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 6H-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](image-url)
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\(^2\)\(^\text{-}12\) the 3,4′- (4,5′-) family less frequently\(^6\)\(^,\)\(^13\)\(^,\)\(^14\) and, finally, 4,4′-bipyrazoles being again quite common.\(^6\)\(^\text{-}22\) The parent compounds are described for 3,3′-bipyrazole\(^2\)\(^,\)\(^7\)\(^,\)\(^11\) and 4,4′-bipyrazole\(^16\)\(^\text{-}20\) 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-ethoxymethylenebutane-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 °C and 1.98 g (10 mmol) of 1,4-bis-ethoxymethylene-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 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.
Identification of the different compounds. Compound 1 (m.p. 258-260 °C) was identified by comparison with an authentic sample.\(^{11}\) \(^1\)H NMR (DMSO-\(d_6\)): \(\delta\) 12.97 (broad s, NH); 7.66 (broad s, H-5); 6.54 (d, \(J = 2.1\) Hz, H-4). \(^{13}\)C NMR (DMSO-\(d_6\) + 1 drop of CF\(_3\)CO\(_2\)H): \(\delta\) 141.41 (C-5); 133.26 (C-3); 102.69 (C-4).

Compound 3 (R = CH\(_3\), m.p. 114-115 °C). HRMS m/z 198.1019 (C\(_9\)H\(_{14}\)N\(_2\)O\(_3\)) requires 198.1004. NMR (CDCl\(_3\)): \(^1\)H \(\delta\) 6.52 (d, \(J = 7.3\) Hz, H-5), 7.97 (d, \(J = 7.3\) Hz, H-6), 3.14 (d, \(J = 5.9\) Hz with H-2', H\(_a\) and H\(_b\) on C-1'), 5.09 (t, \(J = 5.8\) Hz with H\(_a\) and H\(_b\) on C-1', H-2'), 3.38 (s, CH\(_3\)O on C-2'), 3.72 (AB\(_X^3\), \(2J_{gem} = -9.5\) Hz, \(3J = 7.1\) Hz with CH\(_3\) on C-4', H\(_a\) on C-4'), 1.20 (t, \(J = 7.0\) Hz with H\(_a\) and H\(_b\) on C-4', CH\(_3\) on C-4'). \(^{13}\)C \(\delta\) 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\(_3\)O 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\(_2\)H\(_5\), m.p. 119-120 °C). HRMS m/z 212.1140 (C\(_{10}\)H\(_{16}\)N\(_2\)O\(_3\)) requires 212.1161. NMR (CDCl\(_3\)): \(^1\)H \(\delta\) 6.51 (d, \(J = 7.4\) Hz, H-5), 7.98 (d, \(J = 7.4\) Hz, H-6), 3.13 (d, \(J = 5.9\) Hz with H-2', Ha and Hb on C-1'), 5.137 (t, \(J = 5.9\) Hz with Ha and Hb on C-1', H-2'), 3.72 (AB\(_X^3\), \(2J_{gem} = -9.5\) Hz, \(3J = 7.1\) Hz with CH\(_3\) on C-4', H\(_b\) on C-4'), 3.56 (AB\(_X^3\), \(2J_{gem} = -9.5\) Hz, \(3J = 7.1\) Hz with CH\(_3\) on C-4', H\(_a\) on C-4'), 1.16 (t, \(J = 7.1\) Hz with Ha and Hb on C-4', CH\(_3\) on C-4'). \(^{13}\)C \(\delta\) 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 Ha and Hb on C-1', but that Ha and Hb 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\(_9\)H\(_{16}\)N\(_4\)O\(_2\), m/z = 212.1 Da.
(N-8), – 68.80 (N-5), –246.55 (N-6). Note that in compound 6, as in compound 3, H₄ and H₅ 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 3_JHH = 2.1 Hz like 3_JH₃-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.

**References**

30. NMRSIM 2.61 from Bruker Analytik GmbH.
31. gNMR 3.6 from Cherwell Scientific Publishing Ltd.