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C-C Bond Cleavage Studies in Bipyrazoles: A Convenient Synthesis of Pyrazolo-5-ols

Shiv P. Singh
Department of Chemistry, Kurukshetra University, Kurukshetra, India

Rajesh Naithani
Department of Chemistry, University of Illinois at Chicago, Chicago, USA

Ranjana Aggarwal and Om Prakash
Department of Chemistry, Kurukshetra University, Kurukshetra, India

Abstract: The treatment of 4-acetoacetyl derivative **(3)** of the pyrazoles with hydrazines in ethanol/HCl furnished a variety of bipyrazoles **(4)**. However, when the reaction was performed in sodium acetate/acetic acid/ethanol, different hydrazines gave different products. Under these conditions an unexpected C-C bond cleavage was observed thus affording a convenient route for the formation of pyrazolo-5-ols **(5** and **6)**.

Keywords: C-C bond cleavage, bipyrazoles, hydrazines, dehydroacetic acid

The reaction between hydrazines and dehydroacetic acid (DHAA) has been under investigation in our laboratory for the last few years.[1] The formation of the hydrazone of DHAA which underwent smooth skeletal rearrangement to yield the corresponding acetoacetyl derivative **(3)** of the pyrazole has already been reported.[2] Treatment of this derivative with hydrazines in ethanol/HCl furnished a variety of bipyrazoles **(4)** in excellent yield (Scheme 1). However, when the reaction is performed in sodium acetate/

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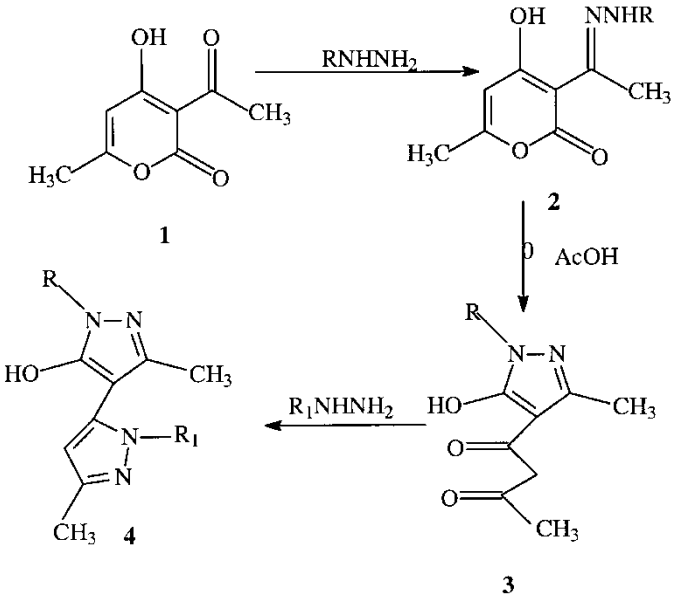
Address correspondence to Rajesh Naithani, Department of Chemistry, University of Illinois at Chicago, Chicago, IL 60607, USA. E-mail: naithani@uic.edu



For 2 and 3 R=
(a) C_6H_5 **(b)** 2,4-DNP **(c)** C_6H_4Cl (*p*) **(d)** 4-methyl-2-quinolyl **(e)** 6-methyl-2-benzothiazolyl

Scheme 1.

acetic acid/ethanol different products were obtained depending upon the nature of the hydrazines employed. In some cases, bipyrazoles were the sole products (Scheme 2), whereas when other hydrazines were employed an unexpected carbon-carbon bond fission was observed (Scheme 4).

In order to shed some light on the mechanistic aspects of this rather unusual C-C bond cleavage and to know the factors responsible for such a fission, the present study was undertaken.[2]

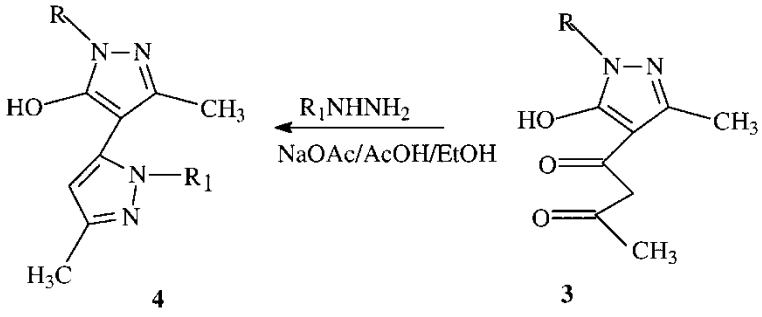
In the present study the experiments were designed to focus our attention on the following studies:

1. Nature of the hydrazines employed in the reaction
2. Stereochemical factors which may affect the course of the reaction

In order to get a generalized picture of these transformations a variety of hydrazines were treated with **3** under the following conditions:

(i) HCl/Ethanol (ii) sodium acetate/acetic acid/ethanol

More specifically **3** was treated with phenylhydrazine, arylhydrazines (having strong electron withdrawing groups) such as *para*-nitrophenyl-hydrazine, 2,4-dinitrophenylhydrazine, and heterocyclylhydrazine such as



4 **3**

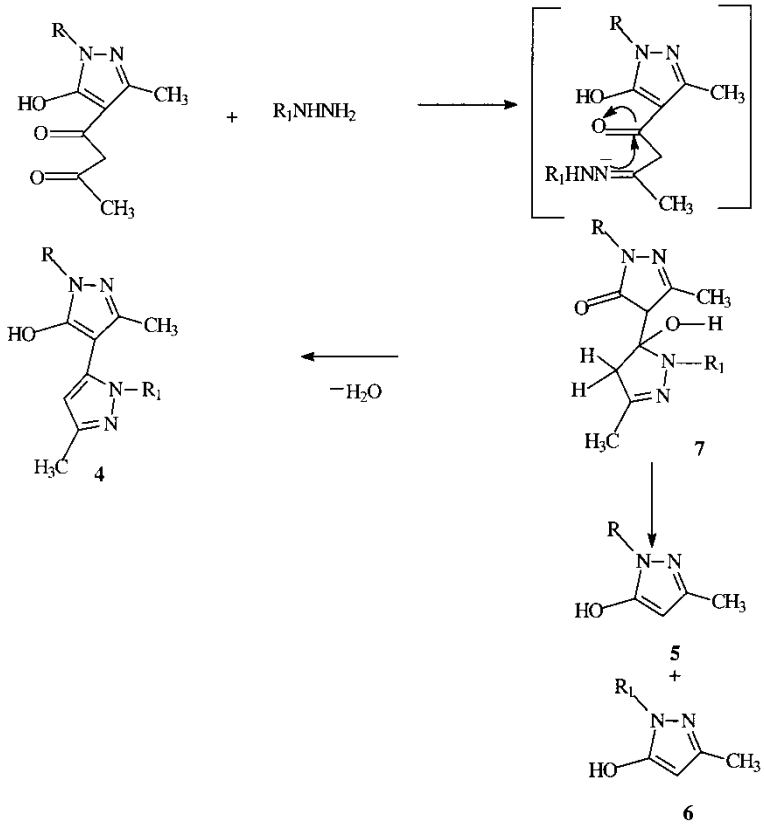
For **4** (**a-g**)

Compound No.	R	R_1
a	Phenyl	Phenyl
b	Phenyl	*p*-nitrophenyl
c	Phenyl	2,4-dinitrophenyl
d	*para*-chlorophenyl	1-naphthyl
e	phenyl	2-pyridyl
f	phenyl	4-methyl-2-quinolyl
g	4-methyl-2-quinolyl	6-methyl-benzothiazolyl

Scheme 2.

2-benzothiazolylhydrazine, 2-quinolylhydrazine, and 2-pyridylhydrazine under both the above conditions. Reactions of **3** with all the hydrazines led to the exclusive formation of bipyrazoles **(4)** in HCl/ethanol. However, when the reaction was carried out in sodium acetate/acetic acid/ethanol, different products were formed depending upon the hydrazine involved. Phenylhydrazine, pyridylhydrazine, and *para*-nitrophenylhydrazine led to the exclusive formation of the bipyrazole **(4)** but in case of 2,4-dinitrophenyl-hydrazine, 2-benzothiazolylhydrazines, 2-quinolylhydrazines a C-C cleavage occurred to give **5** and **6** under the identical conditions (Scheme 2). It may be suggested that electron withdrawing nature of hydrazines play a role in the bond fission. Pyrazol-5-ols can be obtained when C-C bond cleavage takes place in the intermediate **7** (Scheme 3). The divergent behavior of the pyridyl and quinolyl hydrazines brings into focus that it may be the bulky nature of the hydrazines which plays a more important role in the C-C cleavage as compared to the electron-withdrawing nature of the hydrazine.

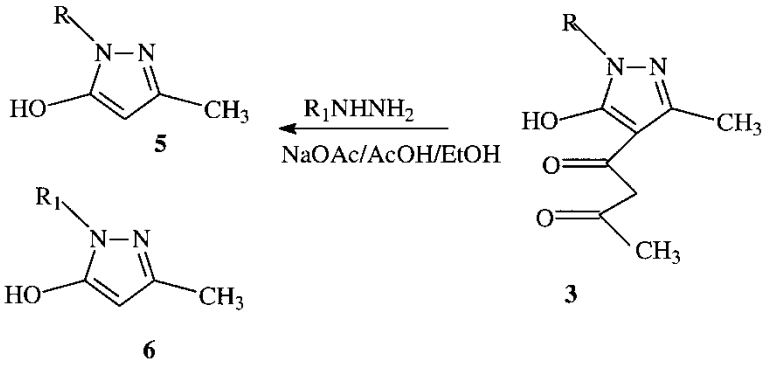
In order to further substantiate this observation, 1-naphthylhydrazine was treated with **3** under identical conditions as used for phenylhydrazine. Indeed it is quite interesting to see that whereas bipyrazolyl was the sole product in the case of phenylhydrazine, products of the C-C bond fission were



Scheme 3.

obtained in case of the naphthylhydrazine (Scheme 4), thus confirming bulk of hydrazine facilitates cleavage. The structure of the all pyrazol-5-ols were confirmed by elemental analysis and their ^{1}H NMR characteristics. A signal around δ 2.34 (s, 3H, CH_3) indicated the presence of CH_3 at position-3 of the pyrazole ring. As expected the characteristics signal due to the methyl group at 3′ of the bipyrazole was absent thereby confirming the bond cleavage. Interestingly this route can be employed for synthesis of the various pyrazolyl-5-ols which may be otherwise difficult to synthesize, thus this route provides a convenient and a high-yield procedure for the pyrazolyl-5-ol.

In one of our earlier study, the C-C bond cleavage in bipyrazole was sought to be correlated to the shielding of the methyl group at position-3 of the bipyrazoles.[3,5] It was suggested that the protons of the two methyl group resonate close to each other in those bipyrazoles whose precursor have a tendancy to undergo bond fission. On the other hand the 4,5′-bipyrazolyles whose precursors do not have a tendency to undergo C-C



For structures of (**5a-d**) and (**6a-d**)

Compound No.	R	R_1
a	Phenyl	1-naphthyl
b	4-methyl-2-quinolyl	4-methyl-2-quinolyl
c	2-benzothiazolyl	2-benzothiazolyl
d	2,4-dinitrophenyl	2,4-dinitrophenyl

Scheme 4.

bond cleavage displays one of the methyl group relatively deshielded. This may be explained by a consideration of chemical shifts of methyl groups in the two pyrazolyls (**4a** and **4d**).

Whereas the signals appeared at δ 1.78 and δ 2.38 in compound **4a** representing the protons of C_3 and C_3' of the two methyl groups, the corresponding signals were observed at δ 2.22 and δ 2.43 for compound **4d**. In other words the difference in the shifts of two methyl groups in **4a** is greater ($\Delta\delta$ 0.5), the cleavage does not take place. Whereas if the difference is less ($\Delta\delta$ 0.2) the cleavage does take place (Table 1).

On basis of our studies it appears that there might be some correlation between the chemical shifts of the two methyl groups of the 4,5′-bipyrazolyls and ability of their precursor to undergo C-C cleavage. However additional experimental data needs to be generated in order to present a comprehensive profile of the mechanistic pathway.

The following two conclusion may be suggested from the present study:

1. The steric factor appears to be playing an important role in the bond cleavage.
2. Nature of the hydrazine employed in the second step of the reaction might have some role in the fission which needs to be investigated in detail.

Table 1.

Compd. no.	R	R_1	Shift value (δ) of C_3	Shift value (δ) of C_3'
4a	Phenyl	Phenyl	1.78	2.30
4b	Phenyl	*p*-nitrophenyl	1.97	2.35
4c	Phenyl	2,4-dinitrophenyl	2.08	2.34
4d	*p*-chlorophenyl	1-naphthyl	2.24	2.40
4e	Phenyl	2-pyridyl	2.25	2.39
4f	Phenyl	4-methyl-2-quinolyl	2.20	2.41
4g	4-methyl-2-quinolyl	6-methyl-2-benzothiazolyl	2.18	2.41

EXPERIMENTAL

All the melting points were determined in open capillaries and are uncorrected. The ^{1}H NMR spectra were recorded on Bruker 300 MHz spectrometer. The elemental analysis was carried out in a Perkin Elmer-2400 instrument and mass spectra were recorded on Kratos MS-50 mass spectrometer.

Phenyl Hydrazone of DHAA (2a)

Dehydroacetic acid (DHAA) (3.36 g, 0.02 mol) was dissolved in ethanol (50 mL) by warming and phenylhydrazine (2 mL, 0.02 mol) was added to the shaken solution. The contents were stirred for 10 min and allowed to stand at the room temperature for 2 h. The yellow solid obtained was filtered and recrystallized from acetonitrile.Yield 81% (4.2 g), m.p. 211–212°C, lit.[4] m.p. 212–213°C.

Other hydrazones **(2a–e)** were also prepared similarly by treating DHAA with the corresponding hydrazines.

(2b) Yield 80% (2.78 g), m.p.192°C; ^{1}H NMR ($CDCl_3$): δ 2.29 (s, 3H, CH_3), 2.75 (s, 3H, CH_3), 6.01(s, 1H, pyrone-5H), 7.43–7.49 (m, 3H, Ar-H). Elemental Analysis: Calculated for $C_{14}H_{12}N_4O_7$ (348.26): C, 48.27; H, 3.44; N, 16.09. Found: C, 48.07; H, 3.14; N, 15.89. The physical data of the other hydrazones are given in Table 2.

5-Hydroxy-3-methyl-1-phenylpyrazol-4-yl-1,3-butanedione (3a)

Phenylhydrazone of DHAA (2.46 g, 0.01 mol) was dissolved in glacial acetic acid and the solution refluxed for 1.5 h. The solvent was distilled off under reduced pressure and residue was crystallized from acetonitrile. Yield 66%

Table 2.

Compound no.	m.p. (°C)	Lit. m.p. (°C)	Reference
2c	251	252	[4]
2d	188	190	[5]
2e	210	212	[5]

(1.7 g), m.p. 101°C, lit.[5] m.p. 101°C. All the other compounds **(3b–e)** were synthesized following the above procedure.

(**3b**)Yield 60% (2.08 g), m.p. 216°C; ^{1}H NMR($CDCl_3$): δ 2.16 (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 3.91 (s, 2H, $COCH_2CO$), 5.90 (s, 1H, vinylic), 8.2–9.2 (m, 3H, Ar-H). Elemental Analysis: Calculated for $C_{14}H_{12}N_4O_7$ (348.26): C, 48.27; H, 3.44; N, 16.09. Found: C, 47.59; H, 3.21; N, 16.21. The physical data of **3c–e** is given in Table 3.

1,1′-Diphenyl-3,3′-dimethyl-(4,5′-bipyrazol)-5-ol (4a)

To an ethanolic solution (30 mL) of **3a** (0.005 mol) was added phenylhydrazine (0.5 mL, 0.005 mol) and the contents were refluxed for 2.5 h. containing a few drops of conc. HCl. The crude solid obtained after concentrating and cooling the reaction mixture was filtered and crystallized from ethanol and *N,N*-dimethylformadide.

(4a) Yield 70% (1.15 g), m.p.258°C, lit.[4] m.p. 260°C. All other 1,1′-disubstituted-3,3′-dimethyl-(4,5-bipyrazol)-5-ols were prepared similarly by treating **3** with various arylhydrazines.

(4b) Yield 58% (2.17 g), m.p. 168°C; ^{1}H NMR ($CDCl_3$): δ 1.97 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 6.31 (C_4'-H), 7.20–8.22 (m, 10H, Ar-H). Elemental Analysis: Calculated for $C_{20}H_{17}N_5O_3$: C, 64.10; H, 4.53; N, 18.20. Found: C, 63.86; H, 4.60; N, 18.56.

(4c) Yield 54% (2.20 g), m.p. 212°C, ^{1}H NMR ($CDCl_3$): δ 2.08 (s, 3H, C_3-CH_3), 2.34 (s, 3H, C_3'-CH_3), 6.28 (s, 1H, C_4'-H), 7.33–8.62 (m, 9H, Ar-H). Elemental

Table 3.

Compound no.	m.p. (°C)	Lit. m.p. (°C)	Reference
3c	150	151	[5]
3d	212	214	[4]
3e	198	199	[5]

Analysis: Calculated for $C_{20}H_{16}N_6O_5$:C, 56.14; H, 3.80; N, 20. Found: C, 57.04; H, 3.40; N, 19.80.

(4d) Yield 58% (2.40 g), m.p. 218°C; ^{1}H NMR ($CDCl_3$): δ 2.24 (s, 3H, CH_3), 2.40 (s, 3H, C'_3-CH_3) 6.40 (s, 1H, C'_4-H), 7.43–8.04 (m, 12H, Ar-H). Elemental Analysis: Calculated for $C_{24}H_{19}ClN_4O$: C, 69.58; H, 4.58; N, 13.52. Found: C, 68.86; H, 4.53; N, 13.41.

(4e) Yield 60% (2.18 g), m.p. 220°C, lit.[6] m.p. 239°C; ^{1}H NMR ($CDCl_3$) δ 2.25 (s, 3H, CH_3), 2.39 (s, 3H, C'_3-CH_3), 6.23 (s, 1H, C'_4H), 7.24–8.31 (m, 9H, Ar-H).

(4f) Yield 69% (2.28 g), m.p. 238°C, lit.[6] m.p. 239°C; ^{1}H NMR ($CDCl_3$): δ 2.20 (s, 3H, C_3-CH_3), 2.41 (s, 3H, C'_3-CH_3), 2.76 (s, 3H, C_4-CH_3 of the quinolyl), 6.38 (s, 1H, C'_4-H), 7.25–8.08 (m, 10H, Ar-H).

(4g) Yield 56% (2.60 g), m.p. 228°C; ^{1}H NMR ($CDCl_3$) δ 2.18 (s, 3H, C_3-CH_3), 2.41 (s, 3H, C_6-CH_3 of the benzothiazolyl), 2.78 (s, 3H, C_4-CH_3 of the quinolyl), 6.35 (s, 1H, C'_4-H), 7.13–8.01 (m, 9H, Ar-H). Elemental Analysis: Calculated for $C_{26}H_{22}N_6OS$: C, 66.95, H, 4.72. N, 18.02. Found: C, 66.67; H, 4.32; N, 17.99.

Reaction in the Presence of Sodium Acetate/Acetic Acid/Ethanol

General Procedure

Equimolar amounts (0.005 moles) of the **3** and the appropriate hydrazine were refluxed for 2 h in ethanol containing acetic acid 0.1 mL/sodium acetate 0.1 gm. After cooling the reaction mixture a solid was obtained which was filtered washed with ethanol and dried. The data of the pyrazol-5-ols (**5** and **6**) have been given below:

(5a) Yield 25% (0.43 g), m.p. 125°C, Lit.[6] m.p. 127°C.

(6a) Yield 28% (0.62g), m.p. 117°C; ^{1}H NMR ($CDCl_3$): δ 2.14 (s, 3H, CH_3), 5.81 (s, 1H, C_4-H), 6.55–7.80 (m, 7H, Ar-H). Elemental Analysis: Calculated for $C_{14}H_{12}N_2O$: C, 75.00; H, 5.31; N, 12.50. Found: C, 75.00; H, 5.21; N, 12.68.

(5b/6b) Yield 56% (1.33 g), m.p. 170°C; ^{1}H NMR ($CDCl_3$) δ 2.29 (s, 3H, CH_3), 2.75 (s, 3H, C_4-CH_3 of the quinolyl), 5.47 (s, 1H, C_4-H), 7.34–7.98 (m, 5H, Ar-H). Elemental Analysis: Calculated for $C_{14}H_{13}N_3O$: C, 70.29; H, 5.40; N, 17.57. Found: C, 70.21; H, 5.38; N, 17.50.

(5c/6c) Yield 56% (1.29 g), m.p. 168°C; ^{1}H NMR ($CDCl_3$): δ 2.29 (s, 3H, CH_3), 5.45 (s, 1H, C_4-H), 7.31–7.83 (m, 4H, Ar-H). Elemental Analysis:

Calculated for $C_{11}H_9N_3SO$: C, 57.14; H, 3.89; N, 18. 18. Found: C, 57.32; H, 3.79; N, 18.32.

(5d/6d) Yield 60% (1.58 g), m.p. 170°C; ^{1}H NMR ($CDCl_3$): δ 2.18 (s, 3H, CH_3), 7.19–9.41(m, 4H, Ar-H). Elemental Analysis: Calculated for $C_{10}H_8N_4O_5$: C, 45.44; H, 30.33; N, 21.21. Found:C, 45.18; H, 30.01; N, 21.20.

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