3.1.0^{2,7}] tridec-2-ene-1,9-dicarbonitrile (**2f**, $C_{28}H_{26}Br_2N_6O_2S$)
Yield 70%; yellowish crystals, mp 234–236°C (acetone); ^{1}H NMR (200 MHz, *DMSO*-d$_6$): $\delta = 1.58$–2.22 (m, $(CH_2)_5$), 3.48–3.81 (2dd, 4H, C(10)H_2 and C(12)H_2 overlapped), 5.09 (m, 2H, C(6)H_2 or

C(4)H_2), 5.70 (dd, 2H, $^2J = 13.5$ Hz, C(4)H_2 or C(6)H_2), 6.75 and 6.97 (2dd, 4H, $^3J = 8.6$ Hz, 2C_6H_4Br-4) ppm; IR (nujol): $\bar{\nu} = 2250$ (C≡N), 1652 (C=N) cm^{-1}.

5,11-Di(3,4-dimethylphenyl)-8-thioxo-13-spiro-1′-cyclohexane-3,5,7,11-tetraazatricyclo [7.3.1.0^{2,7}]tridec-2-ene-1,9-dicarbonitrile (**2g**, $C_{32}H_{36}N_6S$)
Yield 84%; yellowish crystals, mp 226–227°C (acetone); ^{1}H NMR (200 MHz, *DMSO*-d$_6$): $\delta = 1.60$–1.95 (m, $(CH_2)_5$), 1.92, 2.00, 2.12, 2.16 (4s, 4CH_3), 3.48–3.75 (2dd, 4H, C(10)H_2 and C(12)H_2 overlapped), 5.06 (dd, 2H, $^2J = 17.1$ Hz, C(6)H_2 or C(4)H_2), 5.63 (dd, 2H, $^2J = 13.4$ Hz, C(4)H_2 or C(6)H_2), 6.31–6.86 (m, 8H, C*H*-arom) ppm; IR (nujol): $\bar{\nu} = 2250$ (C≡N), 1654 (C=N) cm^{-1}.

X-Ray Structure Determination of ***2a***
Crystal data: $C_{29}H_{30}N_6S$, M = 494.7, orthorhombic, $a = 17.619(5)$, $b = 10.010(2)$, $c = 28.966(11)$ Å, $V = 5108.9$ Å^3, space group *Pbca* (N 61), $Z = 8$, $d = 1.29$ g · cm^{-1}, $\mu = 13.52$ cm^{-1}, $F(000) = 2096$, crystal size *ca.* $0.21 \times 0.41 \times 0.45$ mm^3. All crystallographic measurements were performed at 18°C on a CAD-4-Enraf-Nonius diffractometer operating in the ω-2θ scan mode (the ratio of the scanning rates $\omega/2\theta = 1.2$). The intensity data were collected within the range $2 < \theta < 65°$ ($-1 < h < 20$, $-1 < k < 11$, $-1 < l < 34$) using graphite monochromated Cu–K_α radiation ($\lambda = 1.54178$ Å). Intensities of 5965 reflections (4280 unique reflection, $R_{int} = 0.017$) were measured. Data were corrected for *Lorentz* and polarization effects and an empirical absorption correction based on azimuthal scan data [27] was applied. The structure was solved by direct methods and refined by full-matrix least-squares technique in the anisotropic approximation using the CRYSTALS program package [28]. In the refinement 2727 reflections with $I > 3\sigma(I)$ were used. All hydrogen atoms were located in the difference *Fourier* map and included in the final refinement with the fixed positional and thermal parameters. Convergence was obtained at $R = 0.050$ and $R_w = 0.054$, $GOF = 1.106$ (325 refined parameters; obs./variabl. 8.3; the largest and minimal peaks in the final difference map, 0.36 and -0.28 e/Å^3). *Chebushev* weighting scheme [29] with parameters 0.94, -0.14, 0.41, and -0.26 was used. Full crystallographic details have been deposited at Cambridge Crystallographic Data Center (CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (internat.) +44-1223/336-033; e-mail: deposit@ccdc.cam.ac.uk, http://www.ccdc.cam.ac.uk)). Any request to the CCDC for this materials should quote the full literature citation and reference number CCDC 609695.

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