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A Double *Mannich*-type Reaction in the 1,4,5,6-Tetrahydropyridine-2-thiolate Series: A Convenient Approach to Functionalized 3,7-Diazabicyclo[3.3.1]nonane Derivatives

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Summary. The reaction of *N*-methylmorpholinium 5-alkoxycarbonyl-4-aryl-3-cyano-2-oxo-1,4,5,6-tetrahydropyridine-2-thiolates with primary amines and formaldehyde under mild conditions afforded 7-substituted alkyl 9-aryl-5-cyano-2-oxo-4-thioxo-3,7-diazabicyclo[3.3.1]nonane-1-carboxylates in fair to good yields (52–74%).

Keywords. Heterocycles; Cyclizations; *Mannich* reaction; 3,7-Diazabicyclo[3.3.1]nonanes; Pyridine-2-thiolates.

Introduction

3,7-Diazabicyclo[3.3.1]nonane (*DABCN*, bispidine) derivatives have proven to be compounds of a great practical interest [1]. Thus, bispidines are known as antitumor [2] and antiarrythmic [3] agents, as well as κ-opioid receptor ligands with analgesic activity [4]. The skeleton of *DABCN* constitutes the central ring of a variety of lupin alkaloids, *e.g.*, (−)-sparteine, multiflorine, or (−)-angustifolline, which were found to be effective muscarinic receptor binding agents [5]. On the other hand, due to specific conformational properties [1, 6], compounds with the *DABCN* system have also been the subjects of considerable interest as rigid pre-organized chelating bidentate ligands towards transition and main group metals, such as palladium [7, 8], copper [8, 9], cobalt [10], platinum [8], manganese [11], *etc*. Recently, bispidines were used as ligands in enantioselectively catalyzed additions of diethylzinc to C=O and C=C groups [12] and were proposed for the synthesis of metallocyclic supramolecular ensembles [13] and new (π-allyl)palladium clusters [7, 14]. Furthermore, *DABCN* derivatives are known as valuable synthons for the synthesis of 1,3-diazaadamantane derivatives [15] and complex thiadiaza-, triaza-, and tetraazatricyclic compounds [16]. Entry into the *DABCN* system is often achieved by means of the *Mannich* reaction [1, 17]. Thus, one of the most convenient and effective protocols commonly used for the preparation of unsymmetrically substituted bispidines is based on the double *Mannich*-type cyclocondensation of primary amines with excessive formaldehyde and *N*-substituted piperidin-4-ones, or another suitable 3,5-binucleophilic partially hydrogenated pyridine species [1, 3b, 3e, 4e–4h, 7, 9a, 10, 18].

In continuation of our work on the chemistry of 3-cyanopyridine-2(1*H*)-thiones and its derivatives [19], and to explore further applications of *Mannich*-type reactions in heterocyclic synthesis [20], herein we report our studies on the aminomethylation of easily accessible *N*-methylmorpholinium 5-(alkoxycarbonyl)-4-aryl-3-cyano-6-oxo-1,4,5,6-tetrahydropyridine-2-thiolates (**1**) [21] under double *Mannich*-type reaction conditions.

A survey of literature revealed that the double *Mannich*-type condensation of 2-mercaptoazoles

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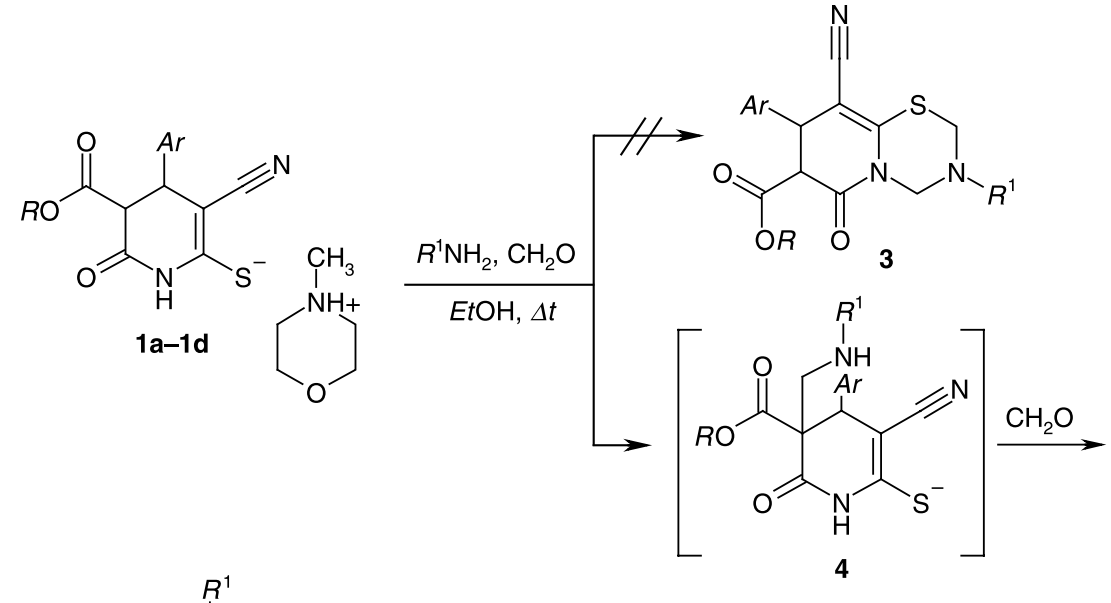
or -azines with primary amines and excessive formaldehyde is the method of choice for the synthesis of ring-fused 1,3,5-thiadiazine derivatives [22]. For instance, this approach was successfully applied for the syntheses of *s*-triazolo[3,4-*b*][1,3,5]thiadiazines [23], thiazolo[3′,4′:1,5][1,2,4]triazolo[3,4-*b*][1,3,5]thiadiazines [24], 1,3,5-thiadiazino[3,2-*a*]benzimidazoles [25], imidazo[2,1-*b*][1,3,5]thiadiazines [20a, 26], and 1,2,4-triazino[3,2-*b*][1,3,5]thiadiazines [26]. In contrast, recently we showed that partially hydrogenated pyridine-2-thiolates could react abnormally under double-*Mannich* conditions to give different results depending on the structure of the starting compound. In fact, at least two types of compounds – pyrido[2,1-*b*][1,3,5]thiadiazines [27] or 3,5,7,11-tetraazatricyclo[7.3.1.$0^{2,7}$]tridec-2-ene derivatives [28] could be obtained following this way. Hence, due to presence of C-, N-, and S-nucleophilic centers, pyridine-2-thiolate species may act as a C(3),C(5)-binucleophile, S,N-1,3-binucleophile, or, in the case of compounds with 2-aminopyridine moiety, as a N,N-1,3-binucleophile. Chosen tetrahydropyridine-2-thiolates **1** have four nucleophilic centers, namely, C(3)-, C(5)-, N-, and S-atoms, so it should be *a priori* expected that compounds **1** should give either *DABCN* derivatives or ring-fused 1,3,5-thiadiazines under double-*Mannich* conditions.

Results and Discussion

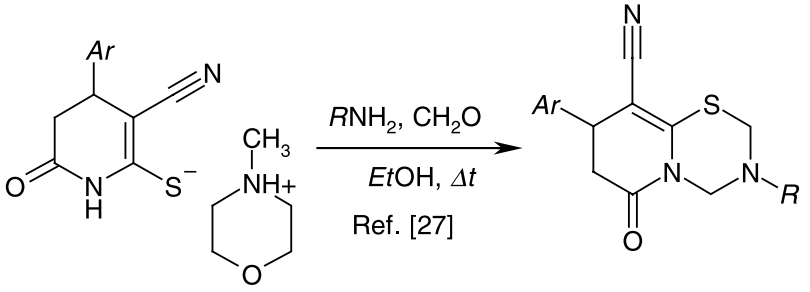
We found that treatment of tetrahydropyridine-2-thiolates **1a**–**1d** with 1 eq. primary amine and ex-



1	R	Ar
a	*Me*	4-ClC_6H_4
b	*Me*	4-*Me*C_6H_4
c	*Me*	4-*Et*C_6H_4
d	*Et*	2-$NO_2C_6H_4$

2	R	Ar	R^1
a	*Me*	4-ClC_6H_4	*Me*
b	*Me*	4-ClC_6H_4	CH_2Ph
c	*Me*	4-*Me*C_6H_4	*Me*
d	*Me*	4-*Me*C_6H_4	$(CH_2)_2CHMe_2$
e	*Me*	4-*Et*C_6H_4	*Me*
f	*Et*	2-$NO_2C_6H_4$	*Me*

Scheme 1



Scheme 2

cessive formaldehyde under short-term heating in *Et*OH led to formation of 7-substituted alkyl 9-aryl-5-cyano-2-oxo-4-thioxo-3,7-diazabicyclo[3.3.1]nonane-1-carboxylates **2a**–**2f** in 52–74% yields as the sole isolable products; no formation of ring-fused 1,3,5-thiadiazine species **3** was observed (Scheme 1). All efforts to put into reaction certain sterically hindered amines, such as *t*-butylamine, 2-ethylaniline, or 2,6-dimethylaniline, failed. We assumed that aminomethylation of **1** occurred predominantly at C(5)-position *via* intermediate **4**, since in the case of related pyridine-2-thiolates lacking of a 5-alkoxycarbonyl group we have not detected even traces of C(3)-aminomethylation products, but only pyrido[2,1-*b*][1,3,5]thiadiazines were formed in good yields (49–95%) [27] (Scheme 2).

The obtained bispidine derivatives **2** are bright-yellow compounds, which readily crystallize and are quite soluble in *DMF*, *DMSO*, or hot acetone, but insoluble in alcohols. The structures of compounds **2** were confirmed by means of elemental analysis, as well as IR and ^{1}H NMR data. The IR spectra of **2** showed the very weak absorption bands of a non-conjugated C≡N group stretching at $\bar{\nu} = 2260$–$2243\,cm^{-1}$, but lacked a characteristic conjugated nitrile band. Furthermore, the intensive bands at $\bar{\nu} = 1765$–1720 and 1720–$1705\,cm^{-1}$ corresponding to the ester and lactam C=O groups stretches were observed. The ^{1}H NMR spectra revealed broadened and partially deuterium-exchanged peaks at $\delta =$ 13.47–13.71 ppm corresponding to NH-protons. The C(6)H_2 and C(8)H_2 protons appeared as two doublets of doublets at $\delta = 3.01$–3.07 ppm ($^2J = 10.8$–11.4 Hz) and 3.12–3.23 ppm ($^2J = 10.6$–11.0 Hz), while C(9)H proton appeared as a sharp singlet resonating at $\delta = 3.94$–4.28 ppm. The ^{1}H NMR spectra of **2a**–**2e** also revealed the sharp singlets at $\delta =$ 3.25–3.31 ppm which are characteristic of CO_2CH_3 protons.

In conclusion, *N*-methylmorpholinium 5-(alkoxycarbonyl)-4-aryl-3-cyano-6-oxo-1,4,5,6-tetrahydropyridine-2-thiolates **1** were found to undergo a regioselective cyclocondensation at both C(3) and C(5) atoms under treatment with primary amines and excessive formaldehyde to afford the functionally substituted bispidine derivatives **2**.

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 Mercury VX-200 (199.97 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 (sorbent – Silpearl, large-pore silicagel after *Pitra* with luminiscent indicator for UV 254 on the aluminum foil, binder – starch) in the acetone:heptane (1:1) system; spots were visualized with iodine vapors and UV light. The starting thiolates **1a**–**1d** were prepared by the ternary condensation of aldehyde, cyanothioacetamide, and corresponding dialkyl malonate in the presence of *N*-methylmorpholine according to Ref. [21].

Diazabicyclo[3.3.1]nonanes ***2***

To the suspension of thiolate **1a**–**1d** (2.5 mmol) in 15–20 cm^3 *Et*OH, 2.5 mmol corresponding primary amine and an excess of 37% aqueous formaldehyde solution (1.5–2.5 cm^3) were added. The mixture was refluxed for 1–3 min, cooled, filtered through a paper filter, and left to stand for 3–5 days at room temperature. The bright-yellow crystals formed were filtered off and recrystallized from an appropriate solvent to afford **2a**–**2f**.

Methyl 9-(4-chlorophenyl)-5-cyano-7-methyl-2-oxo-4-thioxo-3,7-diazabicyclo[3.3.1]nonane-1-carboxylate

(**2a**, $C_{17}H_{16}ClN_3O_3S$)

Yield 60%; mp 237–239°C (acetone:*DMF* = 2:1); ^{1}H NMR (200 MHz, *DMSO*-d_6): $\delta = 2.29$ (s, NCH_3), 3.02 (dd,

$^2J = 11.0$ Hz, C(6)H_2 or C(8)H_2), 3.14 (dd, $^2J = 10.8$ Hz, C(8)H_2 or C(6)H_2), 3.31 (s, CO_2CH_3), 4.11 (s, C(9)*H*), 7.32 (q, $^3J = 8.6$ Hz, 4H–*Ar*) ppm. Signal of NH-proton wasn't detected, probably due to proton-deuterium exchange; IR (nujol): $\bar{\nu} = 3180$ (N–H), 2250 (C≡N), 1760 and 1707 (2 C=O) cm^{-1}.

Methyl 7-benzyl-9-(4-chlorophenyl)-5-cyano-2-oxo-4-thioxo-3,7-diazabicyclo[3.3.1]nonane-1-carboxylate

(**2b**, $C_{23}H_{20}ClN_3O_3S$)

Yield 52%; mp 190–192°C (*i–Pr*OH:acetone = 1:1); ^{1}H NMR (200 MHz, *DMSO*-d$_6$): $\delta = 3.07$ (dd, $^2J = 11.1$ Hz, C(6)H_2 or C(8)H_2), 3.23 (dd, $^2J = 10.6$ Hz, C(8)H_2 or C(6)H_2), 3.28 (s, CO_2CH_3), 3.71 (q, $^2J = 15.2$ Hz, CH_2Ph), 4.16 (s, C(9)*H*), 7.15–7.47 (m, C_6H_5, 4-ClC_6H_4), 13.67 (br, s, N*H*) ppm; IR (nujol): $\bar{\nu} = 3180$ (N–H), 2260 (C≡N), 1740 and 1718 (2C=O) cm^{-1}.

Methyl 5-cyano-7-methyl-9-(4-methylphenyl)-2-oxo-4-thioxo-3,7-diazabicyclo[3.3.1]nonane-1-carboxylate

(**2c**, $C_{18}H_{19}N_3O_3S$)

Yield 61%; mp 250–252°C (acetone:*DMF* = 1:1); ^{1}H NMR (200 MHz, *DMSO*-d$_6$): $\delta = 2.26$ and 2.28 (both s, *Ar*–CH_3 and N–CH_3), 3.02 (dd, $^2J = 10.9$ Hz, C(6)H_2 or C(8)H_2), 3.20 (dd, $^2J = 11.0$ Hz, C(8)H_2 or C(6)H_2), 3.27 (s, CO_2CH_3), 3.94 (s, C(9)*H*), 7.09 (q, $^3J = 8.3$ Hz, 4-$CH_3C_6H_4$), 13.47 (br, s, N*H*) ppm; IR (nujol): $\bar{\nu} = 3200$ (N–H), 2243 (C≡N), 1765 and 1707 (2C=O) cm^{-1}.

Methyl 5-cyano-7-(3-methylbutyl)-9-(4-methylphenyl)-2-oxo-4-thioxo-3,7-diazabicyclo[3.3.1]nonane-1-carboxylate

(**2d**, $C_{22}H_{27}N_3O_3S$)

Yield 63.5%; mp 221–223°C (acetone:*Et*OH = 1:2); ^{1}H NMR (200 MHz, *DMSO*-d$_6$): $\delta = 0.79$ (d, $^3J = 7.0$ Hz, CH(CH_3)$_2$), 1.22 (m, CH_2CH(CH$_3$)$_2$), 1.46 (m, C*H*(CH$_3$)$_2$), 2.26 (s, *Ar*–CH_3), 2.44 (m, NCH_2CH_2CH(CH$_3$)$_2$), 3.06 (dd, $^2J = 10.8$ Hz, C(6)H_2 or C(8)H_2), 3.22 (dd, $^2J = 10.8$ Hz, C(8)H_2 or C(6)H_2), 3.28 (s, CO_2CH_3), 3.96 (s, C(9)*H*), 7.09 (q, $^3J = 8.3$ Hz, 4-$CH_3C_6H_4$), 13.47 (br, s, N*H*) ppm; IR (nujol): $\bar{\nu} = 3195$ (N–H), 2245 (C≡N), 1726 and 1705 (2C=O) cm[1].

Methyl 5-cyano-9-(4-ethylphenyl)-7-methyl-2-oxo-4-thioxo-3,7-diazabicyclo[3.3.1]nonane-1-carboxylate

(**2e**, $C_{19}H_{21}N_3O_3S$)

Yield 53%; mp 202–203°C (acetone:*Et*OH = 1:1); ^{1}H NMR (200 MHz, *DMSO*-d$_6$): $\delta = 1.14$ (t, $^3J = 7.5$ Hz, CH_2CH_3), 2.28 (s, NCH_3), 2.57 (q, $^3J = 7.5$ Hz, CH_2CH_3), 3.01 (dd, $^2J = 11.0$ Hz, C(6)H_2 or C(8)H_2), 3.12 (dd, $^2J = 10.8$ Hz, C(8)H_2 or C(6)H_2), 3.25 (s, CO_2CH_3), 3.95 (s, C(9)*H*), 7.13 (q, $^3J = 7.0$ Hz, 4-$CH_3C_6H_4$), 13.47 (br, s, N*H*) ppm; IR (nujol): $\bar{\nu} = 3200$ (N–H), 2248 (C≡N), 1730 and 1720 (2C=O) cm^{-1}.

Ethyl 5-cyano-7-methyl-9-(2-nitrophenyl)-2-oxo-4-thioxo-3,7-diazabicyclo[3.3.1]nonane-1-carboxylate

(**2f**, $C_{18}H_{18}N_4O_5S$)

Yield 74%; mp 230–232°C (acetone:*Et*OH = 1:1); ^{1}H NMR (200 MHz, *DMSO*-d$_6$): $\delta = 0.64$ (t, $^3J = 7.2$ Hz, $CO_2CH_2CH_3$), 2.30 (s, N–CH_3), 3.03 (dd, $^2J = 11.4$ Hz, C(6)H_2 or C(8)H_2), 3.19 (dd, $^2J = 10.8$ Hz, C(8)H_2 or C(6)H_2), 3.75 (q, $^3J = 7.2$ Hz, $CO_2CH_2CH_3$), 4.28 (s, C(9)*H*), 7.44 (br, d, $^3J = 7.8$ Hz, C(6)H_{Ar}), 7.67 (pseudo-t, $^3J_{C(3)H–C(4)H} = 7.8$ Hz, $^3J_{C(4)H–C(5)H} = 7.4$ Hz, C(4)H_{Ar}), 7.80 (pseudo-t, $^3J_{C(5)H–C(6)H} = 7.8$ Hz, $^3J_{C(5)H–C(4)H} = 7.4$ Hz, C(5)H_{Ar}), 7.99 (br, d, $^3J = 7.8$ Hz, C(2)H_{Ar}), 13.71 (br, s, N*H*) ppm; IR (nujol): $\bar{\nu} = 3220$ (N–H), 2252 (C≡N), 1720 and 1709 (2C=O) cm^{-1}.

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