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Selectivity of methylation of some new [1,2,3]triazolo[4,5-*d*]pyridazines and structure elucidation by $^{1}H-^{15}N$ NMR spectroscopy

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Abstract

Alkylation of some selected [1,2,3]triazolo[4,5-*d*]pyridazines having five or more nitrogen atoms capable for alkylation was investigated. Pyridyl derivatives substituted also on the [1,2,3]triazole ring gave quaternary pyridinium salts, whereas in the case of the analogues compounds unsubstituted at the triazole moiety, the alkylation of the triazole ring was also observed. Unambiguous structure elucidation was provided by $^{1}H-^{15}N$ HMBC experiments which also allowed the assignment of the ^{15}N NMR shifts.

Keywords: Selectivity; Methylation; ^{15}N NMR spectroscopy; 2D NMR; Fused pyridazines

1. Introduction

Recently we have published a new straightforward synthetic pathway [1] to some new [1,2,3]triazolo[4,5-*d*]pyridazines starting from tricyclic zwitterionic fused triazines [2]. Since the new products contained five or more nitrogen atoms that could, in principle, undergo alkylation reaction, we decided to investigate this reactivity, too, in order to check if any selectivity can be observed in such processes.

We found that (5-Methyl-2-(4′-chlorophenyl)-7-phenyl-2,5-dihydro[1,2,3]triazolo[4,5-*d*]pyridazine-4-ylidene)-pyridin-2-yl-amine (**1**) [1] when treated with trimethyloxonium tetrafluoroborate at room temperature afforded a salt in good yield, which proved to be a quaternary methylated derivative (**2**) of the starting material. Compound **3** [1] containing the unsubstituted triazole moiety was reacted with methyl iodide under basic conditions in order to ensure the possibility for alkylation of the triazole ring, too. According to our expectations, besides the quaternarization (like with **2**) an additional methylation at the triazole ring also took place and $^{1}H-^{15}N$ HMBC experiments unambiguously revealed that the derivative **4** was formed (Scheme 1).

In contrast to these selective alkylations, the pyridazinone compound **5** when methylated under the same conditions yielded a mixture of two products (**6** and **7**) which was separated by column chromatography. This non-selective reaction is obviously due to the absence of the steric hinderance of the pyridylimino moiety in position 4.

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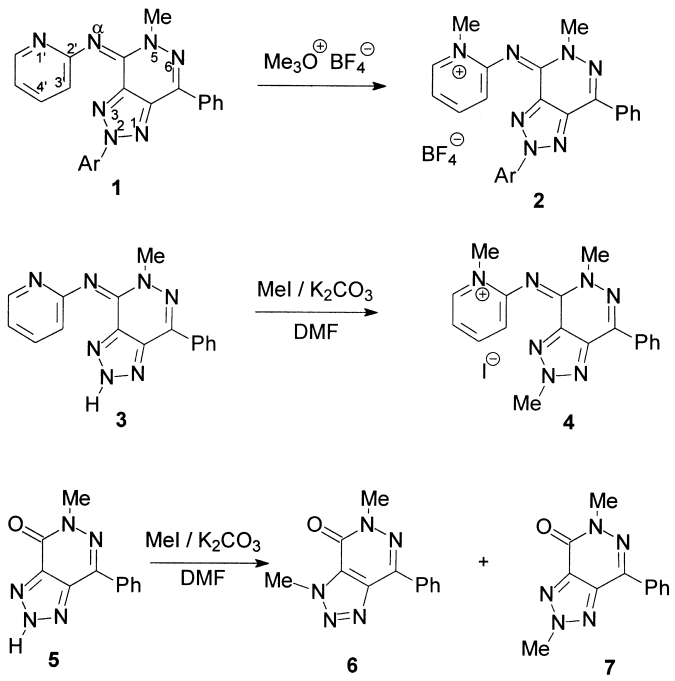

Scheme 1.

The structure determination of the studied compounds is based mainly on 2D HMBC $^{1}H-^{15}N$ NMR measurements revealing correlations between such protons and nitrogens that are separated by two, three or, occasionally, four bonds [3]. The 2D spectra of **2** is depicted in Fig. 1.

Fig. 1 reveals that position of the methyl group at the pyridine nitrogen (N1′) in quaternary salts **2** and **4** is evidenced by the cross peak of N1′ with the methyl protons (H–N1′–Me) originating from the alkylating agent. Furthermore, this nitrogen can unambiguously be identified by its correlations with H-6′ and H-3′,5′ protons through two and three bonds, respectively. Assignment of the nitrogen atom linking pyridine and triazolopyridazine rings (i.e. Nα) is straightforward due its cross peaks with H-3′ pyridine hydrogen as well as H–N1′–Me and H–N5–Me methyl hydrogens. The latter two correlations, apparently transmitted by four bonds, can probably be ascribed to weak hydrogen bonds between H–N1′–Me and Nα and H–N5–Me and Nα, respectively. These interactions, resulting in two cross peaks of approximately equal intensity, point to a restricted rotation about C2′–Nα bond favouring the sterically less crowded conformation in which N1′–Me group gets as far as possible from the condensed triazole ring.

Pyridazine nitrogens N-6 and N-5 are correlated with H–N5–Me methyl protons through two and three bonds, respectively. On the scale based on reference signal of liquid ammonia ($\delta = 0$ ppm) the resonance of N6 atom having considerable sp^2 character is more downfield shifted than that of the tri-coordinated N5 atom. A significant increase in the degree of lone pair delocalization from N5 towards the pyridinium moiety in quaternary salt **2** is reflected by the downfield shift of N5 resonance relative to that of precursor **1** [4–9]. On the other hand, the downfield shifted N-5 signal and the irregularly upfield shifted N1′ and Nα signals in precursor **3** indicate the presence of N1′ and Nα-protonated tautomeric forms (**3**/I and **3**/II: Fig. 2) which are in a fast equilibrium in $CDCl_3$ and can be represented by a number of resonance structures (e.g. A–C). Due to this fast equilibrium the measured values must be considered as time-averaged chemical shifts. A certain degree of quaternarization by protonation inducing upfield shift must take place on N1′ and Nα atoms as can be deduced from the analogous

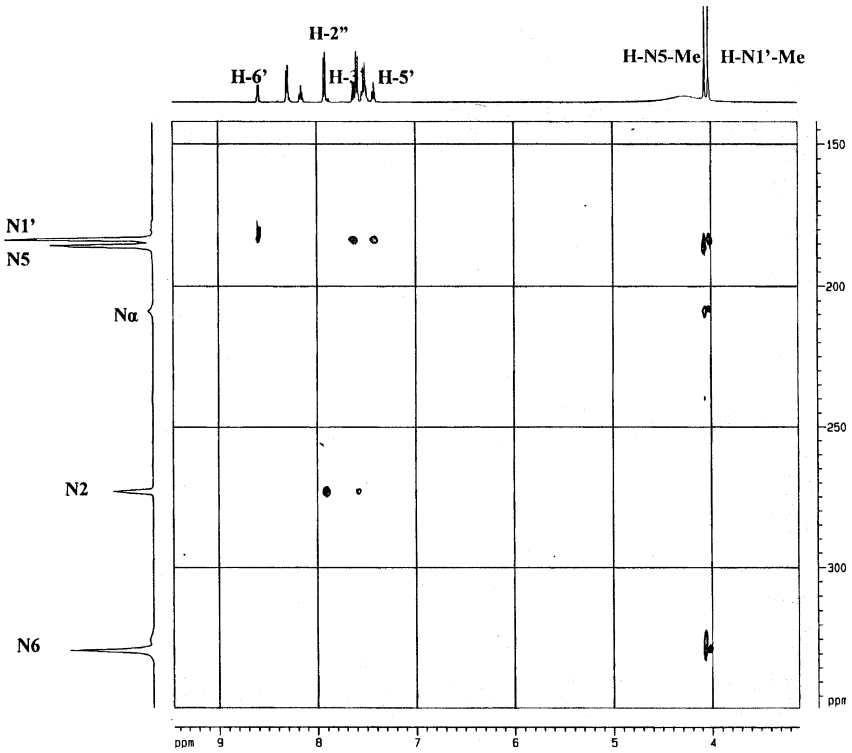

Fig. 1. 2D HMBC $^{1}H-^{15}N$ NMR spectra of compound **2**.

phenomenon observable for the methylation of N1′ atom ($\delta = 287.1$ ppm for **1** and 183.8 ppm for **2**).

This view is also supported by the upfield shifted N6-resonance (317.8 ppm for **3** and 330.2 ppm for **1** in $CDCl_3$) which is due to the enhanced electron-donation of the deprotonated triazole ring as shown by resonance structures of type C. It is also worth to point out that the very similar chemical shifts of the two methylated nitrogens (N1′ and N5) in **2** and **4** refer to a considerable delocalization of the positive charge between them.

The two isomeric dimethyltriazolopyridazinones **6** and **7** were unequivocally identified on the basis of $^{1}H-^{15}N$ HMBC correlations. In the 3,5-dimethyl derivative **6** only N1 and N2 atoms give correlation with the protons of the methyl group attached to the triazole ring, while N1, N2 and N3 signals give crosspeak with the corresponding methyl protons in the 2D spectrum taken of **7**.

Our results show that $^{1}H-^{15}N$ HMBC correlation experiments can be applied successfully in structure elucidation of polyaza heterocycles as well as in assignment of ^{15}N shifts in the NMR spectra.

2. ^{15}N NMR measurements

The 2D $^{1}H-^{15}N$ HMBC spectra were recorded with a Bruker DRX 500 spectrometer at 50.58 MHz using the standard Bruker gradient pulse program INV4GSLPLRND with the deuterium signal of the solvent as the lock. The resolution in the ^{15}N dimension was 4.9 Hz/point (SW = 200 ppm and TD = 2 K) to give ^{15}N-resonances (downfield from the signal of liquid ammonia as external reference) with the accuracy of one decimal number.

3. Experimental part

*3.1. (5-Methyl-2-(4′-chlorophenyl)-7-phenyl-2,5-dihydro[1,2,3]triazolo[4,5-d]pyridazine-4-ylidene)-pyridin-2-yl-amine (**1**)*

A mixture of 1-Methyl-3-phenyl-4-(4′-chlorophenylazo)pyrido[1,2-*b*]pyridazo[4,3-*e*][1,2,4]triazine HBF_4 salt [1] (1.8 g), tenfold amount of

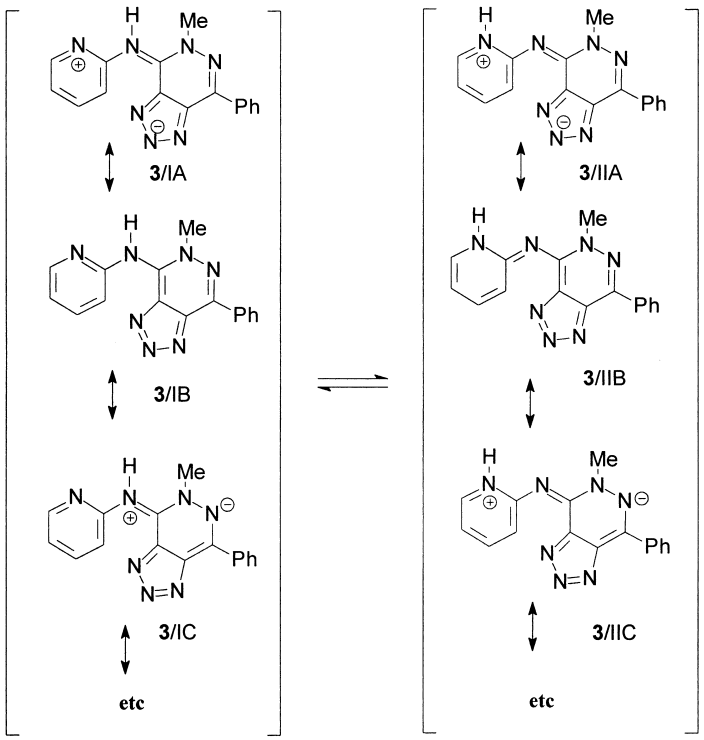

Fig. 2. Selected resonance structures of two alternative tautomeric forms (**3/I** and **3/II**) of **3**.

potassium carbonate (18 g), and toluene (100 ml) was stirred and refluxed for 10–15 min. The mixture was then filtered, and the filtrate evaporated. The residue was crystallized from acetonitrile to yield yellow needles: 1.1 g (74%), mp 225–227 °C. ^{1}H NMR δ($CDCl_3$): 4.06 (3H, s, 5-Me), 6, 99 (1-H, m, J_o = 8 Hz, J_m = 1 Hz, J_p = 1 Hz, H-3′-pyridyl), 7.08 (1H, m, J_o = 7 Hz, J_o = 5 Hz, J_m = 1 Hz, H-5′-pyridyl), 7.42 (2H, m, J = 9 Hz, H-3″, 5″-p-Cl–Ph); 7.48 (1H, m, H-4‴-Ph), 7, 52 (2H, m, H-3‴, 5‴-Ph), 7.72 (1H, m, J_o = 7 Hz, J_o = 8 Hz, J_m = 2 Hz, H-4′-pyridyl), 7.80 (2H, m, J = 9 Hz, H-2″, 6″-p-subst.-Ph), 8.32 (2H, m, H-2‴, 6‴-Ph), 8.44 (1H, m, J_o = 5 Hz, J_m = 2 Hz, J_p = 1 Hz, H-6′-pyridyl); ^{13}C NMR δ($CDCl_3$): 43.1, 117.7, 119.4, 122.2, 128.1, 129.6, 130.4, 130.5, 134.3, 136.3, 136.3, 138.6, 138.7, 138.8, 146.0, 149.6, 163.6; ^{15}N NMR δ($CDCl_3$): 173.9 (N5), 238.2 (Nα), 268.3 (N2), 287.1 (N1′), 310.9 and 320.5 (N1 and N3, interchangeable assignments), 330.2 (N6); MS, M_{calcd}: 413.1156, M_{found}: 413.1157 ± 5 ppm.

*3.2. (1′,5-Dimethyl-2-(4′-chloroyphenyl)-7-phenyl-2,5-dihydro[1,2,3]triazolo[4,5-d]pyridazine-4-ylidene)-pyridinium-2-yl-amine tetrafluoroborate (**2**)*

To a solution of 1 (400 mg) in abs CH_2Cl_2 (15 ml) was added 200 mg trimethyloxonium fluoroborate. The mixture was stirred for several hours at room temperature and was monitored by TLC. After disappearance of the starting material, ether was added to the mixture in portions, the precipitated solid was filtered off and crystallized from acetonitrile to give 450 mg (90%) of product, mp 253–255 °C.

^{1}H NMR δ(DMSO-d_6): 4.02 (3H, s, N-1′-Me), 4.06 (3H, s, 5-Me), 7.41 (1H, t, J_o = 8 Hz, J_o = 6 Hz, H-5′), 7.47–7.55 (3H, m, H-3‴, 4‴, 5‴-Ph), 7.62 (1H, d, J_o = 8.5 Hz, H-3′), 7.91 (2H, d, J_o = 8.6 Hz, H-2″, 6″-p-Cl–Ph), 8.15 (1H, dd, J_o = 8.5 Hz, J_o = 8 Hz, H-4′), 8.29 (2H, d, J_o = 8.6 Hz H-2‴, 6‴-Ph), 8.58 (1H, dd, J_o = 6 Hz, J_m = 1.5 Hz, H-6′); ^{15}N NMR δ(DMSO-d_6): 183.8 (N1′), 185.5 (N5), 209.9(Nα), 273.4 (N2), 314.9 (N1 and N3, overlapping signals), 329.6 (N6).

3.3. 5-Methyl-7-phenyl-2,5-dihydro[1,2,3]triazolo[4,5-d]pyridazine-4-ylidene)-pyridin-2-yl-amine (**3**)

To a solution of (5-Methyl-2-(4′-nitrophenyl)-7-phenyl-2,5-dihydro[1,2,3]triazolo[4,5-*d*]pyridazine-4-ylidene)-pyridin-2-yl-amine (4b) [1] (500 mg) in abs DMF (40 ml) was added methanolic (4 M) sodium methoxide solution (1.5 equiv, 0.3 ml) and the mixture was heated at 100 °C for 24 h. The DMF was evaporated and the residue was suspended in water and acidified with 10% HCl, extracted with CH_2Cl_2 the organic phase was dried and evaporated. Column chromatography of the residue (silica $CHCl_3$: MeOH 100:2) yielded 263 mg (70%) of product, mp 260 °C. ^{1}H NMR δ(DMSO-d_6): 4.18 (3H, s, 5-Me), 7.15 (1H, m, $J_o = 7$ Hz, $J_o = 5$ Hz, $J_m = 1$ Hz, H-5′-pyridyl), 7.4 (1H, m, $J_o = 8$ Hz, $J_m = 1$ Hz, $J_p =$ Hz, H-3′-pyridyl), 7.55–7.6 (3H, m, H-3″, 4″, 5″-Ph), 7.99 (1H, m, $J_o = 8$ Hz, $J_o = 7$ Hz, $J_p = 2$ Hz, H-4′-pyridyl), 8.21 (1H, m, $J_o = 5$ Hz, $J_m = 2$ Hz, $J_p =$ 1 Hz, H-6′-pyridyl), 8.65 (2H, m, H-2′, 6′-Ph), 14.6 (1H, b, 5-NH); ^{13}C NMR δ(DMSO-d_6): 43.3, 115.9, 121.7, 128.7, 129.1, 130.4, 137.7, 136.9, 138.7, 141.3, 142.0, 142.1, 150.3, 156.5; ^{15}N NMR δ($CDCl_3$): 186.1 (N1′); 190.0 (Nα); 191.1 (N5); 317.8 (N6); MS, M_{calcd}: 303.1232, M_{found}: 303.1233 ± 5 ppm.

3.4. (1′,2,5-Trimethyl-7-phenyl-2,5-dihydro[1,2,3]triazolo[4,5-d]pyridazine-4-ylidene)-pyridinium-2-yl-amine iodide (**4**)

A mixture of **3** (300 mg), abs DMF (10 ml) potassium carbonate (500 mg) and MeI (1 ml) was stirred at room temperature for 1 h. The mixture was then was filtered and the filtrate evaporated. The residue was crystallized from acetonitrile to yield colourless crystals: yield 410 mg (90%), mp 263–264 °C. ^{1}H NMR δ($CDCl_3$–CD_3OD 1:1): 4.12 (3H, s, N-1′-Me), 4.22 (3H, s, 5-Me), 4.49 (3H, s, 2-Me), 7.33 (1H, t, $J_o = 7$ Hz, $J_o = 6.2$ Hz, H-5′), 7.45 (1H, d, $J_o = 7.5$ Hz), 7.54 (3H, m, H-3″, 4″, 5″-Ph), 8.07 (1H, t, $J_o = 7.5$ Hz, $J_o = 7$ Hz, H-4′), 8.36 (2H, m, H-2″, 6″-Ph), 8.46 (1H, d, $J_o = 6.2$ Hz, H-6′); ^{13}C NMR δ(DMSO-d_6): 42.4, 43.2, 44. 2, 118.2, 120.1, 127.6, 129.2, 9, 132.2, 136.7, 139.9, 140.4, 142.8, 143.5, 147.3, 156.4; ^{15}N NMR δ($CDCl_3$–CD_3OD 1:1): 180.1 (N1′), 188.4 (N5), 202.0 (Nα), 268.8 (N2), 325.3 (N6 and N1 or N3, two overlapping signals), 328.3 (N1 or N3, interchangeable assignments); MS: 332 (M^+), 791 $[2M + I]^+$.

3.5. 5-Methyl-7-phenyl-2,5-dihydro[1,2,3]triazolo[4,5-d]pyridazin-4-one (**5**)

To a solution of 2-(4′-nitrophenyl)-5-methyl-7-phenyl-2,5-dihydro[1,2,3]triazolo[4,5-*d*]pyridazin-4-one [1] (500 mg) in 40 ml abs DMF was added methanolic a solution (4 M) of sodium methoxide (1.5 equiv. 0.5 ml) and the mixture was heated at 100 °C for 6 h. The solvent was removed, the residue was suspended in water, acidified with 10% HCl, filtered off and the solid was crystallized from acetonitrile to give 227 mg (70%) of product, mp 245–246 °C; ^{1}H NMR δ(DMSO-d_6): 3.82 (3H, s, 5-Me), 7.5–7.6 (3H, m, H-3′, 4′, 5′-Ph), 8.3 (2H, m, H-2′, 6′-Ph); ^{13}C NMR δ(DMSO-d_6): 39.0, 127.5, 128.8, 130.0, 133.1, 133.8, 137.6, 140.7, 153.8; ^{15}N NMR δ($CDCl_3$): 194.3 (N5); 324.3 (N6); MS, M_{calcd}: 227.0807, M_{found}: 227.0808 ± 5 ppm.

3.6. Alkylation of **5**

To a mixture of a solution of **5** (300 mg) in abs DMF (10 ml) and potassium carbonate (500 mg) was added methyl iodide (1 ml). The reaction mixture was stirred at room temperature for 1 h, filtered and evaporated. The residue was submitted to column chromatography (silica, $CHCl_3$: MeOH 100:2) to yield two products: **6** (with a higher R_f value) and **7** (lower R_f).

3.7. 3,5-Dimethyl-7-phenyl-3,5-dihydro[1,2,3]triazolo[4,5-d]pyridazin-4-one (**6**)

Yield: 170 mg (53%); mp 184–186 °C, ^{1}H NMR δ($CDCl_3$): 3.96 (3H, s, 3-Me), 4.55 (3H, s, 5-Me), 7.58–7.64 (3H, m, H-3′, 4′, 5′-Ph), 8.32 (2H, m, H-2′, 6′-Ph); ^{13}C NMR δ($CDCl_3$): 39.2, 43.6, 127.5, 128.7, 129.9, 133.1, 138.4, 139.7, 142.4, 155.5; no NOE effect between 5-Me and the phenyl protons; HMBC: enhancement of the C-3a absorption (128.7 ppm) when irradiating the 3-Me proton at 4.57 ppm; ^{15}N NMR δ($CDCl_3$): 195.7 (N5), 231.0 (N1), 323.6 (N6), 383.8 (N2); MS: M_{calcd}: 241.0964, M_{found}: 241.0954 ± 5 ppm.

*3.8. 2,5-Dimethyl-7-phenyl-2,5-dihydro[1,2,3]triazolo[4,5-d]pyridazin-4-one (**7**)*

Yield: 130 mg (41%); mp 172–173 °C; ^{1}H NMR $\delta(CDCl_3)$: 3.93 (3H, s, 2-Me), 4.56 (3H, s, 5-Me), 7.58–7.64 (3H, m, H-3′, 4′, 5′-Ph), 8.32 (2H, m, H-2′, 6′-Ph); ^{13}C NMR $\delta(CDCl_3)$: 36.7, 39.0, 127.9, 128.7, 132.7, 139.5, 143.2, 153.4; no NOE and HMBC effects; ^{15}N NMR $\delta(CDCl_3)$: 192.4 (N5); 264.5 (N2); 327.2 (N6); 325.3 and 329.2 (N1 and N3, interchangeable assignments); MS, M_{calcd}: 241.0964, M_{found}: 241.0959 ± 5 ppm.

Acknowledgements

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