A Facile Procedure for the Synthesis of Condensed Dipyrazoles

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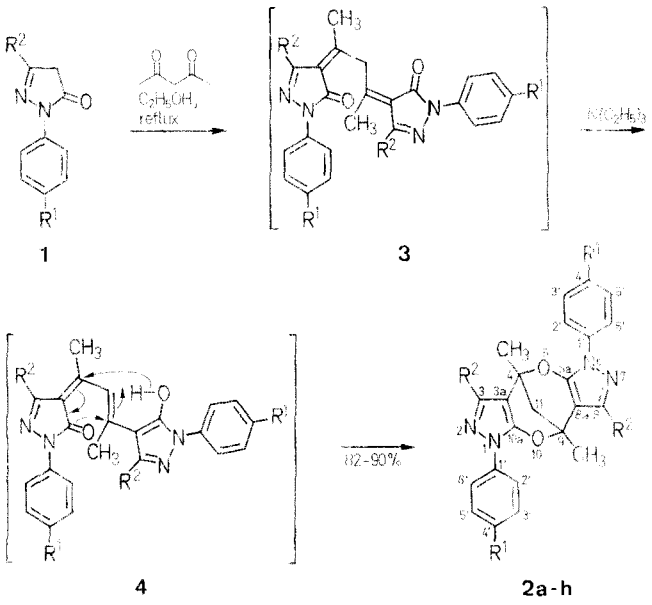
Utilizing the tautomeric property of 1,3-disubstituted-4,5-dihydropyrazol-5-ones **1**, a facile one-pot synthesis of highly substituted 1,4,6,9-tetrahydro-4,9-methano-1,5-dioxocin[2,3-*c*:6,7-*c'*]dipyrazoles **2** has been achieved.

The tautomerism of 1,3-disubstituted-4,5-dihydro-pyrazol-5-ones such as **1** has been widely investigated[1-5]. However, utilization of the tautomeric property of them in organic synthesis has not been in detail. In the course of our work to utilize this characteristic tautomerism of 1,3-disubstituted-4,5-dihydro-pyrazol-5-ones (**1**) in organic synthesis, we

found a general procedure to prepare 1,5-dioxocin dipyrazoles[6]. In this paper we wish to report a facile one-pot synthesis of condensed dipyrazoles **2** from the reaction of various 1,3-disubstituted-4,5-dihydro-pyrazol-5-ones **1** with acetylacetone in basic medium.



1 **3** **4** **2a–h**

Reaction of 1,3-disubstituted-4,5-dihydro-pyrazol-5-ones **1a–h** with acetylacetone in ethyl alcohol containing triethylamine at reflux gives 4,9-dimethyl-1,3,6,8-tetrasubstituted-1,4,6,9-tetrahydro-4,9-methano-1,5-dioxocin[2,3-*c*:6,7-*c'*] dipyrazoles **2a–h** in high yields.

The plausible reaction mechanism for the formation of **2a–h** can be depicted as follows. It has been well known that active methylene positions of **1a–h**, are reactive enough to condense with carbonyl compounds to afford 4-alkylidene-1,3-disubstituted-4,5-dihydropyrazol-5-ones[5-7]. This can be applied in the reactions of **1a–h** with acetylacetone and as a result, [2:1] adducts **3a–h** are formed in the initial stage of the reaction. In the reaction conditions employed, [2:1] adducts **3a–h** are isomerized to their enol tautomers **4a–h** by the action of triethylamine as those observed in our case[6]. Intramolecular cyclization of **4a–h** takes place accompanying with the hydrogen migration to afford dipyrazoles **2a–h** as final products. In these conversions, isomerizations of **3a–h** to **4a–h** caused by triethylamine play the crucial role.

The structures of **2a–h** are fully supported by the IR, ^{1}H-NMR, and ^{13}C-NMR spectra (Tables 1 and 2).

3,4,8,9-Tetramethyl-1,6-diphenyl-1,4,6,9-tetrahydro-4,9-methano-1,5-dioxocin[2,3-*c*:6,7-*c'*]dipyrazole (*2a*); Typical Procedure:

A solution of 3-methyl-1-phenyl-4,5-dihydro-1H-pyrazol-5-one (**1a**, 1.74 g, 0.01 mol) and dry acetylacetone (10.0 g, 0.1 mole) in dry ethyl

Table 1. Condensed Dipyrazoles **2** Prepared

Product No.	R^1	R^2	Yield[a] [%]	m.p. [°C]	Molecular Formula[b]	IR (Film) ν [cm^{-1}]	^{1}H-NMR ($CDCl_3$/TMS_{int}) δ [ppm]
2a	H	CH_3	90	169–171	$C_{25}H_{24}N_4O_2$ (412.5)	2990, 2930 1600, 1580 1515, 1460 1405, 1385	1.97 (s, 6H, CH_3 at C-4, C-9); 2.15 (s, 2H, CH_2); 2.37 (s, 6H, CH_3 at C-3, C-8); 7.20 (dd, 2H, J = 1.22, 7.32 Hz); 7.38 (dd, 4H, J = 7.32, 8.32 Hz); 7.69 (dd, 4H, J = 1.22, 8.32 Hz)
2b	Br	CH_3	87	180–182	$C_{25}H_{22}Br_2N_4O_2$ (570.3)	2990, 2935 1590, 1575 1510, 1500 1410, 1395	1.98 (s, 6H, CH_3 at C-4, C-9); 2.16 (s, 2H, CH_2), 2.34 (s, 6H, CH_3 at C-3, C-8), 7.49 (d, 4H, J = 9.04 Hz); 7.60 (d, 4H, J = 9.04 Hz)
2c	Cl	CH_3	85	196–198	$C_{25}H_{22}Cl_2N_4O_2$ (491.4)	2980, 2935 1590, 1575 1510, 1500 1410, 1395	1.98 (s, 6H, CH_3 at C-4, C-9); 2.17 (s, 2H, CH_2), 2.35 (s, 6H, CH_3 at C-3, C-8); 7.35 (d, 4H, J = 8.79 Hz); 7.65 (d, 4H, J = 8.79 Hz)
2d	CH_3	CH_3	82	183–184	$C_{27}H_{28}N_4O_2$ (440.5)	2990, 2930 1595, 1575 1515, 1490 1415, 1395	1.94 (s, 6H, CH_3 at C-4, C-9); 2.11 (s, 2H, CH_2); 2.32 (s, 6H, CH_3 at C-4', CH_3 at C-3, C-8); 2.34 (s, 6H, CH_3 at C-4' or CH_3 at C-3, C-8); 7.16 (d, 4H, J = 8.54 Hz); 7.55 (d, 4H, J = 8.54 Hz)
2e	H	C_6H_5	89	195–197	$C_{35}H_{28}N_4O_2$ (536.6)	2990, 2940 1590, 1575 1515, 1485 1415, 1390	1.75 (s, 6H, CH_3 at C-4, C-9); 2.20 (s, 2H, CH_2); 7.23–7.50 (m, 12H); 7.684 (m, 4H); 7.91 (dd, 4H, J = 1.22, 8.64 Hz)
2f	Br	C_6H_5	90	185–187	$C_{35}H_{26}Br_2N_4O_2$ (694.4)	2990, 2940 1590, 1565 1500, 1485 1410, 1390	1.75 (s, 6H, CH_3 at C-4, C-9); 2.22 (s, 2H, CH_2); 7.35–7.65 (m, 14H); 7.83 (d, 4H, J = 8.79 Hz)
2g	Cl	C_6H_5	86	199–201	$C_{35}H_{26}Cl_2N_4O_2$ (605.5)	2990, 2940 1595, 1565 1510, 1485 1415, 1390	1.76 (s, 6H, CH_3 at C-4, C-9); 2.22 (s, 2H, CH_2); 7.35–7.69 (m, 14H); 7.89 (d, 4H, J = 8.79 Hz)
2h	CH_3	C_6H_5	86	186–188	$C_{37}H_{32}N_4O_2$ (564.7)	2980, 2930 1595, 1565 1520, 1490 1415, 1390	1.74 (s, 6H, CH_3 at C-3 at C-4, C-9); 2.18 (s, 2H, CH_2); 2.39 (s, 6H, CH_3 at 4'); 7.22–7.38 (m, 10H); 7.71–7.73 (m, 4H); 7.78 (d, 4H, J = 8.30 Hz)

[a] Yield of recrystallized product.

[b] Mass spectra and microanalyses were in satisfactory agreement with the calculated values: C ± 0.25, H ± 0.17, N ± 0.28, Cl ± 0.33, Br ± 0.36.

Table 2. ^{13}C-NMR Data of Compound **2** Prepared[a]

Compound No.	CH_3 at C-3 and C-8	CH_3 at C-4 and C-9	C-11	C-4 C-9	C-3a C-8a	C-3 C-8	C-5a C-10a	Phenyl groups
2a	14.862 (q, 2C)	23.797 (q, 2C)	44.208 (t, 1C)	77.350 (s, 2C)	99.804 (s, 2C)	145.677 (s, 2C)	152.656 (s, 2C)	120.478 (d, 4C), 125.646 (d, 2C), 125.858 (d, 4C), 138.582 (s, 2C)
2b	14.838 (q, 2C)	23.716 (q, 2C)	43.882 (t, 1C)	77.523 (s, 2C)	99.927 (s, 2C)	146.071 (s, 2C)	152.615 (s, 2C)	118.827 (s, 2C), 121.673 (d, 4C), 131.938 (d, 4C), 137.023 (s, 2C)
2c	14.838 (q, 2C)	23.741 (q, 2C)	44.028 (t, 1C)	77.207 (s, 2C)	99.927 (s, 2C)	146.023 (s, 2C)	152.663 (s, 2C)	121.436 (d, 4C), 129.019 (d, 4C), 131.087 (s, 2C), 137.023 (s, 2C)
2d	14.813 (q,CC)	23.789 (q, 2C)	44.198 (t, 1C)	77.231 (s, 2C)	99.635 (s, 2C)	145.390 (s, 2C)	152.469 (s, 2C)	20.919 (q, 2C, 4'-CH_3), 120.554 (d, 4C), 129.433 (d, 4C), 135.393 (s, 2C), 136.122 (s, 2C)
2e	–	23.330 (q, 2C)	45.113 (t, 1C)	77.408 (s, 2C)	99.483 (s, 2C)	149.824 (s, 2C)	152.977 (s, 2C)	121.033 (d, 4C), 126.289 (d, 2C), 128.216 (d, 4C), 128.332 (d, 2C), 128.916 (d, 8C), 134.202 (s, 2C), 138.523 (s, 2C)
2f	–	23.272 (q, 2C)	44.880 (t, 1C)	77.379 (s, 2C)	96.688 (s, 2C)	150.203 (s, 2C)	152.977 (s, 2C)	119.573 (s, 2C), 122.230 (d, 4C), 128.362 (d, 4C), 128.683 (d, 2C), 128.858 (d, 4C), 132.070 (d, 4C), 133.793 (s, 2C), 137.530 (s, 2C)
2g	–	23.301 (q, 2C)	44.938 (t,1C)	77.642 (s, 2C)	99.629 (s, 2C)	150.086 (s, 2C)	152.948 (s, 2C)	121.879 (d, 4C), 128.384 (d, 4C), 128.858 (d, 6C), 129.004 (d, 4C), 131.720 (s, 2C), 133.910 (s, 2C), 137.122 (s, 2C)
2h	–	23.376 (q, 2C)	45.195 (t, 1C)	77.231 (s, 2C)	99.270 (s, 2C)	149.477 (s, 2C)	152.785 (s, 2C)	20.992 (q, 2C, 4'-CH_3), 121.041 (d, 4C), 128.192 (d, 6C), 128.971 (d, 4C), 129.457 (d, 4C), 134.347 (s, 2C), 136.001 (s, 2C), 136.171 (s, 2C)

[a] The assignment of signals to C-3, C-8, C-5a and C-10a are done analogous to the reported [8–10] values for 5-alkoxy (hydroxy, thiohydroxy) pyrazoles.

alcohol (300 ml) containing dry triethylamine (10.1 g, 0.1 mole) is refluxed for 24 h. The solvent ist then removed *in vacuo* at room temperature to leave a dark brown oily residue, which is washed with 10% acetic acid (100 ml) and filtered to afford crude **2a** as a white precipitate. Recrystallization from dry acetone (10 ml) gives analytically pure **2a**: yield: 1.85 g (90%); m.p. 169–171°C

$C_{25}H_{24}N_4O_2$	calc.	C 72.79	H 5.87	N 13.58
(412.5)	found	72.61	5.92	13.49

MS: m/e = 412 (M^+, 5%), 278 (13), 238 (88), 174 (100).

UV (CH_3CN): λ = 255 nm (log ε = 4.28).

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[1] Katritzky, A.R., Maine, F.W. *Tetrahedron* **1964**, *20*, 299.
[2] Newman, G.A., Pauwels, P.J.S. *Tetrahedron* **1970**, *26*, 1571.
[3] Newman, G.a., Pauwels, P.J.S. *Tetrahedron* **1970**, *26*, 3429.
[4] Dorn, H. *J. Prakt. Chem.* **1973**, *315*, 382.
[5] Arriau, J., Deschamps, J., Teysseyre, J., Maquestiau, A., van Heverbeke, Y. *Tetrahedron* **1974**, *30*, 1225.
[6] Matsugo, S., Saito, M., Takamizawa, A. *Synthesis* **1983**, 482.
[7] Desimoni, G., Tacconi, G. *Gazz. Chim. Itel.* **1968**, *98*, 1329.
[8] Feeny, J., Newman, G.A., Pauwels, P.J.S. *J. Chem. Soc.* (C) **1970**, 1842.
[9] Bergman, J.J., Lynch, B.M. *J. Het. Chem.* **1974**, *11*, 135.
[10] Hawkes, G.E., Randall, E.W., Elugero, J., Marzin, C.J. *J. Chem. Soc. Perkin* 2, **1977**, 1024.