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

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

The derivatives of a pyrazole ring linked to an aromatic or heteroaromatic have been found anti-inflammatory and antipyretic properties. The compounds such as antipyrine, dipyrone, phenylbutorazone, and meprobamate are well known drugs. Although many syntheses for various pyrazolyl isomers are reported in literature, only a few derivatives have been reported for 3,5'-bipyravalyls.

The usual method for the synthesis of such compounds involves the reaction of hydrazines with 1,3,4,6-tetraketone or β-pyravalyl diketone. The disadvantage of this method is that an unsymmetrical tetraketone can theoretically yield four bipyravalyls, and a symmetrical tetraketone three whereas pyrazolyl β-diketone can lead to two possible isomers. In this paper it was thought worthwhile to investigate the synthetic potentiality of hydrazonyl bromide 1 in the synthesis of 3,5'-bipyravalyls 21-28. For this purpose we studied the reaction of N-phenyl-C-cinnamoylhydrazonyl 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'-bipyravalyls.

Treatment of (E)-N-phenyl-C-cinnamoylhydrazonyl 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

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\begin{align*}
\text{C}_6\text{H}_5\text{C} &= \text{C}^\equiv \text{C}^\equiv \text{C}^\equiv \text{N} = \text{C} = \text{C} = \text{N} = \text{C}_6\text{H}_5 \quad + \quad \left[ \text{RCHCOR}^+ \right]^+ \text{Na}^- \\
\text{C}_6\text{H}_5\text{C} &= \text{C}^\equiv \text{C}^\equiv \text{C}^\equiv \text{N} = \text{C} = \text{C} = \text{N} = \text{C}_6\text{H}_5 + \text{RCHCOR}^+ \\
\end{align*}
\]

N-Phenylcinnaminitriline 3, generated in situ from the bromide 1 and triethylamine in dry benzene reacted with p-nitrobenzylidenecyanocacetanilide 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 \(^1\)H nmr spectrum showed no signal due to 4-H or 5-H characteristic of 2-pyrazoline derivative 18. Similarly, nitriline 3 reacts with

<table>
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<th>(R^+R^-)</th>
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<tr>
<td>6 (\text{CH}_3/\text{COCH}_3)</td>
<td>9 (\text{C}_6\text{H}_5/\text{CN})</td>
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<tr>
<td>7 (\text{CH}_3/\text{COOC}_2\text{H}_5)</td>
<td>10 (\text{C}_6\text{H}_5/\text{COOC}_6\text{H}_5)</td>
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Scheme 1
fumaronitrile 15 and benzyldenemalononitrile 16 under similar conditions to afford exclusively the corresponding 3-alkenylpyrazoles 11, 15 and 12, 16, respectively (Scheme 2).

Scheme 2

Refluxing of N-phenylbenzohydrazonyl chloride 19 with 4-acetyl-5-methyl-1-phenyl-3(E)-alkenylpyrazole 6 in chloroform in the presence of triethylamine yielded a product which analysed for C_{33}H_{28}N_{4}O. Its 1H nmr spectrum revealed the absence of the signals of the ethylenic protons, instead it shows two doublets at 6.47 (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'-bipyrrolopyrazolyl (Scheme 3). Other 3(E)-alkenylpyrazoles

Scheme 3
7-13 react with diphenyltrinitrilime 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 ($J = 6$ Hz) near 6 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, 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 dimesicloroform 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 $^1$19 and the dipolarophiles (bezylidene malononitrile $^1$19 and p-nitrobenzyldieneacetonilide ) 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-cinnamoyldrazonyl bromide 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 %); 6 (CDCl$_3$) 2.4 (s, 3H), 2.5 (s, 3H), 7.0-7.9 (m, 12H) ppm; $\nu$ (KBr) 1650 (C=O), 1595 (C=N) cm$^{-1}$. Anal. Calcd for C$_{20}$H$_{18}$N$_2$O: 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 %); 6 (CDCl$_3$) 1.4 (t, $J = 7$Hz, 3H), 2.5 (s, 3H), 4.4 (q, $J = 7$Hz, 2H), 6.9-8.0 (m, 12H) ppm; $\nu$ (KBr) 1695 (C=O), 1595 (C=N) cm$^{-1}$. Anal. Calcd for C$_{21}$H$_{20}$N$_2$O$_2$: C, 75.9; H, 6.1; N, 8.4. Found: C, 76.1; H, 5.8; N, 8.3.

**Compound 8** had mp 160°C, 1.5g (70 %) (Lit. mp 160°C).20

**Compound 9** had mp 168°C, 1.40 g (80 %); $\nu$ (KBr) 2220 (C=O), 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-cinnamoylhydrazonyl 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 collected and recrystallized from acetic acid gave 3-styrylpyrazoles 11-13.

Compound 11 had mp 144-146 °C, 1.1 g (80 %) (Lit. mp 144°C).14

Compound 12 had mp 146-148 °C, 1.9 g (85 %) (Lit. mp 144°C).15

Compound 13 had mp 223-225 °C, 1.94 g (80 %); δ (CDCl₃) 6.9-8.3 (m, Ar-H) ppm; σ (KBr) 3380 (NH) 1690 (C = O) cm⁻¹. Anal. Caled for C₃₀H₂₂N₄O₁₂: C, 79.6; H, 5.3; N, 12.7. Found: C, 79.2; H, 5.4; N, 12.9.

Preparation of 4,5-dihydro-4'i,5'i-disubstituted 1,1',3,4-tetraphenyl-3,5-bipyrazoles 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 added 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 188-189 °C, 1.98 g (80 %); δ (CDCl₃) 2.3 (s, 3H), 2.5 (s, 3H), 4.7 (d, J = 6Hz, 1H), 5.6 (d, J = 6Hz, 1H), 5.6-7.2 (m, 20H) ppm; σ (KBr) 1760 (C = O), 1600 (C = N) cm⁻¹. Anal. Caled for C₃₁H₄₁N₄O₂: C, 79.8; H, 5.7; N, 11.3. Found: C, 79.9; H, 5.6; N, 11.2.

Compound 22 had mp 146-148 °C, 2.23 g (85 %); δ (CDCl₃) 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; σ (KBr) 1750 (C = O), 1600 (C = N) cm⁻¹. Anal. Caled for C₃₄H₄₄N₄O₂: C, 77.5; H, 5.7; N, 10.6. Found: C, 77.6; H, 5.6; N, 10.7.

Compound 23 had mp 168-169 °C, 2.28 g (80 %); δ (CDCl₃) 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; σ (KBr) 1745 (C = O), 1600 (C = N) cm⁻¹. Anal. Caled for C₃₉H₄₂N₄O₂: C, 79.7; H, 5.5; N, 9.5. Found: C, 79.3; H, 5.8; N, 9.7.

Compound 24 had mp 125-127 °C, 2.29 g (85 %); δ (CDCl₃) 4.8 (d, J = 6Hz, 1H), 5.4 (d, J = 6Hz, 1H), 7.0-7.7 (m, 25H) ppm; σ (KBr) 2220 (C = N), 1595 (C = N) cm⁻¹. Anal. Caled for C₃₇H₄⁰N₅O: C, 82.0; H, 5.0; N, 12.9. Found: C, 81.6; H, 5.3; N, 12.7.

Compound 25 had mp 110-111 °C, 2.17 g (70 %); δ (CDCl₃) 5.1 (d, J = 6Hz, 1H), 5.5 (d, J = 6Hz, 1H), 6.9-7.4 (m, 30H) ppm; σ (KBr) 1690 (C = O), 1595 (C = N) cm⁻¹. Anal. Caled for C₃₅H₃₈N₄O: 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 (CDCl₃) 4.8 (d, J = 6Hz, 1H), 5.4 (d, J = 6Hz, 1H), 6.8-8.2 (m, 12H) ppm; ν (KBr) 2250 (C=N), 1595 (C=N) cm⁻¹. Anal. Caled for C₃₁H₂₃N₅: 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 (CDCl₃) 4.7 (d, J = 6Hz, 1H), 5.5 (d, J = 6Hz, 1H), 6.8-7.8 (m, 25H) ppm; ν (KBr) 2220 (C=N), 1595 (C=N) cm⁻¹. Anal. Caled for C₃₇H₂₇N₅: C, 82.0; H, 5.0; N, 12.9. Found: C, 81.7; H, 5.4; N, 12.6.

Compound 28 had mp 137°C, 2.72 g (80%); δ (CDCl₃) 4.5 (d, J = 6Hz, 1H), 5.4 (d, J = 6Hz, 1H), 6.8-7.9 (m, 30H) ppm; ν (KBr) 3300 (NH), 1690 (C=O) cm⁻¹. Anal. Caled for C₄₃H₃₂N₆O₃: C, 75.9; H, 4.7; N, 12.4. Found: C, 75.9; H, 4.8; N, 12.6.

REFERENCES


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