SYNTHESIS AND CYCLOADDITION REACTIONS OF N-PHENYL-C-STYRYLMETHANOHYDRAZONYL BROMIDE

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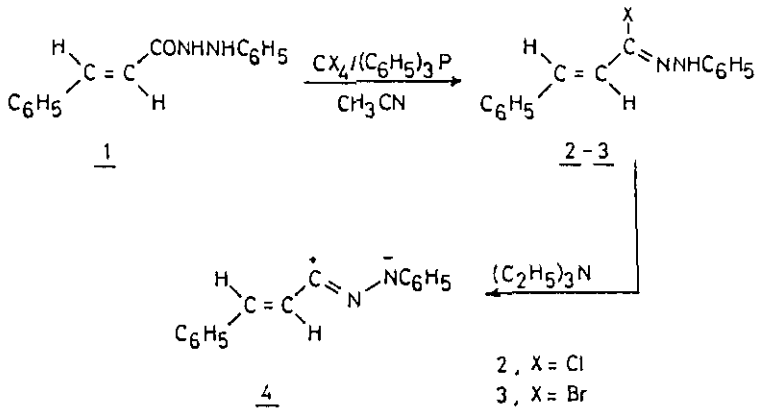
Abstract — N-Phenyl-C-styrylnitrilimine **4** reacts with arylidenesulphonylacetonitriles **5a-c** or arylidenemalononitriles **6a-c** to give exclusively 5-cyanopyrazoles **9a-c**. On the other hand cycloaddition of ethyl arylidenecyanoacetate **11a,c**, α-cyanoarylideneacetophenones **12b-d** and benzylidene α-cynoacetanilide **13a** with **4** yields 2-pyrazoline derivatives **14a,c**, **15b-d**, and **16a**, respectively. Also, nitrilimine **4** reacts with N-arylmaleimides **18a-d** to give the corresponding pyrrolopyrazoles **19a-d**.

In continuation of our studies on the chemistry of α,β-unsaturated hydrazonyl chlorides **2**[1,2] we considered the previously unknown N-phenyl-C-styrylmethanohydrazonyl bromide **3** as an entry to 3-styrylpyrazole derivatives needed for biological investigation. This report deals with the preparation of N-phenyl-C-styrylmethanohydrazonyl bromide **3** and its reaction with various dipolarophiles. Although the phenyl analog of **3** has been extensively studied,[3-5] little is known of the chemistry of α,β-unsaturated hydrazonyl halides.[1,2] Bromination of 1-cinnamoyl-2-phenylhydrazine **1** was carried out using the method of Wolkoff.[6] Thus, addition of carbon tetrabromide to a suspension of **1** and triphenylphosphine in dry acetonitrile afforded the bromide **3** in 70 % yield (Scheme 1). Treatment of arylidenesulphonylacetonitriles **5a-c**[7] with N-phenyl-C-styrylmethanohydrazonyl bromide **3** in refluxing benzene in the presence of triethylamine yielded products that were identified as 1-phenyl-4-aryl-3-styryl-5-cyanopyrazoles **9a-c** respectively (Scheme 2). Similarly, reaction of **3** with benzylidenemalononitrile **6a** and its substituted derivatives **6b,c** under the same conditions afforded products identical in all respects (ir, ^{1}H nmr, mp, mixed mp) with **9a-c** respectively.

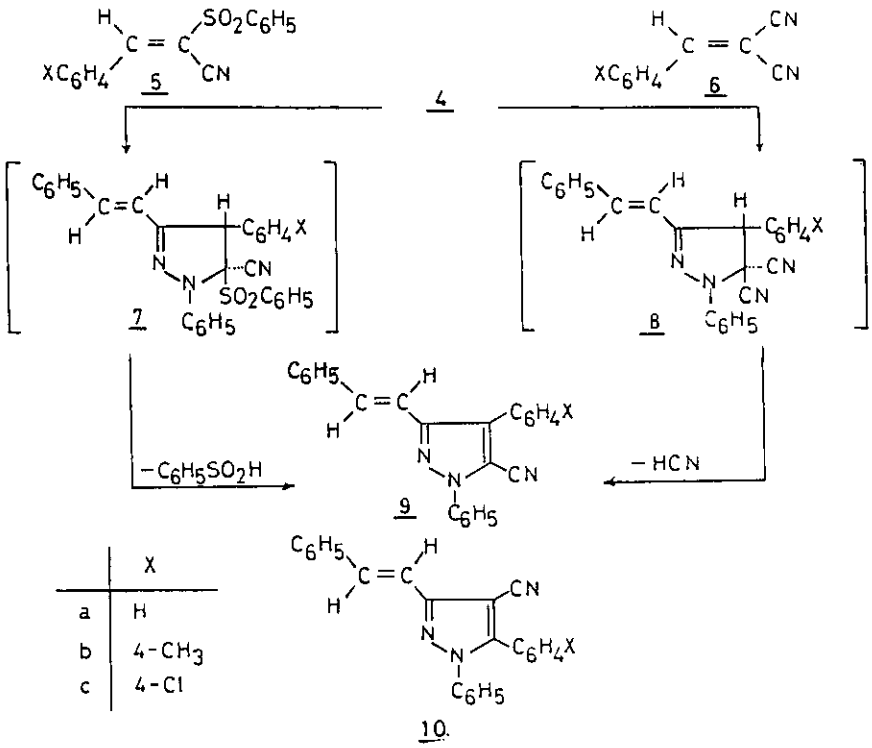


1 2 - 3 4

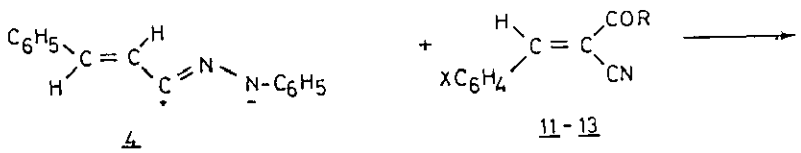
Scheme 1

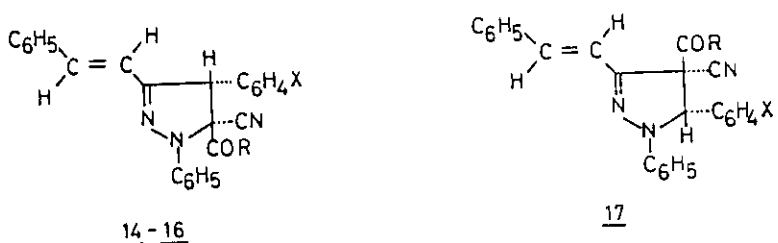
All attempts to isolate the intermediate pyrazolines **7a-c** and **8a-c** were unsuccessful. The structure of products **9a-c** was elucidated from their elemental analysis and spectral data. The ^{1}H nmr revealed, in each case, the absence of signals assignable to the 4-CH and 5-CH protons of the corresponding pyrazoline derivatives.[8] These results suggest that the cycloadducts **7a-c** and **8a-c** undergo thermal elimination of benzenesulfinic acid and hydrogen cyanide to give **9a-c** respectively. Such elimination is analogous to the elimination of 5-azido, 5-benzenesulfonyl, 5-benzoyl derivatives from 1,3-diphenyl-4-benzoyl-2-pyrazoline.[8-10] The regiochemistry of **9a** was confirmed by comparison of melting point of **9a** with that of the pertinent regioisomer, 1,5-diphenyl-3-styryl-4-cyanopyrazole **10**. The latter was prepared by reaction of **3** with phenacyl cyanide in the presence of ethanolic sodium ethoxide solution at room temperature. It is well documented that reaction of phenacyl cyanide with hydrazonyl halides yields the corresponding 4-cyanopyrazole derivatives.[11]

The reaction of the Z-dipolarophiles **11-13**[12] with the nitrilimine **4** when carried out in a similar manner, gave the corresponding 2-pyrazoline derivatives **14-16** respectively (Scheme 3). In no case was thermal elimination of hydrogen cyanide from the reaction products **14-16** observed. The structures of these products were in agreement with their spectral (ir, ^{1}H nmr) and elemental analysis data. The assignment of the 5,5-disubstituted 2-pyrazoline structure is confirmed by the absence of the nitrile absorption in the ir spectra of **14-16**. This is similar to the case of aliphatic nitriles activated by a nitrogen or oxygen atom in the α -position.[13] Also, the configuration indicated for the products **14-16** follows from the stereospecifity of the 1,3-dipolar cycloaddition of nitrilimines.[14] The absence of the nitrile absorption in the ir spectra together with the chemical shift value



Scheme 2



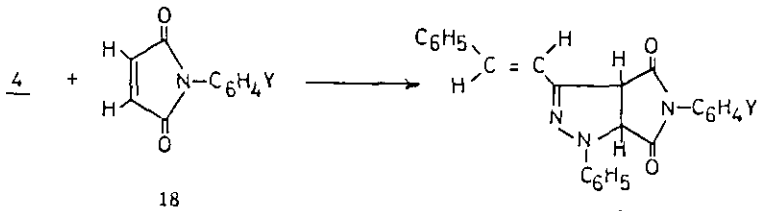


11(14), R = OC_2H_5
12(15), R = C_6H_5
13(16), R = NHC_6H_5
a, X = H ; b, X = 4-CH_3 ; c, X = 4-Cl ; d, X = 4-CH_3O

Scheme 3

δ 5.1 ppm observed for the methine proton also exclude the possibility of the regioisomeric structure **17** for the product isolated. This is because compounds of type **17** are expected to exhibit strong nitrile absorption in their ir spectra[13] and their methine chemical shift at the 5-position would appear at lower field (i.e. 5.1).[15]

Refluxing equimolar quantites of **3** and N-phenylmaleimide **18a** in benzene in the presence of triethylamine gave a quantitative yield of cycloadduct **19a** (Scheme 4). The other substituted N-pnenylmaleimides **18b-d** reacted similarly with **3** and afforded the corresponding pyrrolopyrazoles **19b-d** (Scheme 4). The ^{1}H nmr spectra of the products **19a-d** isolated showed in each case, two doublets (J = 9 Hz) near 5.0 and 5.8 ppm assignable for 3a and 6a protons. The value of the coupling constant is compatible with cis configuration expected.[16]



18 19

	Y
a	H
b	4-CH_3
c	4-Cl
d	4-CH_3O

Scheme 4

EXPERIMENTAL

All melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Infrared spectra (KBr) were measured on a Perkin Elmer 257 spectrophotometer. ^{1}H Nmr spectra were obtained in deuteriochloroform on a Varian Associate model T60-A spectrometer using tetramethylsilane as internal reference. Microanalyses were performed at microanalytical unit of University of Cairo, Giza, Egypt. The dipolarophiles **5**, **6**, **11-13** and **18** were prepared as previously described.[17]

Preparation of N-phenyl-C-styrylmethanohydrazonyl bromide 3. Carbon tetrabromide (6.64 g, 20 mmol) was added to a stirred suspension of 1-cinnamoyl-2-phenylhydrazine **1** (6.67 g, 20 mmol) and triphenylphosphine (6.6 g, 25 mmol) in dry acetonitrile (40 ml). The mixture was stirred for 1 h. During this period, the hydrazide **1** dissolved and a yellow solid precipitated. This was collected and crystallized from acetic acid to give **3**, mp 153^{o}C, 1.05 g (70 %); δ ($CDCl_3$) 6.8 (d, J = 15Hz,

1H), 7.7 (d, J = 15Hz, 1H), 7.0-8.0 (m, 10H) ppm; υ (KBr) 1600 (C = N) cm^{-1}. Anal. Calcd for $C_{15}H_{13}BrN_2$: C, 59.8; H, 4.3; N, 9.3. Found: C, 59.7; H, 4.1; N, 9.1.

Reaction of N-phenyl-C-styrylmethanohydrazonyl bromide 3 with dipolarophiles 5, 6, 11-13 and 18. General method - To a suspension of N-phenyl-C-styrylmethanohydrazonyl bromide (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 red 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 recrystallization from acetic acid gave the corresponding cycloadducts **9a-c, 14a,c, 15b-d** and **16a.**

Compound **9a** had mp 140°C, 1.14 g (70 %); δ ($CDCl_3$) 6.8 (d, J = 15Hz, 1H), 7.6 (d, J = 15Hz, 1H), 7.2-7.8 (m, 15H) ppm; υ (KBr) 2250 (C ≡ N) cm^{-1}. Anal. Calcd for $C_{24}H_{17}N_3$: C, 82.9; H, 4.9; N, 12.1. Found: C, 83.0; H, 5.1; N, 11.9.

Compound **9b** had mp 146°C, 1.17 g (65 %); δ ($CDCl_3$) 2.3 (s, 3H), 6.8 (d, J = 15Hz, 1H), 7.5 (d, J = 15Hz, 1H), 7.2-7.8 (m, 14H) ppm; υ (KBr) 2250 (C = N) cm^{-1}. Anal. Calcd for $C_{25}H_{19}N_3$: C, 83.1; H, 5.3; N, 11.6. Found: C, 83.1; H, 5.1; N, 11.2.

Compound **9c** had mp 199°C, 1.43 g (75 %); δ ($CDCl_3$) 6.9 (d, J = 15Hz, 1H), 7.7 (d, J = 15Hz, 1H), 7.2-7.9 (m, 14H) ppm; υ (KBr) 2250 (C ≡ N) cm^{-1}. Anal. Calcd for $C_{24}H_{16}ClN_3$: C, 75.5; H, 4.2; N, 11.1. Found: C, 75.3; H, 4.1; N, 11.3.

Compound **14a** had mp 126°C, 1.26 g (60 %); δ ($CDCl_3$) 1.3 (t, J = 7Hz, 3H), 4.4 (q, J = 7Hz, 2H), 5.1 (s, 1H), 6.7 (d, J = 15Hz, 1H), 7.6 (d, J = 15Hz, 1H), 7.0-7.8 (m, 15H) ppm; υ (KBr) 1740 (C = O) cm^{-1}. Anal. Calcd for $C_{27}H_{23}N_3O_2$: C, 76.9; H, 5.5; N, 9.9. Found: C, 77.0; H, 5.7; N, 9.7.

Compound **14c** had mp 108°C, 1.64 g (72 %); δ ($CDCl_3$) 1.3 (t, J = 7Hz, 3H), 4.3 (q, J = 7Hz, 2H), 5.1 (s, 1H), 6.6 (d, J = 15Hz, 1H), 7.5 (d, J = 15Hz, 1H), 7.2-7.8 (m, 14H) ppm; υ (KBr) 1740 (C = O) cm^{-1}. Anal. Calcd for $C_{27}H_{22}ClN_3O_2$: C, 71.1; H, 4.9; N, 9.2. Found: C, 71.1; H, 4.8; N, 9.3.

Compound **15b** had mp 152°C, 1.63 g (70 %); δ ($CDCl_3$) 2.4 (s, 3H), 5.1 (s, 1H), 6.5 (d, J = 15Hz, 1H), 7.7 (d, J = 15Hz, 1H), 7.0-8.0 (m, 19H) ppm; υ (KBr) 1705 (C = O) cm^{-1}. Anal. Calcd for $C_{32}H_{25}N_3O$: C, 82.2; H, 5.3; N, 8.9. Found: C, 81.1; H, 5.5; N, 9.1.

Compound **15c** had mp 146°C, 1.80 g (74 %); δ ($CDCl_3$) 5.1 (s, 1H), 6.6 (d, J = 15Hz, 1H), 7.5 (d, J = 15Hz, 1H), 6.8-8.0 (m, 19H) ppm; υ (KBr) 1695 (C = O) cm^{-1}. Anal. Calcd for $C_{31}H_{22}ClN_3O$: C, 76.3; H, 4.5; N, 8.6. Found: C, 76.6; H, 4.7; N, 8.8.

Compound **15d** had mp 166°C, 1.57 g (65 %); δ ($CDCl_3$) 3.8 (s, 3 H), 5.1 (s, 1H), 6.4 (d, J = 15Hz, 1H), 7.6 (d, J = 15Hz, 1H), 6.8-8.0 (m, 19H) ppm; υ (KBr) 1700 (C = O) cm^{-1}. Anal. Calcd for $C_{32}H_{25}N_3O_2$: C, 79.5; H, 5.2; N, 8.7. Found: C, 79.1; H, 5.3; N, 9.2.

Compound **16a** had mp 210°C, 1.87 g (80 %); δ ($CDCl_3$) 5.3 (s, 1H), 6.6 (d, J = 15Hz, 1H), 7.7 (d, J = 15Hz, 1H), 7.0-7.8 (m, 20H), 8.3 (s, 1H) ppm; υ (KBr) 3300 (NH), 1690 (C = O) cm^{-1}. Anal. Calcd for $C_{31}H_{24}N_4O$: C, 79.4; H, 5.2; N, 12.1. Found: C, 79.7; H, 4.9; N, 12.3.

Preparation of 1,5-diphenyl-3-styryl-4-cyanopyrazole 10. To an ethanolic sodium ethoxide solution [prepared from sodium metal (0.1 g, 0.005 g atom) and absolute ethanol (20 ml)] was added phenacyl cyanide (0.73 g, 5 mmol) with stirring. To the resulting solution N-phenyl-C-styrylmethanohydrazonyl bromide **3** (1.5 g, 5 mmol) was added at room temperature and the mixture was stirred for 6 h. During this period, the bromide **3** dissolved and the crude 4-cyanopyrazole **10** was precipitated. The latter was collected, washed with methanol and recrystallized from acetic acid to give compound **10**, mp 168°C, 1.91 g (85 %); δ ($CDCl_3$) 6.8 (d, J = 15Hz, 1H), 7.7 (d, J = 15Hz, 1H), 7.2-7.8 (*m, 15H*) *ppm*; υ (KBr) 2250 (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.

Preparation of 3a,4,6,6a-tetrahydro-1-phenyl-3-styryl-5-aryl-1H,5H-pyrrolo[3,4-c]pyrazole-4,6-diones 19a-d. To a solution of *E-N-phenyl-C-styrylmethanohydrazonyl bromide* **3** (*1.5 g, 5 mmol*) and the appropriate N-arylmaleimides **18a-d** (5 mmol) in chloroform (40 ml), triethylamine (0.7 ml, 5 mmol) was added at room temperature. The mixture was refluxed for 12 h then cooled. The reaction mixture was washed three times with water, and the organic layer was collected, dried over anhydrous sodium sulfate, and then filtered. The solvent was evaporated and the residue left was triturated with a small amount of methanol where it solidified. The crude solid was collected and recrystallization from acetic acid gave the corresponding cycloadducts **19a-d.**

Compound **19a** had mp 200°C, 1.78 g (90 %); δ ($CDCl_3$) 4.8 (d, J = 9Hz, 1H), 5.3 (d, J = 9Hz, 1H), 6.8-7.9 (m, 17H) ppm; υ (KBr) 1720 (C=O) cm^{-1}. Anal. Calcd for $C_{25}H_{19}N_3O_2$: C, 76.3; H, 4.9; N, 10.7. Found: C, 76.0; H, 4.9; N, 10.2.

Compound **19b** had mp 237°C, 1.87 g (92 %); δ ($CDCl_3$) 2.5 (s, 3H), 4.8 (d, J = 9Hz, 1H), 5.2 (d, J = 9Hz, 1H), 6.9-7.8 (m, 16H) ppm; υ (KBr) 1720 (C=O) cm^{-1}. Anal. Calcd for $C_{26}H_{21}N_3O_2$: C, 76.6; H, 5.2; N, 10.3. Found: C, 76.4; H, 5.2; N, 10.1.

Compound **19c** had mp 221°C, 1.90 g (89 %); δ ($CDCl_3$) 4.8 (d, J = 9Hz, 1H), 5.2 (d, J = 9Hz, 1H), 7.0-7.8 (m, 16H) ppm; υ (KBr) 1720 (C=O) cm^{-1}. Anal. Calcd for $C_{25}H_{18}ClN_3O_2$: C, 70.2; H, 4.2; N, 9.8. Found: C, 70.3; H, 4.7; N, 9.7.

Compound **19d** had mp 227°C, 1.90 g (90 %); δ ($CDCl_3$) 3.8 (s, 3H), 4.8 (d, J = 9Hz, 1H), 5.2 (d, J = 9Hz, 1H), 6.9-7.8 (m, 16H) ppm; υ (KBr) 1720 (C=O) cm^{-1}. Anal. Calcd for $C_{26}H_{21}N_3O_3$: C, 73.7; H, 5.0; N, 9.9. Found: C, 73.2; H, 5.1; N, 9.5.

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