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Mendeleev Commun., 2017, **27**, 462–463

Mendeleev Communications

Acetonylation of 5(3)-(1*H*-tetrazol-1-yl)-3(5)-nitro-1*H*-pyrazole

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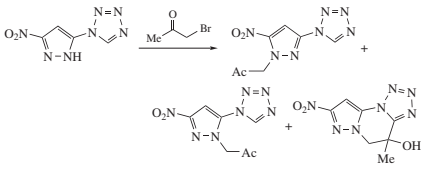
DOI: 10.1016/j.mencom.2017.09.010

N-Acetonylation of 5(3)-(1*H*-tetrazol-1-yl)-3(5)-nitro-1*H*-pyrazole with bromoacetone in the presence of $NaHCO_3$ at 60 °C gave, along with expected isomeric *N*-acetonyl derivatives, a tricyclic product of the intramolecular electrophilic attack at the carbon atom of the tetrazole cycle.



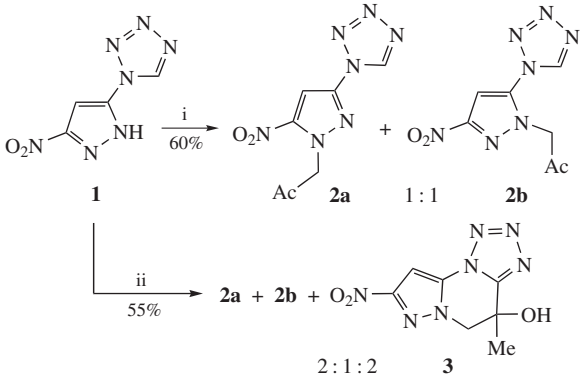
N-Acetonylazoles are extensively applied as highly reactive building blocks in heterocyclic chemistry. The electron-withdrawing *N*-azole substituent located in the α-position to the carbonyl group enhances reactivity of the methylene group with respect to C- and N-centered electrophiles, which is used for the synthesis of *N*-azolyl-substituted carbo- and heterocycles,[1] including annulated heterocyclic systems.[2] *N*-Acetonylazoles play a significant role in chemistry of high energy materials: they enable a one-step synthesis of *N*-dinitromethyl- and *N*-trinitromethylazoles by destructive nitration.[3,4]

As a rule, to prepare *N*-acetonylazoles, the anion generated from the corresponding NH-azole in the presence of base is alkylated with haloacetone to result either in the single isomer or in a mixture of regioisomeric derivatives depending on the type of azole and its substitution pattern.[5,6]

Following on from our previous research of N-functionalization of non-symmetrically substituted 3(5)-hetarylnitropyrazoles,[6,7] we report herein that acetonylation of 5(3)-(1*H*-tetrazol-1-yl)-3(5)-nitro-1*H*-pyrazole **1**[7] can proceed in a specific way. In fact, reaction of nitropyrazole **1** with bromoacetone in the presence of the equimolar NaOH amount in the water–acetone medium at room temperature affords the mixture of regioisomers **2a** and **2b** in the 1 : 1 ratio (Scheme 1).† Previously,[7] we noted the competing orienting influence of rather similar nitro group and *N*-tetrazole moiety on the direction of N-functionalization of compound **1** during its N-amination.[7]

Variation of acetonylation conditions for compound **1** brought about an unexpected result. Running the reaction with an excess of a deprotonating reagent ($NaHCO_3$) and at higher temperature as 60 °C led to formation of a new product **3**. At that, the total yield of *N*-acetonyl derivatives **2a** and **2b** dropped to 31% and their ratio changed to 2:1, *i.e.* the fraction of compound **2b** with spatially close *N*-acetonyl and tetrazole substituents reduced. Compound **3** turned to possess a tricyclic structure (see Scheme 1) on the basis of ^1H and ^{13}C NMR, IR spectroscopy, mass spectrometry and elemental analysis data.

Apparently, compound **3** is the product of the intramolecular electrophilic attack of the carbonyl C atom at the C^5 atom of the tetrazole fragment. Although similar reactions are known,[8] they remain a relatively rare phenomenon in tetrazole chemistry.[9]



Scheme 1 *Reagents and conditions*: i, $BrCH_2C(O)Me$, NaOH, H_2O–acetone, 25 °C, 80 h; ii, $BrCH_2C(O)Me$, $NaHCO_3$, H_2O–acetone, 60 °C, 10 h.

† IR spectra were recorded on a BrukerALPHA instrument in KBr pellets. ^1H, ^{13}C, ^{14}N NMR spectra were acquired on a Bruker AM-300 instrument (300.13, 75.47 and 21.69 MHz, respectively), 2D spectra NOESY ^1H–^1H and HMBC ^1H–^{13}C were acquired on a Bruker DRX-500 instrument (500.13 MHz for ^1H and 125.76 MHz for ^{13}C) in DMSO-d_6 at 299 K. The chemical shifts were reported relative to TMS (for ^1H and ^{13}C) and $MeNO_2$ (^{14}N). HRMS with electrospray ionization were recorded on a Bruker MicroOTOF II instrument. Elemental analysis was performed on a PerkinElmer 2400 Series II instrument. Melting points were determined by Kofler method on a Boetius bench (heating rate 4 K min^{-1}) and were not corrected. The reaction progress and purity of the obtained compounds were controlled by TLC on Merck Silica gel 60 F_{254} plates.

The starting 5(3)-(1*H*-tetrazol-1-yl)-3(5)-nitro-1*H*-pyrazole **1** was obtained according to a published procedure.[7]

Synthesis of compounds **2a**,**b** *and* **3**.

Method A. Tetrazolylpyrazole **1** (0.54 g, 2.98 mmol) was added to a solution of NaOH (0.27 g, 7.25 mmol) in H_2O (5 ml). A solution of bromoacetone (0.33 ml, 3.98 mmol) in acetone (5 ml) was then added dropwise. The mixture was maintained at 20 °C for 84 h. The precipitate that formed was filtered off, washed with water, and air-dried. The filtrate was extracted with EtOAc (2×25 ml), the extract was dried over anhydrous $MgSO_4$. The solvent was evaporated *in vacuo* to leave the second crop of the product. Both precipitates were combined. The product was a 1 : 1 mixture of isomers **2a** and **2b** (0.42 g, 60%), which were separated by column chromatography (eluent $CHCl_3$).

Method B. Compound **1** (0.50 g, 2.76 mmol) was added to a solution of $NaHCO_3$ (0.70 g, 8.33 mmol) in H_2O (10 ml). A solution of bromoacetone (0.30 ml, 3.58 mmol) in acetone (10 ml) was then added dropwise. The mixture was stirred at 60 °C for 10 h. The solvent was evaporated to dryness at reduced pressure. The product was a 2 : 1 : 2 mixture (0.36 g, 55%) of isomers **2a** and **2b** and annulated compound **3**, respectively, which were separated by column chromatography (eluent $CHCl_3$).

To our knowledge, such a coupling requires preparing appropriate C^5-lithium tetrazolates in absolute solvents (THF, Et_2O) and low temperatures (–70 to –90 °C).[10] In our case, the reaction proceeds under exceptionally mild conditions with weak base ($NaHCO_3$) in water. This opens up new opportunities in tetrazole chemistry. The presence of the electron-withdrawing nitropyrazole fragment in the N^1 atom of the tetrazole moiety in compound **2b** is likely to facilitate its deprotonation by the C^5 atom followed by the intramolecular attack at the spatially adjacent carbonyl atom of the *N*-acetonyl substituent.

The structure of each product was confirmed by elemental analysis, IR and NMR spectroscopy, and high resolution mass spectrometry. Signals in the NMR spectra were assigned on the basis of regularities established for the 3(5)-hetarylnitropyrazole series.[6,7] The assignment was ascertained using 2D correlation spectroscopy ^1H–^1H NOESY and ^1H–^{13}C HMBC (Figure 1).

In the case of isomer **2a**, the HMBC spectrum showed correlation of hydrogen atoms of the methylene group with the carbon atom bound to the nitro group (δ 146.7 ppm), *viz.* with the C^5 atom of the pyrazole cycle. In compound **2b**, correlation with the other carbon atom (δ 134.5 ppm) in the analogous spectrum was observed. HMBC spectrum of annulated compound **3**, apart from similar correlation of hydrogen atoms of the methylene group with the C^5 atom of the pyrazole group, contained correlation of this group with the C^5 atom of the tetrazole cycle and correlation of hydrogen atoms of methyl, methylene and hydroxyl groups with neighboring carbon atoms, which was indicative of the atom chain C^5_{Pz}–N^1_{Pz}–$CH_2C(OH)Me$–C^5_{Tetr}.

In conclusion, the possibility of intramolecular cyclization with participation of the spatially close *N*-acetonyl group and C^5 atom of the tetrazole cycle has been for the first time revealed in the course of N-acetonylation of 5(3)-(1*H*-tetrazol-1-yl)-3(5)-nitro-1*H*-pyrazole.

This work was supported by the Russian Science Foundation (project no. 14-13-01153).

*1-Acetonyl-5-nitro-3-(1*H*-tetrazol-1-yl)-1*H*-pyrazole* **2a**. Yield 0.21 g (30%, method A), 0.14 g (21%, method B); R_f 0.67 ($CHCl_3$–MeOH, 10:1), mp 153–154 °C ($CHCl_3$–MeOH, 10:1, white needles). IR (ν/cm^{-1}): 3132 (w), 2960 (w), 1720 (s), 1564 (s), 1516 (vs), 1408 (m), 1356 (s), 1256 (m), 1184 (m), 1092 (s), 1012 (w), 956 (m), 844 (m), 772 (s), 744 (m), 656 (w). ^1H NMR, δ: 2.29 (s, 3H, Me), 5.70 (s, 2H, CH_2), 7.92 (s, 1H, H-4), 10.06 (s, 1H, H_{Tetr}). ^{13}C NMR, δ: 200.8 (C=O), 146.7 (br. s, C^5), 143.4 (C_{Tetr}), 141.0 (C^3), 100.0 (C^4), 62.9 (CH_2), 27.4 (Me). ^{14}N NMR, δ: –26.08 (NO_2). HRMS, *m*/*z*: 260.0505 $[M+Na]^+$ (calc., *m*/*z*: 260.0503). Found (%): C, 35.45; H, 2.94; N, 41.17. Calc. for $C_7H_7N_7O_3$ (%): C, 35.45; H, 2.97; N, 41.34.

*1-Acetonyl-3-nitro-5-(1*H*-tetrazol-1-yl)-1*H*-pyrazole* **2b**. Yield 0.21 g (30%, method A), 0.07 g (11%, method B); R_f 0.57 ($CHCl_3$–MeOH, 10:1), mp 135–136 °C ($CHCl_3$–MeOH, 10:1, white needles). IR (ν/cm^{-1}): 3160 (w), 3132 (w), 1736 (vs), 1588 (m), 1572 (s), 1544 (s), 1516 (s), 1488 (s), 1356 (m), 1340 (s), 1304 (s), 1212 (w), 1176 (s), 1084 (s), 1004 (m), 992 (m), 880 (w), 828 (w), 756 (w), 588 (w). ^1H NMR, δ: 2.16 (s, 3H, Me), 5.49 (s, 2H, CH_2), 7.75 (s, 1H, H-4), 9.99 (s, 1H, H_{Tetr}). ^{13}C NMR, δ: 200.5 (C=O), 154.2 (br. s, C^3), 145.8 (C_{Tetr}), 134.5 (C^5), 100.3 (C^4), 60.8 (CH_2), 27.4 (Me). ^{14}N NMR, δ: –22.03 (NO_2). HRMS, *m*/z: 238.0688 $[M+H]^+$ (calc., *m*/*z*: 238.0683). Found (%): C, 32.80; H, 3.72; N, 38.68. Calc. for $C_7H_7N_7O_3{\cdot}H_2O$ (%): C, 32.95; H, 3.55; N, 38.42.

*4-Methyl-8-nitro-4,5-dihydropyrazolo[1,5-*a*]tetrazolo[1,5-*c*]pyrimidin-4-ol* **3**. Yield 0.15 g (23%, method B); R_f 0.50 ($CHCl_3$–MeOH, 10:1), mp 187–188 °C ($CHCl_3$–MeOH, 10:1, light yellow needles). IR (ν/cm^{-1}): 3384 (s), 3147 (m), 1610 (s), 1548 (s), 1532 (s), 1487 (m), 1421 (m), 1337 (s), 1298 (m), 1213 (m), 1147 (s), 1111 (m), 976 (w), 831 (w), 817 (w), 790 (w), 754 (w). ^1H NMR, δ: 1.87 (s, 3H, Me), 4.73 (d, 1H, CH^aH^b, ^2J 13.7 Hz), 4.61 (d, 1H, CH^aH^b, ^2J 13.7 Hz), 6.97 (s, 1H, OH), 7.84 (s, 1H, H-4). ^{13}C NMR, δ: 154.6 (br. s, C^3), 153.5 (C_{Tetr}), 133.6 (C^5), 91.6 (C^4), 64.7 (C–OH), 58.1 (CH_2), 22.4 (Me). ^{14}N NMR, δ: –16.31 (NO_2). HRMS, *m*/*z*: 260.0494 $[M+Na]^+$ (calc., *m*/*z*: 260.0503). Found (%): C, 32.89; H, 3.60; N, 37.93. Calc. for $C_7H_7N_7O_3{\cdot}H_2O$ (%): C, 32.95; H, 3.55; N, 38.42.

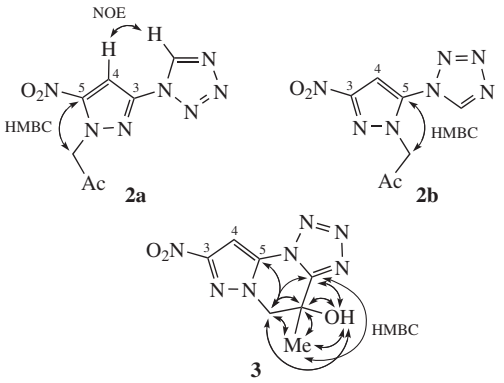


Figure 1 The main correlation pattern in NOESY ^1H–^1H and HMBC ^1H–^{13}C spectra of compounds **2a**, **2b**, and **3**.

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Received: 22nd March 2017; Com. 17/5206