

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

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Dedicated to Professor Mieczyslaw Makosza on his 70th anniversary

(received 19 May 03; accepted 14 Aug 03; published on the web 11 Sept 03)

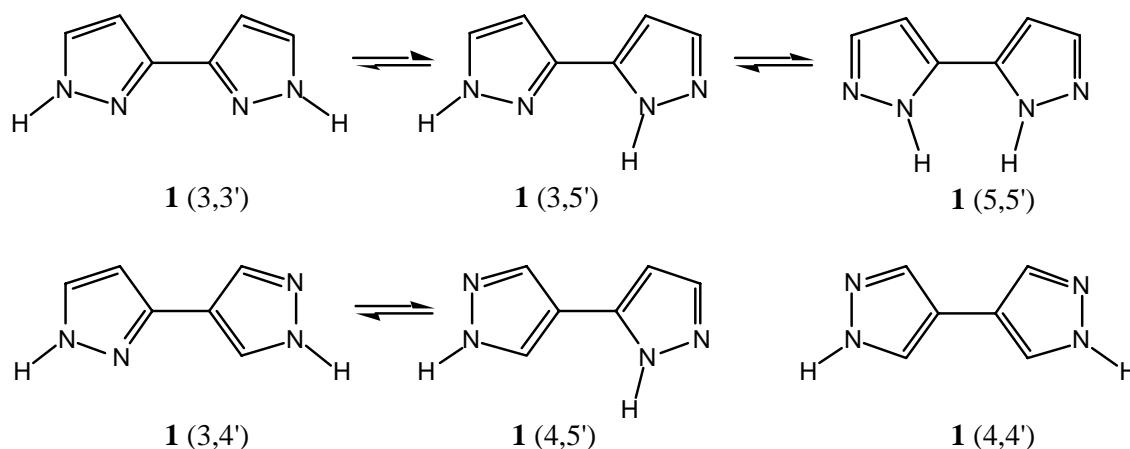
Abstract

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 ¹H and ¹³C 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. Effenberger² 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 Schwab⁷ obtained **1** from 1,1,6,6-tetraethoxy-2,4-hexadiyne and hydrazide hydrochloride with a yield of 34% and reported its ¹H 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

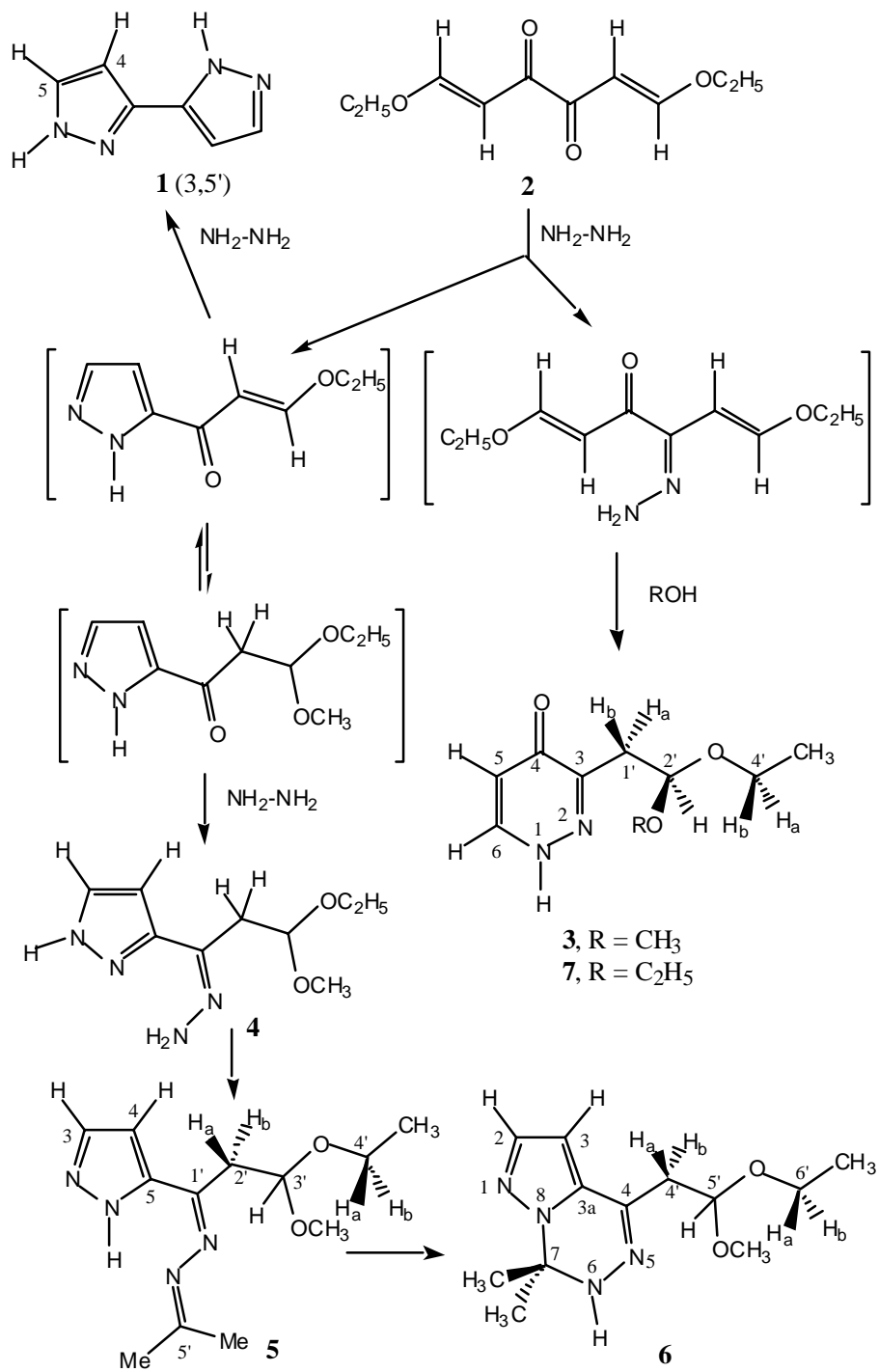
Effenberger's synthesis of hydrazine is reported like this:² First, free hydrazine was prepared adding sodium methoxide in methanol (1.84 g of sodium, 80 mmol, in 40 mL of anhydrous methanol) to 4.2 g (40 mmol) of hydrazonium dichloride in 10 mL of anhydrous methanol. Sodium chloride was filtered off and the methanolic hydrazine solution was cooled down to -10 °C 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 °C for 24 h.** Compound **1** precipitates: 1.0 g (75% yield), m.p. 257 °C. Crystallized from ethanol, 0.8 g (60% yield), pure **1** m.p. 261 °C.

Following exactly this procedure, an identical result was obtained, but if instead of keeping the solution at -10 °C for 24 h, **the solution was abandoned at room temperature (in our case 21 °C)**, then nothing precipitates. The solution was evaporated to dryness and an orange solid was obtained. A ¹H 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 ¹H and ¹³C 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 different compounds. Compound **1** (m.p. 258-260 °C) was identified by comparison with an authentic sample.¹¹ ¹H NMR (DMSO-*d*₆): δ 12.97 (broad s, NH); 7.66 (broad s, H-5); 6.54 (d, ³*J* = 2.1 Hz, H-4). ¹³C NMR (DMSO-*d*₆ + 1 drop of CF₃CO₂H): δ 141.41 (C-5); 133.26 (C-3); 102.69 (C-4).

Compound **3** (R = CH₃, m.p. 114-115 °C). HRMS *m/z* 198.1019 (C₉H₁₄N₂O₃) requires 198.1004. NMR (CDCl₃): ¹H δ 6.52 (d, ³*J* = 7.3 Hz, H-5), 7.97 (d, ³*J* = 7.3 Hz, H-6), 3.14 (d, ³*J* = 5.8 Hz with H-2', H_a and H_b on C-1'), 5.09 (t, ³*J* = 5.8 Hz with H_a and H_b on C-1', H-2'), 3.38 (s, CH₃O on C-2'), 3.73 (ABX₃, ²*J*_{gem} = -9.5 Hz, ³*J* = 7.0 Hz with CH₃ on C-4', H_b on C-4'), 3.59 (ABX₃, ²*J*_{gem} = -9.5 Hz, ³*J* = 7.0 Hz with CH₃ on C-4', H_a on C-4'), 1.20 (t, ³*J* = 7.0 Hz with H_a and H_b on C-4', CH₃ on C-4'). ¹³C 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 (CH₃O on C-2'), 61.72 (C-4'), 15.18 (CH₃ 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 = C₂H₅, m.p. 119-120 °C). HRMS *m/z* 212.1140 (C₁₀H₁₆N₂O₃) requires 212.1161. NMR (CDCl₃): ¹H δ 6.51 (d, ³*J* = 7.4 Hz, H-5), 7.98 (d, ³*J* = 7.4 Hz, H-6), 3.13 (d, ³*J* = 5.9 Hz with H-2', H_a and H_b on C-1'), 5.137 (t, ³*J* = 5.9 Hz with H_a and H_b on C-1', H-2'), 3.72 (ABX₃, ²*J*_{gem} = -9.5 Hz, ³*J* = 7.1 Hz with CH₃ on C-4', H_b on C-4'), 3.56 (ABX₃, ²*J*_{gem} = -9.5 Hz, ³*J* = 7.1 Hz with CH₃ on C-4', H_a on C-4'), 1.16 (t, ³*J* = 7.1 Hz with H_a and H_b on C-4', CH₃ on C-4'). ¹³C 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 (CH₃ 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 C₉H₁₆N₄O₂, *m/z* = 212.1 Da.

Compound **5** (oil). HRMS *m/z* 252.1579 (C₁₂H₂₀N₄O₂) requires 252.1586. NMR (CDCl₃): ¹H δ 6.66 (d, ³*J* = 2.1 Hz, H-4), 7.535 (d, ³*J* = 2.1 Hz, H-3), 1.90 and 2.05 (CH₃ groups on C-5'), 3.27 (s, CH₃O on C-3'), 3.159 (m, ²*J*_{gem} = -12.7 Hz, ³*J* = 5.7 Hz with H-3', H_a), 3.11 (ABX, ²*J*_{gem} = -12.7 Hz, ³*J* = 5.7 Hz with H-3', H_b), 4.76 (t, ³*J* = 5.7 Hz with H_a and H_b on C-2', H-3'), 3.62 (ABX₃, ²*J*_{gem} = -9.4 Hz, ³*J* = 7.0 Hz with CH₃ on C-4', H_b), 3.43 (ABX₃, ²*J*_{gem} = -9.4 Hz, ³*J* = 7.0 Hz with CH₃ on C-4', H_a), 1.09 (t, ³*J* = 7.0 Hz with H_a and H_b on C-4', CH₃ on C-4'). ¹³C 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 (CH₃O on C-3'), 15.00 (CH₃ on C-4'), 162.43 (C-5'), 25.02 and 18.59 (CH₃ groups on C-5').

Compound **6**, 6*H*-6,7-dihydropyrazolo[1,5-*d*]-1,2,4-triazine, m.p. 132-134 °C. HRMS *m/z* 252.1618 (C₁₂H₂₀N₄O₂) requires 252.1586. NMR (CDCl₃): ¹H δ 7.52 (d, ³*J* = 2.1 Hz, H-2), 6.35 (d, ³*J* = 2.1 Hz, H-3), 2.88 (d, ³*J* = 6.0 Hz with H-5', H_a and H_b on C-4'), 4.82 (t, ³*J* = 6.0 Hz with H_a and H_b on C-4'), 3.36 (s, CH₃O on C-5'), 3.70 (ABX₃, ²*J*_{gem} = -9.4 Hz, ³*J* = 7.1 Hz with CH₃ on C-6', H_a on C-6'), 3.52 (ABX₃, ²*J*_{gem} = -9.4 Hz, ³*J* = 7.1 Hz with CH₃ on C-6', H_b on C-6'), 1.18 (t, ³*J* = 7.1 Hz with H_a and H_b on C-6', CH₃ on C-6'). ¹³C δ 138.59 (C-2), 102.57 (C-3), 137.25 (C-3a), 130.53 (C-4), 71.54 (C-7), 24.31 (two CH₃ groups on C-7), 37.04 (C-4'), 101.61 (C-5'), 61.51 (C-6'), 52.76 (CH₃O on C-5'), 15.01 (CH₃ on C-6'). ¹⁵N 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-CH₂-CO-CO-CH₂-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 CDCl₃ 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 ppm²⁵ 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-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 CDCl₃ solution of **5** is found by ¹H NMR to evolve in 24 h to 100% of **6**).

Experimental Section

General Procedures. ¹H NMR spectra were recorded on a Bruker Avance-250 spectrometer working at 250.130 for ¹H, 62.896 for ¹³C and 25.355 MHz for ¹⁵N. Chemical shifts are expressed in ppm/TMS for ¹H and ¹³C and in ppm/external NO₂Me for ¹⁵N spectra. Coupling constants are in Hertz. Solvent was CDCl₃ unless stated otherwise. All the structures were determined by mass spectrometry and NMR spectroscopy. Signals of ¹H and ¹³C NMR spectra were assigned with the help of HMQC and HMBC experiments. Assignments of signals of the ¹⁵N spectrum of compound **6** were made according to Gouesnard *et al.*²⁸ and Claramunt *et al.*²⁹ Non first-order spectra were calculated using NMRSIM³⁰ and gNMR³¹ 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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