The Effenberger's synthesis of 3,3'-bipyrazole revisited

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Dedicated to Professor Mieczyslaw Makosza on his 70th anniversary

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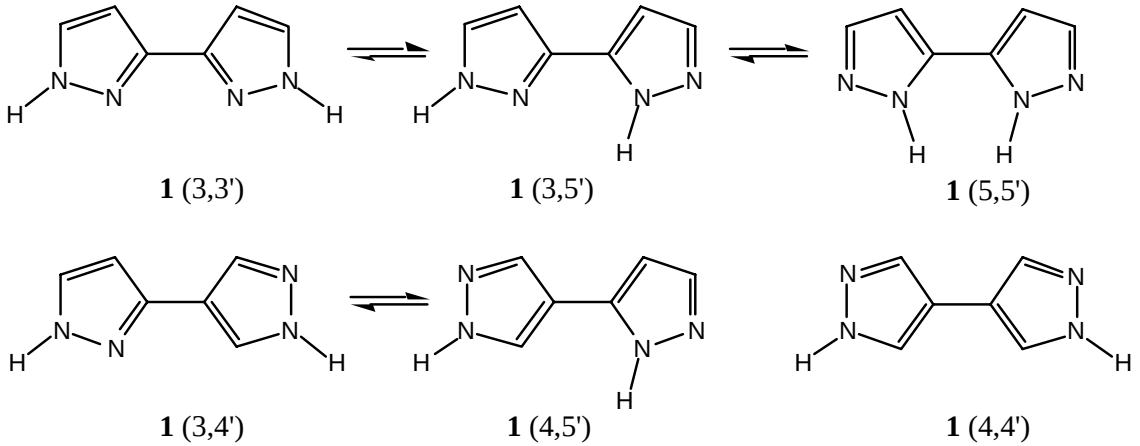
Abstract

When 1,4-bis-ethoxymethylen-2,3-butanedione **2** reacts with hydrazine, following a slightly modified Effenberger's procedure, other compounds than the expected 3,5'-bipyrazole **1** are obtained. This paper describes the isolation, besides **1**, of two pyridazinones and one 6*H*-6,7-dihydropyrazolo[1,5-*d*]-1,2,4-triazine and the determination of their structure by mass spectrometry and by ^{1}H and ^{13}C NMR.

Keywords: Effenberger's procedure, bipyrazoles, pyridazinones, pyrazolotriazines

Introduction

There are six derivatives of bipyrazole **1** which differ from the position of the C-C bond between the two pyrazole rings (Scheme 1).



Scheme 1

All of these compounds, except the 4,4'-derivative, exist separately when they are *N*-

substituted, but the NH forms represented in Scheme 1 are subject to annular tautomerism.[1] All of them have been prepared: the family of 3,3'-, 3,5'- and 5,5'- derivatives by many authors, generally with substituents on the carbon atoms,[2-12] the 3,4'- (4,5'-) family less frequently[6,13,14] and, finally, 4,4'-bipyrazoles being again quite common.[6,15-22] The parent compounds are described for 3,3'-bipyrazole[2,7,11] and 4,4'-bipyrazole[16,18-20] but that of 3,4'-bipyrazole has not been prepared yet. All of these compounds have important uses in coordination chemistry as polydentate ligands.

3,3'-Bipyrazole **1** (3,3') has been reported three times. Effenberger[2] prepared it from 1,4-bis-ethoxymethylenbutane-2,3-dione **2** and hydrazine with a yield of 75% (60% after crystallization) and a m.p. of 257 °C. Then Wille and Schwab[7] obtained **1** from 1,1,6,6-tetraethoxy-2,4-hexadiyne and hydrazide hydrochloride with a yield of 34% and reported its ^{1}H NMR spectrum in DMSO-d_6 but not its melting point. Finally, some of us prepared again **1** using the Effenberger's procedure, determined its X-ray structure and discussed its tautomerism in solution.[11] We should note that Habraken *et al*.[6] prepared the three bis-*N*-methyl derivatives of **1** (3,3'-, 3,5'- and 5,5'-) using the method of Effenberger with methylhydrazine instead of hydrazine, the total yield being between 25 and 34%. Since we needed compound **1** for synthesizing new ligands, we decided to prepare it again.

Results and Discussion

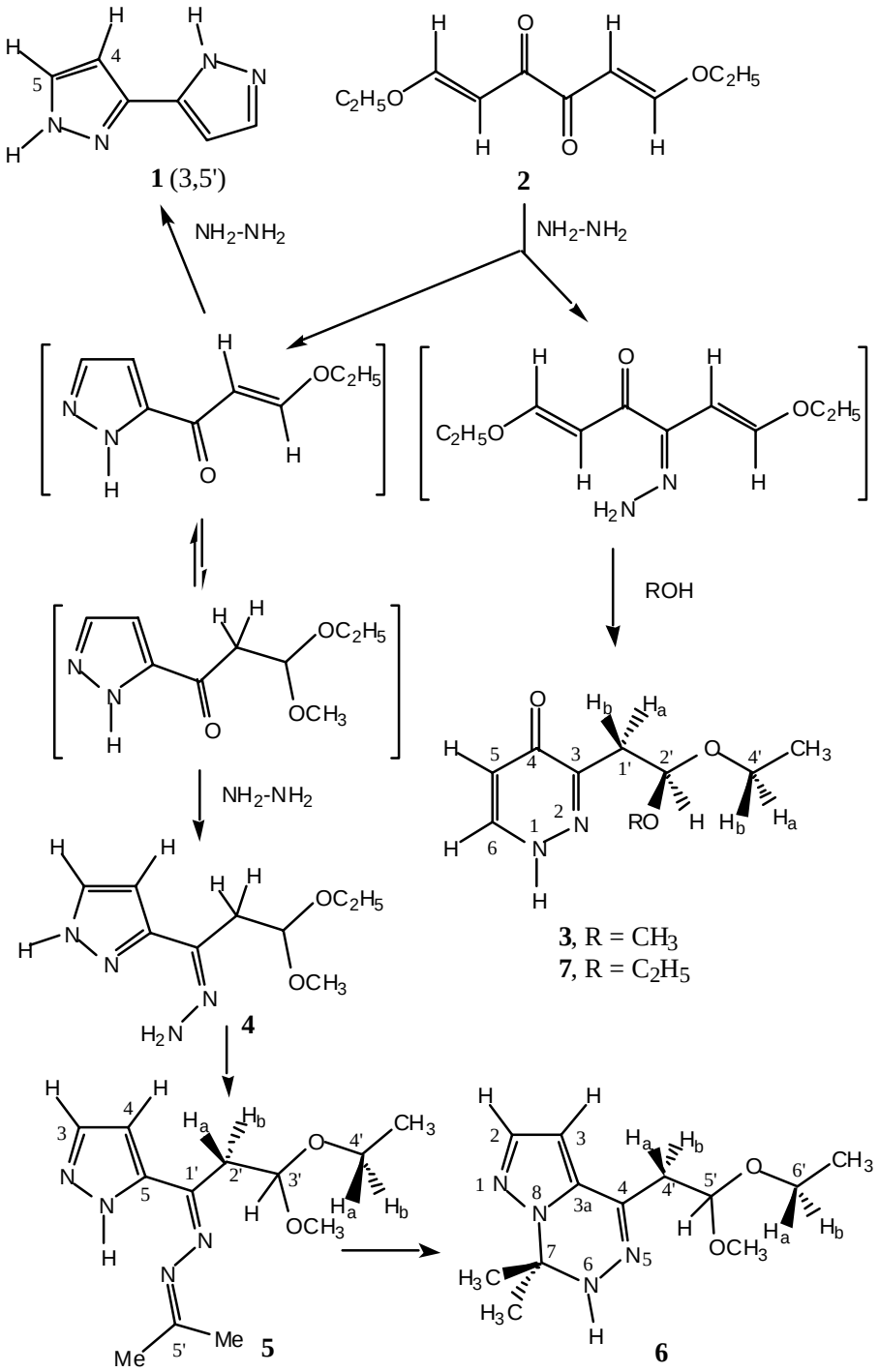
Effenberger's synthesis of hydrazine is reported like this:[2] First, free hydrazine was prepared adding sodium methoxide in methanol (1.84 g of sodium, 80 mmol, in 40 mL of anhydrous methanol) to 4.2 g (40 mmol) of hydrazonium dichloride in 10 mL of anhydrous methanol. Sodium chloride was filtered off and the methanolic hydrazine solution was cooled down to –10 ºC and 1.98 g (10 mmol) of 1,4-bis-ethoxymethylen-butane-2,3-dione **2** in 20 mL of anhydrous ether was added. **The solution was kept at –10 ºC for 24 h**. Compound **1** precipitates: 1.0 g (75% yield), m.p. 257 ºC. Crystallized from ethanol, 0.8 g (60% yield), pure **1** m.p. 261 ºC.

Following exactly this procedure, an identical result was obtained, but if instead of keeping the solution at –10 ºC for 24 h, **the solution was abandoned at room temperature (in our case 21 ºC)**, then nothing precipitates. The solution was evaporated to dryness and a orange solid was obtained. A ^{1}H NMR of the crude in DMSO-d_6 shows that it is a 55-30-15% mixture of three compounds (**A**-**B**-**C**). When the crude was dissolved in acetone and evaporated, compound **B** (30%) disappeared and two new compounds **D** and **E**, in comparable proportions, were formed, the first one evolving on standing to **E**. These compounds were isolated by flash chromatography, but **B** proved too unstable to be fully characterized. We have determined the structure of all these compounds by a combination of mass spectrometry and ^{1}H and ^{13}C NMR: **A** is **3**, **B** is probably **4**, **C** is the desired **1**, **D** is **5** and **E** is **6** (see Scheme 2).

We have found another procedure to prepare **1** which uses **hydrazine hydrate**: 40.0 mmol of hydrazine hydrate in 12 mL of THF were added to 20.0 mmol of diketone **2** and a few grains of *p*-toluenesulfonic acid in 20 mL of anhydrous THF. The mixture was **left under stirring for 24 h**

at room temperature and then filtered off. The insoluble solid was washed with THF and dried under vacuum. Bipyrazole **1** was obtained with a yield of 75% (note that once in the solid state, **1** is a very insoluble compound).

The different compounds and their numbering are reported in Scheme 2. Postulated intermediaries are in brackets; compound **4** has no numbering system because no NMR spectrum could be obtained.



Scheme 2

Identification of the diferent compounds. Compound **1** (m.p. 258-260 ºC) was identified by comparison with an authentic sample.[11] ^{1}H NMR (DMSO-d_6): δ 12.97 (broad s, NH); 7.66 (broad s, H-5); 6.54 (d, ^3J = 2.1 Hz, H-4). ^{13}C NMR (DMSO-d_6 + 1 drop of CF_3CO_2H): δ 141.41 (C-5); 133.26 (C-3); 102.69 (C-4).

Compound **3** (R = CH_3, m.p. 114-115 ºC). HRMS m/z 198.1019 ($C_9H_{14}N_2O_3$) requires 198.1004. NMR ($CDCl_3$): ^{1}H δ 6.52 (d, ^3J = 7.3 Hz, H-5), 7.97 (d, ^3J = 7.3 Hz, H-6), 3.14 (d, ^3J = 5.8 Hz with H-2', H_a and H_b on C-1'), 5.09 (t, ^3J = 5.8 Hz with H_a and H_b on C-1', H-2'), 3.38 (s, CH_3O on C-2'), 3.73 (ABX$_3$, $^2J_{gem}$ = –9.5 Hz, ^3J = 7.0 Hz with CH_3 on C-4', H_b on C-4'), 3.59 (ABX$_3$, $^2J_{gem}$ = –9.5 Hz, ^3J = 7.0 Hz with CH_3 on C-4', H_a on C-4'), 1.20 (t, ^3J = 7.0 Hz with H_a and H_b on C-4', CH_3 on C-4'). ^{13}C δ 157.01 (C-3), 171.57 (C-4), 114.25 (C-5), 139.81 (C-6), 34.89 (C-1'), 100.78 (C-2'), 52.96 (CH_3O on C-2'), 61.72 (C-4'), 15.18 (CH_3 on C-4'). Note that in compound **3**, H_a and H_b on C-1' are diastereotopic but accidentally isochronous at 250 MHz.

Compound **7** (R = C_2H_5, m.p. 119-120 ºC). HRMS m/z 212.1140 ($C_{10}H_{16}N_2O_3$) requires 212.1161. NMR ($CDCl_3$): ^{1}H δ 6.51 (d, ^3J = 7.4 Hz, H-5), 7.98 (d, ^3J = 7.4 Hz, H-6), 3.13 (d, ^3J = 5.9 Hz with H-2', H_a and H_b on C-1'), 5.137 (t, ^3J = 5.9 Hz with H_a and H_b on C-1', H-2'), 3.72 (ABX$_3$, $^2J_{gem}$ = –9.5 Hz, ^3J = 7.1 Hz with CH_3 on C-4', H_b on C-4'), 3.56 (ABX$_3$, $^2J_{gem}$ = –9.5 Hz, ^3J = 7.1 Hz with CH_3 on C-4', H_a on C-4'), 1.16 (t, ^3J = 7.1 Hz with H_a and H_b on C-4', CH_3 on C-4'). ^{13}C δ 156.79 (C-3), 171.52 (C-4), 113.99 (C-5), 140.29 (C-6), 35.41 (C-1'), 100.04 (C-2'), 61.38 (C-4'), 15.07 (CH_3 on C-4'). Note that in compound **7** the two OEt group on C-2' are enantiotopic just as H_a and H_b on C-1', but that H_a and H_b on each OEt group are diastereotopic.

Compound **4** was not isolated, only a GC/MS spectrum was obtained, 213 Da $[M+H]^+$, calculated for $C_9H_{16}N_4O_2$, m/z = 212.1 Da.

Compound **5** (oil). HRMS m/z 252.1579 ($C_{12}H_{20}N_4O_2$) requires 252.1586. NMR ($CDCl_3$): ^{1}H δ 6.66 (d, ^3J = 2.1 Hz, H-4), 7.535 (d, ^3J = 2.1 Hz, H-3), 1.90 and 2.05 (CH_3 groups on C-5'), 3.27 (s, CH_3O on C-3'), 3.159 (m, $^2J_{gem}$ = –12.7 Hz, ^3J = 5.7 Hz with H-3', H_a), 3.11 (ABX, $^2J_{gem}$ = –12.7 Hz, ^3J = 5.7 Hz with H-3', H_b), 4.76 (t, ^3J = 5.7 Hz with H_a and H_b on C-2', H-3'), 3.62 (ABX$_3$, $^2J_{gem}$ = –9.4 Hz, ^3J = 7.0 Hz with CH_3 on C-4', H_b), 3.43 (ABX$_3$, $^2J_{gem}$ = –9.4 Hz, ^3J = 7.0 Hz with CH_3 on C-4', H_a), 1.09 (t, ^3J = 7.0 Hz with H_a and H_b on C-4', CH_3 on C-4'). ^{13}C δ 145.44 (C-5), 105.14 (C-4), 135.23 (C-3), 151.36 (C-1'), 33.83 (C-2'), 101.55 (C-3'), 62.13 (C-4'), 53.41 (CH_3O on C-3'), 15.00 (CH_3 on C-4'), 162.43 (C-5'), 25.02 and 18.59 (CH_3 groups on C-5').

Compound **6**, 6*H*-6,7-dihydropyrazolo[1,5-*d*]-1,2,4-triazine, m.p. 132-134 ºC. HRMS m/z 252.1618 ($C_{12}H_{20}N_4O_2$) requires 252.1586. NMR ($CDCl_3$): ^{1}H δ 7.52 (d, ^3J = 2.1 Hz, H-2), 6.35 (d, ^3J = 2.1 Hz, H-3), 2.88 (d, ^3J = 6.0 Hz with H-5', H_a and H_b on C-4'), 4.82 (t, ^3J = 6.0 Hz with H_a and H_b on C-4'), 3.36 (s, CH_3O on C-5'), 3.70 (ABX$_3$, $^2J_{gem}$ = – 9.4 Hz, ^3J = 7.1 Hz with CH_3 on C-6', H_a on C-6'), 3.52 (ABX$_3$, $^2J_{gem}$ = – 9.4 Hz, ^3J = 7.1 Hz with CH_3 on C-6', H_b on C-6'), 1.18 (t, ^3J = 7.1 Hz with H_a and H_b on C-6', CH_3 on C-6'). ^{13}C δ 138.59 (C-2), 102.57 (C-3), 137.25 (C-3a), 130.53 (C-4), 71.54 (C-7), 24.31 (two CH_3 groups on C-7), 37.04 (C-4'), 101.61 (C-5'), 61.51 (C-6'), 52.76 (CH_3O on C-5'), 15.01 (CH_3 on C-6'). ^{15}N δ – 88.53 (N-1), – 163.82

(N-8), – 68.80 (N-5), –246.55 (N-6). Note that in compound **6**, as in compound **3**, H_a and H_b on C-1' are diastereotopic but accidentally isochronous at 250 MHz.

Mechanism. Scheme 2 is not a mechanistic one, but only a naive representation of the origin of the compounds in the different procedures described above as well as in other attempts. For instance, using an ethanolic solution of hydrazine hydrate and *p*-toluenesulfonic acid as catalyst, the reaction gave 50% of bipyrazole **1** and 50% of the pyridazin-4-one derivative **7**. This last compound is a proof of the attack of one double bond of the starting ketone by the solvent ROH. Actually, the diketone **2** behaves like a protected dialdehyde that reacts like a tetracarbonyl compound, that is, OHC-CH_2-CO-CO-CH_2-CHO. Reaction of the β-dicarbonyl part would lead to pyrazoles but reacting as a γ-dicarbonyl compound corresponds to the well-known synthesis of pyridazines. [23,24]

Tautomerism. The compounds described in this paper deserve some comments concerning their tautomerism. Compound **1** exists in solution as tautomer 3,5' (see Scheme 1).[11] The pyridazine derivatives **3** and **7** exist in $CDCl_3$ solution as oxo tautomers (pyridazinones), according to the signal of the C-4 (171.5 ppm). In the related case of 4-hydroxypyridine in equilibrium with 4-pyridone, C-4 appears at 167.8 and 180.9 ppm[25] respectively, but these values have to be corrected by –8.6 ppm corresponding to the effect of the N-2 atom.[26] Thus, the predicted values are 159.2 ppm for the 4-hydroxypyridazine and 172.3 ppm for the 4-pyridazinone. This conclusion is consistent with other pyridazinones [see ref. 1, p. 122]. Finally, pyrazole **5** is probably a 5-substituted tautomer because $^3J_{HH}$ = 2.1 Hz like $^3J_{H3\text{-}H4}$ in compound **6** and because 135.23 ppm corresponds to a C-3 signal.[27] Note that **6** is a ring-chain isomer of **5** (a $CDCl_3$ solution of **5** is found by ^{1}H NMR to evolve in 24 h to 100% of **6**).

Experimental Section

General Procedures. ^{1}H NMR spectra were recorded on a Bruker Avance-250 spectrometer working at 250.130 for ^{1}H, 62.896 for ^{13}C and 25.355 MHz for ^{15}N. Chemical shifts are expressed in ppm/TMS for ^{1}H and ^{13}C and in ppm/external NO_2Me for ^{15}N spectra. Coupling constants are in Hertz. Solvent was $CDCl_3$ unless stated otherwise. All the structures were determined by mass spectrometry and NMR spectroscopy. Signals of ^{1}H and ^{13}C NMR spectra were assigned with the help of HMQC and HMBC experiments. Assignments of signals of the ^{15}N spectrum of compound **6** were made according to Gouesnard *et al.*[28] and Claramunt *et al.*[29] Non first-order spectra were calculated using NMRSIM[30] and gNMR[31] softwares affording chemical shifts with three decimal places. Exact masses were determined using electron impact technique and PFK as reference (VG AutoSpec), accuracy ± 0.0025 daltons.

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