HETEROCYCLES, Vol. 31, No. 6, 1990

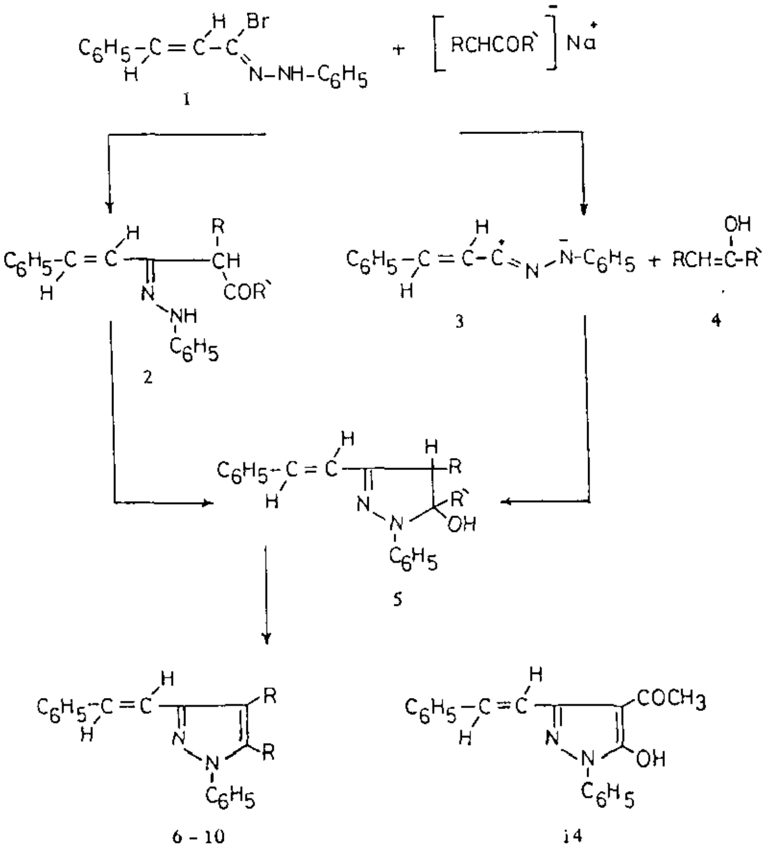
A CONVENIENT SYNTHESIS OF 3,5'-BIPYRAZOLYL DERIVATIVES VIA HYDRAZONYL HALIDES

Hamdi M. Hassaneen*, Ahmad S. Shawali, and Nehal M. Elwan
Department of Chemistry, Faculty of Science, University of Cairo, Giza, Egypt

Abstract - Cycloaddition of N-phenyl-C-cinnamonitrilimine 3 with enolates of various active methylene compounds afforded the 3-styrylpyrazole derivatives 6-10 in high yields. 3-Styrylpyrazoles 6-13 reacted with diphenylnitrilimine 20 to give the corresponding 3,5'-bipyrazolyl derivatives 21-28, respectively.

The derivatives of a pyrazole ring linked to an aromatic or heteroaromatic have been found antirheumatic and antipyretic properties.[1,2] The compounds such as antipyrine,[3] dipyrone,[4] phenylbutzone,[5] and mepyrazole[6] are well known drugs. Although many syntheses for various bipyrazolyl *isomers are reported* in literatures, only a few derivatives have been reported for 3,5'-bipyrazolyls.[7-9] The usual method for the synthesis of such compounds involves the reaction of hydrazines with 1,3,4,6-tetraketone or β-pyrazolyl diketone.[7] The disadvantage of this method is that an unsymmetrical tetraketone can theoretically yield four bipyrazolyls, and a symmetrical tetraketone three whereas pyrazolyl β-diketone can lead to two possible isomers.[10,11] In this paper it was thought worthwhile to investigate the synthetic potentiality of hydrazonyl bromide 1 in the synthesis of 3,5'-bipyrazolyls 21-28. For this purpose we studied the reaction of N-phenyl-C-cinnamohydrazonyl bromide 1 with active methylene compounds to get the previously unreported pyrazole derivatives with styryl group at position 3. The latter products were used as dipolarophiles and their reactions with diphenylnitrilimine 20 gave the corresponding 3,5'-bipyrazolyls.

Treatment of (E)-N-phenyl-C-cinnamohydrazonyl bromide 1 with acetylacetone in ethanolic sodium ethoxide solution at room temperature gave 4-acetyl-5-methyl-1-phenyl-3(E)-styrylpyrazole 6 in good yield (Scheme 1). Similarly, other active methylene compounds reacted with 1 under similar conditions and yielded the corresponding pyrazole derivatives 7-10 (Scheme 1). In no case, the acyclic hydrazone 2 was detected. This finding together with the fact that no 5-hydroxypyrazole derivative 14 was formed from 1 and ethyl acetoacetate indicates that the pyrazole derivatives 6-10 are probably formed by a concerted cycloaddition of 3 to the enol tautomers of the active methylene compounds used **4** to give the intermediate 5, which then lose one molecule of water (Scheme 1).[12]

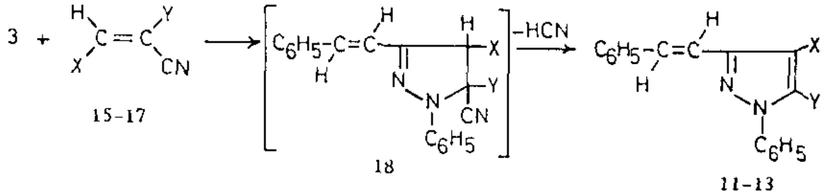


	R'/R
6	$CH_3/COCH_3$
7	$CH_3/COOC_2H_5$
8	$C_6H_5/COOC_6H_5$

	R'/R
9	C_6H_5/CN
10	C_6H_5/COC_6H_5

Scheme 1

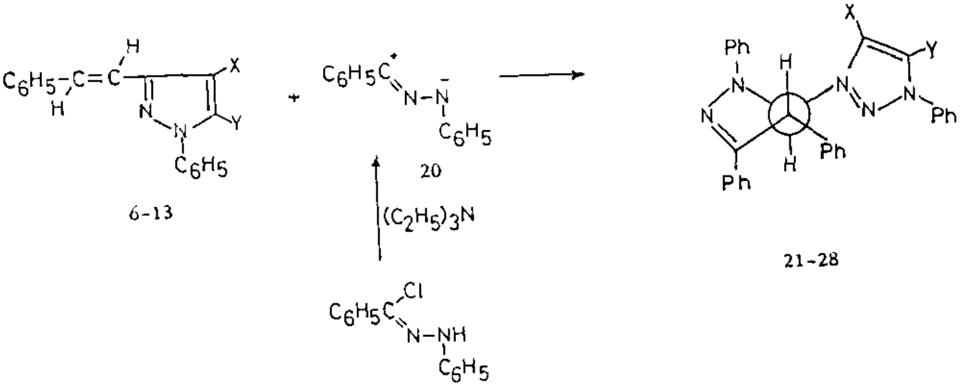
N-Phenylcinnamonitrilimine 3 , generated in situ from the bromide 1 and triethylamine in dry benzene reacted with p-nitrobenzylidenecyanoacetanilide 17 and afforded 4-(p-nitrophenyl)-1-phenyl-5-phenylaminocarbonyl-3-styrylpyrazole 13 (Scheme 2). The latter product undoubtedly resulted via thermal elimination of hydrogen cyanide from the corresponding cycloadduct 18.[13] The assigned structure 13 was supported by analytical and spectral data. Its ^1H nmr spectrum showed no signal due to 4-H or 5-H characteristic of 2-pyrazoline derivative 18. Similarly, nitrilimine 3 reacts with fumaronitrile 15 and benzylidenemalononitrile 16 under similar conditions to afford exclusively the corresponding 3-styrylpyrazoles 11[14] and 12[15], respectively (Scheme 2).



	X/Y
11, 15	CN/H
12, 16	C_6H_5/CN
13, 17	$C_6H_4NO_2$-p/C_6H_5NHCO

Scheme 2

Refluxing of N-phenylbenzohydrazonyl chloride 19 with 4-acetyl-5-methyl-1-phenyl-3(E)-styrylpyrazole 6 in chloroform in the presence of triethylamine yielded a product which analysed for $C_{33}H_{28}N_4O$. Its ^1H nmr spectrum revealed the absence of the signals of the ethylenic protons, instead it shows two doublets at δ 4.7 (1H) and 5.6 (1H) ppm assignable to 4 and 5 protons in the pyrazoline ring, respectively. On the basis of these data the product 21 was assigned the structure 4-acetyl-4',5'-dihydro-5-methyl-1',1',3',4'-tetraphenyl-3,5'-bipyrazolyl (Scheme 3). Other 3(E)-styrylpyrazoles



	X/Y
6, 21	CH_3CO/CH_3
7, 22	$COOC_2H_5/CH_3$
8, 23	$COOC_2H_5/C_6H_5$
9, 24	CN/C_6H_5

	X/Y
10, 25	COC_6H_5/C_6H_5
11, 26	H/CN
12, 27	C_6H_5/CN
13, 28	$C_6H_4NO_2$-p/C_6H_5NHCO

Scheme 3

7-13 react with diphenylnitrilimine **20** under similar conditions to give the corresponding cycloadducts **22-28**, respectively (Scheme 3). ^{1}H Nmr spectra of **21-28** were characterized by the presence of two doublets (J = 6Hz) near δ 4.7-5.1 and 5.4-5.8 ppm assignable to 4-H and 5-H, respectively. As 1,3-dipolar cycloaddition reactions are known to be concerted and thus stereospecific[16], it is expected that the trans configuration about the styryl group in **6-13** would be retained in the products **21-28**. This was confirmed by the value of the two doublets of the 4-H and 5-H. For example, the value of the coupling constant was found to be 6 Hz which is compatible with the indicated trans configuration. This is because the values of the coupling constants for cis- and trans- isomers of 4,5-disubstituted 2-pyrazolines are 12 and 6 Hz respectively.[17,18]

EXPERIMENTAL

All melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Infrared spectra (KBr) were determined on a Perkin Elmer 257 Spectrophotometer. ^{1}H Nmr spectra were obtained in deteriochloroform on a Varian Associate model T60-A spectrometer using tetramethylsilane as an internal reference. Microanalyses were performed at microanalytical unit of University of Cairo, Giza, Egypt. Hydrazonyl halides 1[15] and 19[18] and the dipolarophiles (bezylidenemalononitrile[19] and p-nitrobenzylidenecyanoacetanilide[19]) were prepared as previously described in literature.

Preparation of 1-aryl-4,5-disubstituted 3(E)-styrylpyrazoles 6-10. General method- To an ethanolic sodium ethoxide solution [prepared from sodium metal (0.1 g, 0.005 g atom) and absolute ethanol (30 ml)] was added the appropriate active methylene compound (5 mmol) with stirring. To the resulting solution, (E)N-phenyl-C-cinnamohydrazonyl beomide 1 (1.5 g, 5 mmol) was added at room temperature. The mixture was stirred for 24 h at room temperature during which the bromide dissolved and the crude pyrazole precipitated. The latter was collected, washed with water, dried and recrystallized from ethanol.

Compound **6** had mp 159°C, 1.20 g (80 %); δ ($CDCl_3$) 2.4 (s, 3H), 2.5 (s, 3H), 7.0-7.9 (m, 12H) ppm; υ (KBr) 1650 (C=O), 1595 (C=N) cm^{-1}. Anal. Calcd for $C_{20}H_{18}N_2O$: C, 79.4; H, 6.0; N, 9.3. Found: C, 79.6; H, 6.1; N, 9.4.

Compound **7** had mp 106°C, 1.30 g (85 %); δ ($CDCl_3$) 1.4 (t, J=7Hz, 3H), 2.5 (s, 3H), 4.4 (q, J=7Hz, 2H), 6.9-8.0 (m, 12H) ppm; υ (KBr) 1695 (C=O), 1595 (C=N) cm^{-1}. Anal. Calcd for $C_{21}H_{20}N_2O_2$: C, 75.9; H, 6.1; N, 8.4. Found: C, 76.1; H, 5.8; N, 8.3.

Compound **8** had mp 166°C, 1.5g (70 %) (Lit. mp 166°C).[20]

Compound **9** had mp 168°C, 1.40 g (80%); υ (KBr) 2220 (C≡N), 1595 (C=N) cm^{-1}. Anal. Calcd for $C_{24}H_{17}N_3$: C, 82.9; H, 4.9; N, 12.1. Found: C, 83.1; H, 4.7; N, 12.2.

Compound **10** had mp 177°C, 1.7 g (80 %) (Lit. mp 177°C).[20]

Reaction of (E)N-phenyl-C-cinnamohydrazonyl bromide 1 with dipolarophiles. To a solution of hydrazonyl bromide 1 (1.5 g, 5 mmol) and the appropriate dipolarophile (5 mmol) in benzene (40 ml) was added triethylamine (0.7 ml, 5 mmol) at room temperature. The mixture was refluxed for 12 h and filtered to get rid of triethylamine hydrobromide. The solvent was evaporated and the residue left was triturated with a small amount of methanol where upon it solidified. The crude solid was collectd and recrystallization from acetic acid gave 3-styrylpyrazoles 11-13.

Compound 11 had mp 144°C, 1.1 g, (80 %) (Lit. mp 144°C).[14]

Compound 12 had mp 140°C, 1.9 g, (85 %) (Lit. mp 144°C).[15]

Compound 13 had mp 223°C, 1.94 g (80 %); δ ($CDCl_3$) 6.9-8.3 (m, Ar-H) ppm; υ (KBr) 3300 (NH) 1690 (C =O) cm^{-1}. Anal. Calcd for $C_{30}H_{22}N_4O_3$: C, 74.1; H, 4.6; N, 11.5. Found: C, 74.6; H, 4.7; N, 11.8.

Preparation of 4,5-dihydro-4',5'-disubstituted 1,1',3,4-tetraphenyl-3,5-bipyrazolyls 21-28 General method-A mixture of N-phenylbenzohydrazonyl chloride 19 (1.2 g, 5 mmol) and the appropriate pyrazole (5 mmol) in chloroform (50 ml) was refluxed for 5 min. To the resulting solution triethylamine (0.7 ml, 5 mmol) was addded and the mixture was refluxed for 15 h. The solvent was evaporated in a rotary evaporator and the residue was triturated with methanol (5 ml). The solid that formed was collected and recrystallized from ethanol.

Compound 21 had mp 188°C, 1.98 g (80 %); δ ($CDCl_3$) 2.3 (s, 3H), 2.5 (s, 3H), 4.7 (d, J=6Hz, 1H), 5.6 (d, J=6Hz, 1H), 6.8-7.7 (m, 20H) ppm; υ (KBr) 1670 (C=O), 1600 (C=N) cm^{-1}. Anal. Calcd for $C_{33}H_{28}N_4O$: C, 79.8; H, 5.7; N, 11.3. Found: C, 79.9; H, 5.6; N, 11.2.

Compound 22 had mp 146°C, 2.23 g (85 %); δ ($CDCl_3$) 1.0 (t, J=7Hz, 3H), 2.5 (s, 3H), 4.0 (q, J=7Hz, 2H), 4.7 (d, J=6Hz, 1H), 5.8 (d, J=6Hz, 1H), 6.7-7.8 (m, 20H) ppm; υ (KBr) 1750 (C=O), 1600 (C=N) cm^{-1}. Anal. Calcd for $C_{34}H_{30}N_4O_2$: C, 77.5; H, 5.7; N, 10.6. Found: C, 77.6; H, 5.6; N, 10.7.

Compound 23 had mp 168°C, 2.28 g (80 %); δ ($CDCl_3$) 0.9 (t, J=7Hz, 3H), 4.0 (q, J=7Hz, 2H), 4.8 (d, J=6Hz, 1H), 5.8 (d, J=6Hz, 1H), 6.9-7.6 (m, 25H) ppm; υ (KBr) 1745 (C=O), 1600 (C=N) cm^{-1}. Anal. Calcd for $C_{39}H_{32}N_4O$: C, 79.7; H, 5.5; N, 9.5. Found: C, 79.3; H, 5.8; N, 9.7.

Compound 24 had mp 125°C, 2.29 g (85 %); δ ($CDCl_3$) 4.8 (d, J=6Hz, 1H), 5.4 (d, J=6Hz, 1H), 7.0-7.7 (m, 25H) ppm; υ (KBr) 2220 (C≡N), 1595 (C=N) cm^{-1}. Anal. Calcd for $C_{37}H_{27}N_5$: C, 82.0; H, 5.0; N, 12.9. Found: C, 81.6; H, 5.3; N, 12.7.

Compound 25 had mp 110°C, 2.17 g (70 %); δ ($CDCl_3$) 5.1 (d, J=6Hz, 1H), 5.5 (d, J=6Hz, 1H), 6.9-7.4 (m, 30H) ppm; υ (KBr) 1690 (C=O), 1595 (C=N) cm^{-1}. Anal. Calcd for $C_{43}H_{32}N_4O$: C, 83.2; H, 5.2; N, 9.0. Found: C, 83.0; H,. 5.6; N, 8.9.

Compound **26** had mp 149°C, 2.10 g (90 %); δ ($CDCl_3$) 4.8 (d, J = 6Hz, 1H), 5.4 (d, J = 6Hz, 1H), 6.8-8.2 (m, 12H) ppm; υ (KBr) 2250 (C≡N), 1595 (C=N) cm^{-1}. Anal. Calcd for $C_{31}H_{23}N_5$: C, 80.0; H, 5.0; N, 15.0. Found: C, 79.6; H, 5.0; N, 15.4.

Compound **27** had mp 225°C, 2.43 g (90 %); δ ($CDCl_3$) 4.7 (d, J = 6Hz, 1H), 5.5 (d, J = 6Hz, 1H), 6.8-7.8 (m, 25H) ppm; υ (KBr) 2220 (C≡N), 1595 (C=N) cm^{-1}. Anal. Calcd for $C_{37}H_{27}N_5$: C, 82.0; H, 5.0; N, 12.9. Founf: C, 81.7; H, 5.4; N, 12.6.

Compound **28** had mp 137°C, 2.72 g (80 %); δ ($CDCl_3$) 4.5 (d, J = 6Hz, 1H), 5.4 (d, J = 6Hz, 1H), 6.8-7.9 (m, 30H) ppm; υ (KBr) 3300 (NH), 1690 (C=O) cm^{-1}. Anal. Calcd for $C_{43}H_{32}N_6O_3$: C, 75.9; H, 4.7; N, 12.4. Found: C, 75.9; H, 4.8; N, 12.6.

REFERENCES

1. V.G. Voronin, Z.I. Shramova, S. Ya. Shachilova, L. D. Kulikova, A. I. Ermakov, A. S. Zaks, and M. L. Suslina, Khim. Farm. Zh., 1985, 19, 1208 (Chem. Abstr., 1986, 104, 61608m).
2. S. Noguchi and S. Kishimoto, (Takeda Chemical Industries, Ltd.) Japan, 1973, 73 28,914 (Cl C 07d, A 61K), 05 Sep. 1973. Appl. 69 28,540, 11 Apr. 1969; 4pp (Chem. Abstr., 1974, 80, 120931c).
3. L. Knorr, Ber., 1884, 17, 546.
4. V. M. L. Farbw, German Patent, 1911, 254,711 (Chem. Abstr., 1913, 47, 1403.
5. H. Stenzl, U. S. Patent, 1951, 2,562,830 (Chem. Abstr., 1953, 47, 1191).
6. T. Natio, T. Yoshikawa, S. Kitahara, and N. Aoki, Chem. Pharm. Bull., 1969, 17, 1467.
7. E. G. Brain and I. L. Finar, J. Chem. Soc., 1958, 2486.
8. P. B. Timmermans, A. P. Uigttewaal, and C. L. Habraken, J. Heterocycl. Chem, 1972, 9, 1373.
9. R. Reimlinger, J. J. Vandewalle, and D. A. Van, Liebigs Ann. Chem., 1969, 720, 124 (Chem. Abstr., 1969, 70, 87650d).
10. I. L. Finar, J. Chem. Soc., 1955, 1205.
11. R. M. Sandifer, L. W. Dasher, W. M. Hollinger, C. W. Thomas, D. C. Reames, C. F. Beam, R. S. Foote, and C. R. Hauser, J. Heterocycl. Chem., 1975, 12, 1159.
12 H. M. Hassaneen, H. A. H. Mousa, N. M. Abed, and A. S. Shawali, Heterocycles, 1988, 27, 695.
13. H. M. Hassaneen, H. A. H. Mousa, S. T. Ezmirly, and A. S. Shawali, Can. J. Chem., 1988, 66, 1386.
14. H. M. Hassaneen, H. A. Ead, N. M. Elwan, and A. S. Shawali, Heterocycles, 1988, 27, 2875.

15. H. M. Hassaneen, A. S. Shawali, and N. M. Elwan, Heterocycles, 1990, 31, 247.

16. T. Oida, T. Shmizu, Y. Hayashi, and K. Teramura, Bull. Chem Soc. Jpn., 1981, 54, 1429.

17. R. Sustman, R. Huisgen, and H. Huber, Chem. Ber., 1967, 100, 1802.

18. A. J. Elliot, M. S. Gibson, M. M. Kayzer, and G. A. Pawelchank, Can. J. Chem., 1973, 51, 4115.

19. J. Zabicky, J. Chem. Soc., 1961, 688.

20. H. M. Hassaneen, R. H. Hilal, N. M. Elwan, A. Harhash , and A. S. Shawali, J. Heterocycl. Chem, 1984, 21, 1013.

Received, 8th January, 1990