Stereoselective Thermal Isomerization of Bis(spiropyrazolone)cyclopropanes into (4*Z*)-4-[(Pyrazol-4-yl)methylene]pyrazolones

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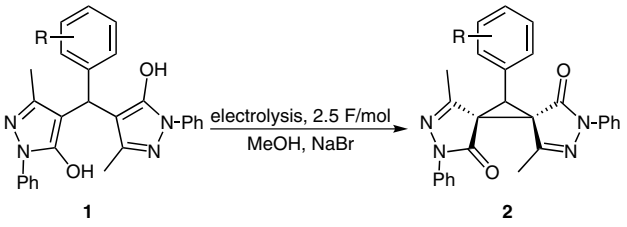
Abstract: Thermal isomerization of bis(spiropyrazolone)cyclopropanes in DMSO at 100 °C results in highly efficient formation of the corresponding 4-[(pyrazol-4-yl)methylene]pyrazolones in 90–98% yields after only five minutes. NMR and single-crystal X-ray diffraction analysis indicate stereoselective formation of the *Z*-isomers.

Key words: isomerization, ring opening, spiro compounds, cyclopropane, pyrazolone

The cyclopropane subunit plays a prominent role in organic chemistry. The high degree of reactivity present in cyclopropane due to its strained structure and unique bonding characteristics determine a variety of chemical transformations available for the three-membered ring.[1] A significant synthetic application of cyclopropane derivatives involves ring-opening rearrangements that can lead to molecular structures inaccessible by other methods.[2] The ever-growing importance of thermal cyclopropane rearrangements, including selective cyclopropane-to-propene isomerizations in various synthetic applications, attests to uniqueness and convenience of methodology especially when the starting cyclopropane is more readily available than isomeric propene.[3]

Among different types of cyclopropane fragments a spirocyclopropyl moiety jointed with a heterocyclic counterpart has attracted particular attention due to its synthetic utility and wide number of pharmacological applications.[4] The pyrazolin-5-one ring is one such heterocyclic motif with pyrazolone derivatives possessing a wide range of biological effects[5] such as analgesic, antipyretic,[6] antiviral,[7] and antitumor activity.[8] Moreover, a bis(spiropyrazolone)cyclopropane was patented recently as an advanced glycation end product (AGE) formation inhibitor intended for treatment of human schizophrenia.[9]

In a course of our studies on electrocatalytic synthesis of cyclopropane derivatives, we recently reported an efficient stereoselective approach to the corresponding bis(spiropyrazolone)cyclopropanes.[10] It was found that indirect electrochemical oxidation of easily accessible 4,4′-(arylmethylene)bis(1*H*-pyrazol-5-ols) **1** in methanol in an undivided cell in the presence of sodium bromide resulted in exclusive formation of the *R**,*R**-isomer of bis(spiro-2,4-dihydro-3*H*-pyrazol-3-one)cyclopropanes **2** in 85–96% yields (Scheme 1).



1 **2**

Scheme 1

Bis(spiropyrazolone)cyclopropanes of type **2** were isolated by direct filtration of the reaction mixture and did not require any further purification. Nevertheless, we noted that recrystallization of pure **2a** from boiling ethanol resulted in formation of an impurity readily visible in the ^{1}H NMR spectrum of the recrystallized product. The above observation led to the conclusion that bis(spiropyrazolone)cyclopropanes **2** are capable of temperature-promoted rearrangement with formation of an apparently single isomeric product.

A detailed literature search revealed only two brief mentions of thermal rearrangements of analogous cyclopropanes.[11,12] Westoo suggested that selected representatives of bis(spiro-3*H*-pyrazol-3-one)cyclopropanes isomerized into linear conjugated 4-[(pyrazol-4-yl)methylene]pyrazolones after 20–24 hours in refluxing ethanol or boiling at 95 °C in a dioxane–water mixture, respectively.[11] Later, Hennig and Haessner mentioned the formation of 4-[(pyrazol-4-yl)methylene]pyrazolone after recrystallizing unsubstituted bis(spiro-3*H*-pyrazol-3-one)cyclopropane from ethanol.[12] Although both papers suggest the possibility of a thermal ring-opening cyclopropane-to-propene isomerization for bis(spiropyrazolone)cyclopropanes, they variously lack product characterization details, yield information or describe a very limited number of examples. Considering the utility of 4-[(pyrazol-4-yl)methylene]pyrazolone derivatives as dyestuffs,[13] their potential

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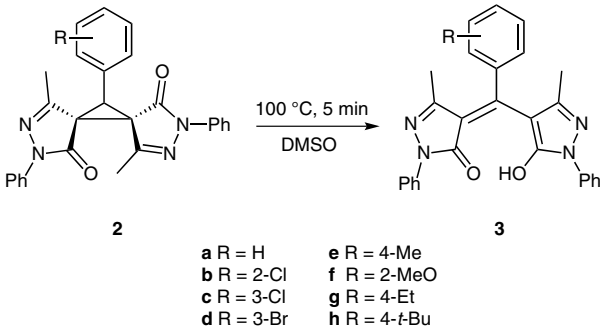
biomedical applications, and the ready availability of bis(spiropyrazolone)cyclopropanes by our electrocatalytic approach (Scheme 1), we were prompted to develop this thermal isomerization protocol to 4-[(pyrazol-4-yl)-methylene]pyrazolones **3** (Scheme 2).



2 **3**

a R = H **e** R = 4-Me
b R = 2-Cl **f** R = 2-MeO
c R = 3-Cl **g** R = 4-Et
d R = 3-Br **h** R = 4-*t*-Bu

Scheme 2

First, to validate our initial observations and evaluate the synthetic potential of this conversion, a thermal isomerization study of bis(spiropyrazolone)cyclopropane **2a** was undertaken (Table 1). Heating **2a** in refluxing water for two hours did not result in any conversion of the starting compound probably due to its insolubility (Table 1, entry 1). After two hours under reflux conditions in ethanol or *n*-propanol **2a** was selectively converted into 4-[(pyrazol-4-yl)methylene]pyrazolone **3a** in 25% and 55% yields, respectively (Table 1, entries 2 and 3). As for aprotic solvents, a solution of **2a** in refluxing chloroform was unreactive; although in refluxing acetone or acetonitrile, selective conversion into **3a** was observed in 10% and 27% yield, respectively (Table 1, entries 4–6). Heating **2a** in toluene to 100 °C similarly resulted in formation of **3a** in 10% yield (Table 1, entries 7); while increased reaction times and temperatures did not significantly influence on the yield of **3a** but led to considerable amounts of decomposition products. A dramatic improvement was achieved with high-boiling polar aprotic solvents. Thus, heating **2a** at 100 °C in DMF for 15 minutes or in DMSO for five minutes resulted in complete consumption of starting compound and exclusive formation of 4-[(pyrazol-4-yl)methylene]pyrazolone **3a** (Table 1, entries 8 and 9). Moreover, these conditions allowed for a 20-fold decrease of the solvent amount required.

Table 1 Thermal Isomerization of **2a** into **3a** in Different Solvents[a]

Entry	Solvent	Temp (°C)	Time (min)	Conv. of **2a** (%)[b]
1	H_2O	100	120	0
2	EtOH	79	120	25
3	*n*-PrOH	97	120	55
4	$CHCl_3$	61	120	0
5	acetone	56	120	10
6	MeCN	82	120	27
7	toluene	100	120	25
8	DMF[c]	100	15	100
9	DMSO[c]	100	5	100

[a] Conditions: **2a** (1 mmol), solvent (10 mL), heating.
[b] Selective conversion into **3a**, ^{1}H NMR data.
[c] Conditions: 0.5 mL of solvent.

Under the optimal conditions (0.5 mL of DMSO at 100 °C for 5 min) the thermal isomerization of bis(spiropyrazolone)cyclopropanes **2a**–**h** afforded the corresponding 4-[(pyrazol-4-yl)methylene]pyrazolones **3a**–**h** in 90–98% yields (Scheme 2, Table 2). The developed isomerization process offers a unique approach to 4-[(pyrazol-4-yl)methylene]pyrazolone derivatives bearing a wide range of aryl substituents. Moreover, products **3a**–**h** can be isolated by simple water-assisted precipitation from the reaction mixture and do not require any further purification.

Table 2 Thermal Isomerization of **2a**–**h** into **3a**–**h**[a]

Entry	Product	R	Yield (%)[b]
1	**3a**	H	98
2	**3b**	2-Cl	96
3	**3c**	3-Cl	98
4	**3d**	3-Br	97
5	**3e**	4-Me	96
6	**3f**	2-MeO	98
7	**3g**	4-Et	96
8	**3h**	4-*t*-Bu	90

[a] Conditions: **2** (1 mmol), DMSO (0.5 mL), 100 °C, 5 min.
[b] Yield of isolated product.

It should be mentioned that the 4-[(pyrazol-4-yl)methylene]pyrazolones **3a**–**h** could exist as a pair of isomers with either *Z*- or *E*-configuration of the double bond. However, in the NMR spectra of **3a**–**h** only a single set of signals was identified indicating stereoselective formation of a single isomer in the thermal isomerization. The ^{1}H NMR and ^{13}C NMR spectra revealed that the methyl groups of the pyrazole rings are spatially similar suggesting a *Z*-configuration of the molecules.

The structure of 4-[(pyrazol-4-yl)methylene]pyrazolone **3a** was further confirmed by a single-crystal X-ray diffraction study (Figure 1). The X-ray diffraction data unambiguously support the *Z*-configuration of **3a** which can profit from stabilization by intramolecular hydrogen bonding between the carbonyl and hydroxyl moieties of the adjacent pyrazole rings (Figure 1). The lengths of the C5–C6 and C6–C7 bonds [1.4414(3) and 1.3951(3) Å, respectively] indicate a strong delocalization between the sp^2 atoms in **3a**. The PBE/L1[13] energy scan in the PRIRODA program[14] along the C1–C5–C6–C7 torsion angle (36

points, 10° step size) shows that the *Z*-configuration of **3a** is by 12 kcal/mol more favorable than the *E*, and the rotational barrier from *E*- to *Z*-configuration is around 11 kcal/mol. Thus, the *E*-isomer should not be present in measurable quantities among the reaction products. Considering the facts given above, compounds **3b**–**h** should also possess the *Z*-configuration.

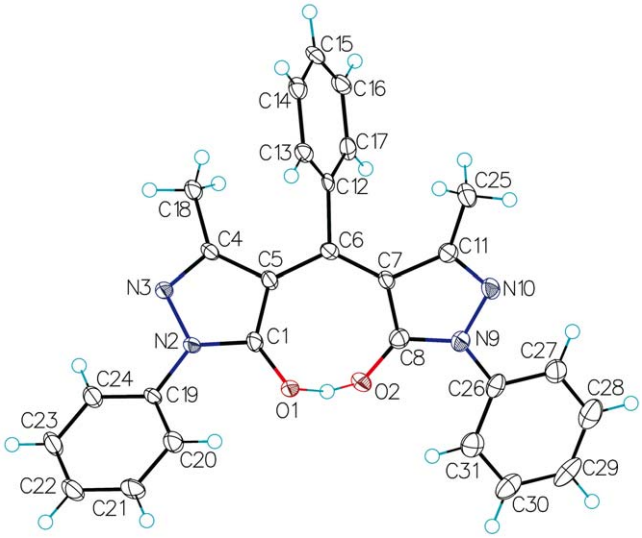


Figure 1 The general view of **3a** in crystal. Atoms are represented by thermal displacement ellipsoids (p = 50%).

In conclusion, we have developed an efficient approach to 4-[(pyrazol-4-yl)methylene]pyrazolone derivatives by thermal isomerization of readily accessible bis(spiropyrazolone)cyclopropanes. The isomerization rapidly proceeds simply on heating in DMSO, does not require any additional reagents or catalysts, and stereoselectively affords the (4*Z*)-4-[(pyrazol-4-yl)methylene]pyrazolones in excellent yields. The isomerization products are isolated by water-assisted precipitation directly from the reaction mixture and do not require any further purification.

General Procedure

A suspension of bis(spiropyrazolone)cyclopropane **2** (1 mmol) in DMSO (0.5 mL) in a 25 mL round-bottom flask was rapidly heated to 100 °C and stirred for 5 min. Then, the reaction mixture was allowed to cool down to r.t. and H_2O (10 mL) was added. The orange precipitate was filtered off, washed with H_2O (2 × 5 mL), and dried under reduced pressure.

X-ray Experiment

Product **3a** was crystallized from an acetone–hexane (1:1) mixture. Data were obtained on a Bruker SMART APEX II diffractometer. The crystal was kept at 100 K during data collection. Using Olex2,[15] the structure was solved with the XS[16] structure solution program using direct methods and refined with the XL refinement package[16] using least-squares minimization.

Crystal Data for 3a

$C_{27}H_{22}N_4O_2$ (M = 434.49): monoclinic, space group $P2_1/c$ (no. 14), a = 17.189(4) Å, b = 13.459(3) Å, c = 9.432(2) Å, β = 90.637(6)°, V = 2182.0(9) Å^3, Z = 4, T = 100 K, μ(MoKα) = 0.086 mm^{-1}, D_{calcd} = 1.323 g/mm^3, 12678 reflections measured (2.36 ≤ 2Θ ≤ 56.56), 5386 unique (R_{int} = 0.1403) which were used in all calculations. The final R_1 was 0.0638 [>2σ(I)] and wR_2 was 0.1324 (all data). CCDC 921007 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Selected Analytical Data

(4*Z*)-4-[(5-Hydroxy-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)(phenyl)methylene]-5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (3a)

Orange solid; mp 246–247 °C (lit.[11] 240–241.5 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.44 (s, 6 H, CH_3), 7.25–7.63 (m, 11 H, Ph), 7.98 (d, J = 7.6 Hz, 4 H, Ph). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.2 (2 C), 113.0, 121.2 (4 C), 126.5 (2 C), 128.6 (2 C), 128.9 (4 C), 130.5 (2 C), 130.6, 137.7 (2 C), 139.9, 151.6 (2 C), 158.3 (2 C), 161.4 (2 C). MS (EI, 70 eV): *m/z* (%) = 435 (3) [M$^+$ + 1], 434 (15) [M$^+$], 417 (6), 227 (11), 226 (100), 106 (24). IR (KBr): 3437, 3064, 1604, 1499, 1488, 1377, 1319, 1011, 757 cm^{-1}. Anal. Calcd for $C_{27}H_{22}N_4O_2$: C, 74.64; H, 5.10; N, 12.89. Found: C, 74.58; H, 5.24; N, 12.81.

(4*Z*)-4-[(2-Chlorophenyl)(5-hydroxy-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)methylene]-5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (3b)

Orange solid; mp 151–152 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.50 (s, 6 H, CH_3), 7.25–7.63 (m, 10 H, Ph), 7.97 (d, J = 7.6 Hz, 4 H, Ph). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.7 (2 C), 112.5, 121.1 (4 C), 126.5 (2 C), 127.1, 128.8 (4 C), 129.9, 131.5, 131.7, 133.8, 137.6 (2 C), 138.1, 150.9 (2 C), 153.7 (2 C), 161.5 (2 C). MS (EI, 70 eV): *m/z* (%) 469 (37) [M$^+$ + 1], 468 (100) [M$^+$], 453 (68), 451 (21), 434 (50), 433 (76), 118 (39), 91 (23), 77 (44). IR (KBr): 3441, 3064, 1600, 1518, 1495, 1378, 1317, 1012, 757 cm^{-1}. Anal. Calcd for $C_{27}H_{21}ClN_4O_2$: C, 69.15; H, 4.51; Cl, 7.56; N, 11.95. Found: C, 69.02; H, 4.63; Cl, 7.42; N, 12.08.

(4*Z*)-4-[(3-Bromophenyl)(5-hydroxy-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)methylene]-5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (3d)

Orange solid; mp 135–136 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.50 (s, 6 H, CH_3), 7.25–7.49 (m, 9 H, Ph), 7.56 (s, 1 H, Ph), 7.96 (d, J = 8.1 Hz, 4 H, Ph). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.5 (2 C), 112.8, 121.1 (4 C), 122.7, 126.6 (2 C), 128.8 (4 C), 129.1, 130.1, 133.2, 133.5, 137.5 (2 C), 141.6, 151.1 (2 C), 155.7 (2 C), 161.3 (2 C). MS (EI, 70 eV): *m/z* (%) = 514 (78) [M$^+$ + 2], 512 (78) [M$^+$], 497 (27), 495 (26), 340 (28), 185 (40), 128 (35), 118 (21), 91 (45), 77 (100). IR (KBr): 3436, 3062, 1680, 1597, 1516, 1378, 1316, 1215, 1013, 757, 690 cm^{-1}. Anal. Calcd for $C_{27}H_{21}BrN_4O_2$: C, 63.17; H, 4.12; Br, 15.56; N, 10.91. Found: C, 63.10; H, 4.21; Br, 15.49; N, 10.98.

(4*Z*)-4-[(5-Hydroxy-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)(4-methylphenyl)methylene]-5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (3e)

Orange solid; mp 221–222 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.47 (s, 6 H, CH_3), 2.50 (s, 3 H, CH_3), 7.23–7.34 (m, 5 H, Ph), 7.46 (t, J = 7.8 Hz, 5 H, Ph), 7.97 (d, J = 7.8 Hz, 4 H, Ph) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.2 (2 C), 21.4, 113.0, 121.1 (4 C), 126.4 (2 C), 128.8 (4 C), 129.3 (2 C), 130.5 (2 C), 136.9, 137.7 (2 C), 141.1, 151.7 (2 C), 158.6 (2 C), 161.3 (2 C). MS (EI, 70 eV): *m/z* (%) = 449 (14) [M$^+$], 448 (26) [M$^+$], 432 (35), 431 (50), 357 (10), 118 (29), 91 (39), 77 (100). IR (KBr): 3034, 1600, 1489, 1375, 1317, 1214, 1014, 810, 757, 689 cm^{-1}. Anal. Calcd for $C_{28}H_{24}N_4O_2$: C, 74.98; H, 5.39; N, 12.49. Found: C, 74.90; H, 5.45; N, 12.41.

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