Chemistry of *C*-Heteroarylnitrilimines. Synthesis and Cycloaddition Reactions of *N*-Phenyl-*C*-(2-thienyl)nitrilimine

Hamdi M. Hassaneen*, Hiyam A. H. Mousa and Ahmad S. Shawali* [1]

Girls College, Science department, General Presidency for Girls Education, Riyadh, Saudi Arabia

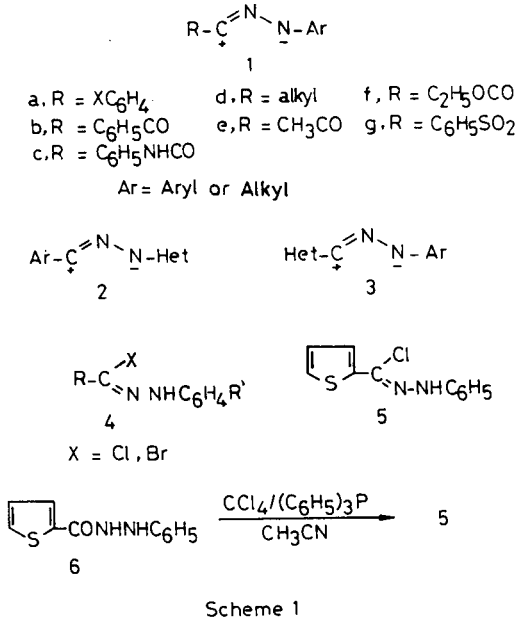
Received May 19, 1987

The nitrilimine **7**, generated *in situ* from *N*-phenyl-*C*-(2-thienyl)formohydrazidoyl chloride **5** in chloroform in the presence of triethylamine, reacts with acrylonitrile, acrylamide and arylidene acetophenones to give exclusively the 5-substituted 2-pyrazoline derivatives **9**, **10** and **16**, respectively. On the other hand, the cycloaddition of **7** to coumarin, benzalmalononitrile and the enolate anions of active methylene compounds yield the pyrazole derivatives **12**, **14** and **23**, respectively. The structures of the cycloadducts prepared were attributed on the basis of spectroscopic and chemical evidence. The regioselectivity in the studied reactions is discussed in terms of the frontier orbital theory.

J. Heterocyclic Chem., **24**, 1665 (1987).

Introduction.

Although nitrilimines of type **1** and **2** with various substituents at the carbon and nitrogen terminals (Scheme 1) have been extensively investigated within the last two decades [2], the *C*-heteroaryl counterparts **3** have not yet been investigated. In continuation of our work on hydrazidoyl halides **4** [2] which are versatile precursors for nitrilimines, we studied the synthesis of *N*-phenyl-*C*-(2-thienyl)-formohydrazidoyl chloride **5** and investigated its reactions with several mono- and di-substituted olefins and the enolate anions of some active methylene compounds. This study was undertaken with the two-fold objective of identifying the regiochemistry of 1,3-dipoles of type **3** and of exploring their use in synthesis of 2-pyrazoline and pyrazole derivatives having a heteroaryl residue at C-3. So far, only four examples of such derivatives, prepared from different starting reagents, have been reported [3].

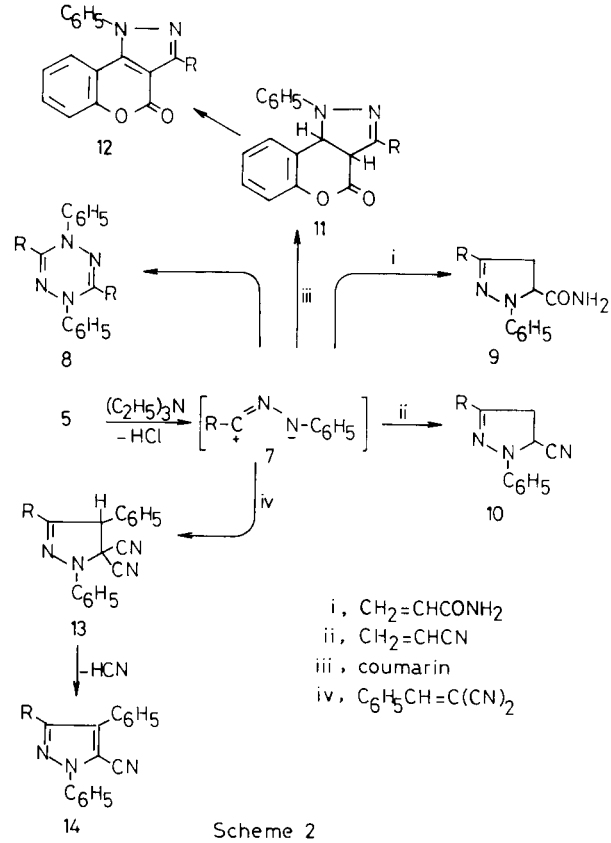


Scheme 1

Results and Discussion.

Addition of carbon tetrachloride to a stirred suspension of 1-phenyl-2-(2-thienoyl)hydrazine **6** and triphenylphosphine in acetonitrile at room temperature afforded *N*-phenyl-*C*-(2-thienyl)formohydrazidoyl chloride **5** in 80% yield (Scheme 1) [4]. The structure of **5** was identified by its spectra, elemental analysis and its reactions outlined in Schemes 2-4.

Treatment of **5** with triethylamine in chloroform at reflux yielded a product identified as 1,4-diphenyl-3,6-di-



Scheme 2

(2-thienyl)-1,4-dihydro-1,2,4,6-tetrazine **8**. The latter product resulted undoubtedly from dimerization of *N*-phenyl-*C*-2-thienylnitrilimine **7**, which is generated *in situ* from dehydrochlorination of **5** (Scheme 2). Generation of **7** in the presence of suitable dipolarophiles afforded the corresponding cycloadducts. Thus, the reflux of **5** with acrylonitrile and acrylamide in chloroform in the presence of triethylamine afforded exclusively the corresponding 5-substituted 3-(2-thienyl)-1-phenyl-2-pyrazolines **9** and **10** respectively in good yield (Scheme 2). The assigned 5-R substituted structures **9** and **10** were supported by analytical and spectral data (ir and ^{1}H nmr). For example, in the ^{1}H nmr spectra of **9** and **10** the 4-CH_2 and 5-CHR hydrogens show A_2X and ABX patterns respectively (Table 1). The chemical shifts of the methine and methylene hydrogens of **9** and **10** are similar to those reported to the corresponding 5-R substituted 1,3-diphenyl-2-pyrazolines [5]. Such spectral similarity, while confirming the assigned structures, it indicates that both substituents, phenyl and 2-thienyl at C-3, would have roughly the same effects on the chemical shifts of the methylene protons at C-4 of substituted 2-pyrazoline derivatives. Also, the structure of **9** was confirmed by the absence of the nitrile absorption in its infrared spectrum, as it is the case in aliphatic nitriles activated by a nitrogen or an oxygen atom in the α-position [6,7].

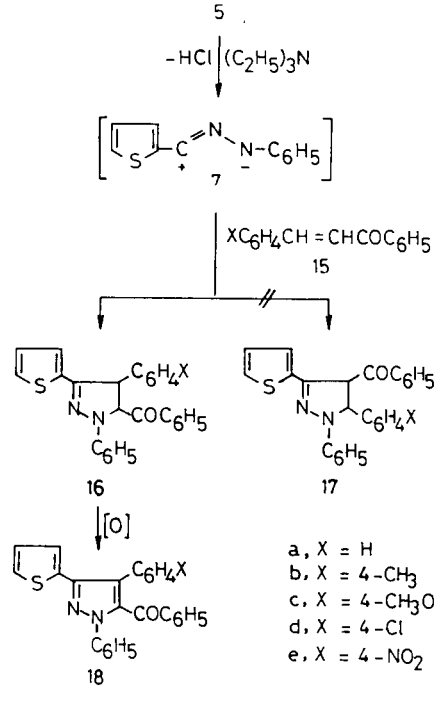
Table 1

Infrared and ^{1}H NMR Spectral Data of Substituted 2-Pyrazolines and Pyrazoles Prepared

Compound No.	ν, cm^{-1}	δ, ppm
9	3360, 3180 (NH_2) 1640 (CO), 1590 (C=N)	3.26 (dd, J = 8, 17 Hz, 1H), 3.74 (dd, J = 12, 17 Hz, 1H), 4.66 (dd, J = 8, 12 Hz, 1H), 7.0-8.0 (m, ArH)
10	1590 (C=N)	3.61 (d, J = 8 Hz, 2H), 4.91 (d, J = 8 Hz, 1H), 7.0-8.0 (m, ArH)
12	1740 (CO), 1610 (C=C), 1585 (C=N)	7.0-8.0 (m, ArH)
14	2230 (C≡N), 1590 (C=N)	6.9-8.0 (m, ArH)
16a	1700 (CO), 1590 (C=N)	4.53 (d, J = 5 Hz, 1H), 5.53 (d, J = 5 Hz, 1H), 6.6-8.0 (m, ArH)
16b	1695 (C), 1590 (C=N)	4.60 (d, J = 5 Hz, 1H), 5.6 (d, J = 5 Hz, 1H), 6.7-8.1 (m, ArH)
16c	1690 (CO), 1590 (C=N)	4.5 (d, J = 5 Hz, 1H), 5.53 (d, J = 5 Hz, 1H), 6.6-8.0 (m, ArH)
16d	1690 (CO), 1590 (C=N)	4.53 (d, J = 5 Hz, 1H), 5.55 (d, J = 5 Hz, 1H), 6.7-8.1 (m, ArH)
16e	1695 (CO), 1590 (C=N)	4.60 (d, J = 5 Hz, 1H), 5.54 (d, J = 5 Hz, 1H), 6.8-8.1 (m, ArH)
23a	1660 (CO), 1590 (C=N)	2.14 (s, 3H), 2.25 (s, 3H), 7.0-8.0 (m, 8H)
23b	1650 (CO), 1595 (C=N)	7.0-7.4 (m)
23c	1700 (CO), 1590 (C=N)	1.17 (t, J = 7 Hz, 3H), 2.29 (s, 3H), 4.17 (q, J = 7 Hz, 2H), 6.9-8.0 (m, 8H)
23d	3300 (NH), 1640 (CO), 1590 (C=N)	2.3 (s, 3H), 7.0-7.5 (m, 13H)
23e	2220 (C≡), 1585 (C=N)	7.0-8.0 (m)

The reaction of **7** with coumarin under the same conditions yield **12**, an oxidation product of the cycloadduct **11** (Scheme 2). The structure of the pyrazole derivative **12** was established by its elemental analysis and ^{1}H nmr spectrum. The absence of the two methine doublets in the ^{1}H nmr spectrum of the product isolated (Table 1) indicates that the cycloadduct **11** is aromatized as it is formed. 2-Pyrazolines are known to be easily aromatized by autoxidation or thermal dehydrogenation, even in the absence of oxygen [8].

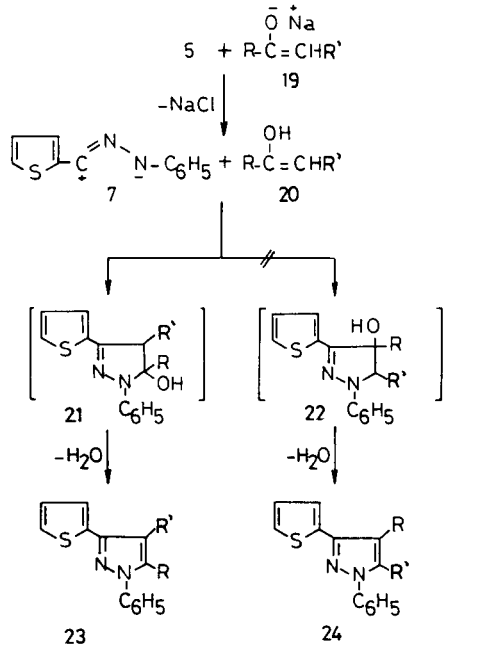
The reflux of **5** with benzalmalonitrile in benzene in the presence of triethylamine yielded 1,4-diphenyl-3-(2-thienyl)-5-cyanopyrazole **14** in good yield. The latter results undoubtedly from elimination of hydrogen cyanide from the expected cycloadduct **13** (Scheme 2). The indicated regiochemistry was established beyond doubt by comparison of the ir and ^{1}H nmr spectra of **14** (Table 1) with those of the pertinent regioisomer namely, 1,5-dephenyl-3-(2-thienyl)-4-cyanopyrazole **23e**. The latter was



Scheme 3

prepared by the reaction of the sodium salt of phenacyl cyanide and **7** in ethanol (Scheme 4).

Next the cycloaddition of **7** to benzalacetophenone and some of its substituted derivatives **15a-e** was studied. Treatment of **7** with **15** in refluxing chloroform in the presence of triethylamine afforded exclusively the 2-pyrazoline derivatives **16a-e** respectively (Scheme 3). Analyses (tlc and ^{1}H nmr) of the reaction products showed that only one regioisomer was formed in each case. The structures of the cycloadducts **16a-e** were assigned on the basis of their elemental analyses, spectra (ir and ^{1}H nmr) and by comparison of their dehydrogenated products with authentic samples of the 4-acyl regioisomers **17**. For example, each of the cycloadducts **16a-e** exhibits two characteristic doublets near δ 4.6 and 5.6 ppm with J value of 6 Hz (Table 1) assignable to the resonances of 4-CHAr and 5-CHCOAr protons respectively. Such assignments are substantiated by comparison of these chemical shifts with those of the throughly studied diphenylnitrilimine cycloadducts [6]. For example, 1,3,4-triphenyl-5-benzoyl-2-pyrazoline exhibits two doublets at δ 4.61 and 5.61 ppm due to the 4-CHC_6H_5 and 5-$CHCOC_6H_5$ methine protons respectively [6].



Scheme 4

Dehydrogenation of **16a** with chloranil in refluxing xylene yielded 1,4-diphenyl-3-(2-thienyl)-5-benzoylpyrazole **18a**. The ir and ^{1}H nmr spectra of **18a** were compatible with its structure. Also, the structure of **18a** was supported by comparison with its 4-benzoyl regioisomer **23b**, prepared from **7** and the sodium salt of dibenzoylmethane (Scheme 4).

We have also explored the reactions of **5** with the sodium salts of some active methylene compounds **20a-e** (Scheme 4). Thus, addition of **5** to equivalent amount of **20** in ethanol at room temperature afforded the corresponding pyrazole derivative **23** in good yield. The structures of the products **23a-e** prepared were identified by their elemental and spectral analyses (Table 1 and 3).

Table 2

Substituted 1-Phenyl-3-(2-thienyl)-2-pyrazolines

Compound No.	Mp, [a] °C	Molecular formula	*Anal.* Calcd./(Found) C,%	H,%	N,%
9	263 (E)	$C_{14}H_{13}N_3OS$	61.97 (61.89)	4.83 (4.70)	15.47 (15.23)
10	150 (E)	$C_{14}H_{11}N_3S$	66.37 (66.14)	4.37 (4.20)	16.58 (16.71)
16a	180 (A)	$C_{26}H_{20}N_2OS$	76.44 (76.60)	4.93 (4.82)	6.85 (6.62)
16b	187 (A)	$C_{27}H_{22}N_2OS$	76.74 (76.61)	5.25 (5.22)	6.63 (6.51)
16c	207 (A)	$C_{27}H_{22}N_2O_2S$	73.94 (73.79)	5.05 (5.11)	6.39 (6.23)
16d	187 (A)	$C_{26}H_{19}ClN_2OS$	70.49 (70.31)	4.32 (4.22)	6.32 (6.21)
16e	150 (A)	$C_{26}H_{19}N_3O_3S$	68.85 (68.58)	4.22 (4.11)	9.26 (9.40)

[a] A, acetic acid; E, ethanol.

Table 3

Substituted 1-Phenyl-3-(2-thienyl)pyrazoles

Compound No.	Mp, [a] °C	Molecular formula	*Anal.* Calcd./(Found) C,%	H,%	N,%
12	295 (A)	$C_{20}H_{12}N_2O_2S$	69.75 (69.55)	3.51 (3.39)	8.31 (8.47)
14	203 (E)	$C_{20}H_{13}N_3S$	73.37 (73.15)	4.00 (3.87)	12.83 (13.02)
23a	84 (M)	$C_{16}H_{14}N_2OS$	68.06 (68.20)	4.99 (5.01)	9.92 (9.62)
23b	205 (A)	$C_{26}H_{18}N_2OS$	76.82 (76.71)	4.46 (4.30)	6.89 (6.72)
23c	75 (M)	$C_{17}H_{16}N_2O_2S$	65.36 (65.22)	5.16 (5.17)	8.97 (9.17)
23d	200 (A)	$C_{21}H_{17}N_3OS$	70.17 (70.05)	4.76 (4.60)	11.69 (11.72)
23e	150 (A)	$C_{20}H_{13}N_3S$	73.37 (73.16)	4.00 (4.01)	12.83 (12.61)

[a] A, acetic acid; E, ethanol; M, methanol.

The foregoing results indicate that the regioselectivity in the reactions of *N*-phenyl-*C*-(2-thienyl)nitrilimine **7** with

the various dipolarophiles examined is similar to that of diphenylnitrilimine [2]. Thus by analogy to the latter 1,3-dipole, the cycloddition of **7** to electron-deficient dipolarophiles such as acrylic acid derivatives, coumarin, benzalacetophenones and benzalmalononitrile are controlled by HOMO(dipole)-LUMO(dipolarophile) interaction [10]. Since both HOMO and LUMO of electron deficient olefins are polarized away from the electron withdrawing substituent [11], the exclusive formation of 5-R substituted 2-pyrazolines from **5** and such dipolarophiles indicate that the larger HOMO orbital coefficient is located on the carbon atom of the dipole **5**. On the other hand, the reaction of **7** with electron rich dipolarophile such as the enolate anions are controlled by LUMO-(Dipole)-HOMO(dipolarophile) interaction.

EXPERIMENTAL

All melting points are uncorrected. The infrared spectra (potassium bromide) were recorded on Perkin Elmer 257 spectrophotometer. The ^{1}H nmr spectra in deuterated chloroform were recorded on a Varian T60-A spectrometer using tetramethylsilane as the internal reference. Elemental analyses were performed at the Microanalytical Laboratory at King Abdulaziz University, Jeddah, Saudi Arabia.

Preparation of *N*-Phenyl-*C*-(2-thienyl)formohydrazidoyl Chloride [5].

Carbon tetrachloride (2 ml, 20 mmoles) was added to a stirred suspension of 1-phenyl-2-(2-thienoyl)hydrazine **4** (4.3 g, 20 mmoles) and triphenylphosphine (6.55 g, 25 mmoles) in acetonitrile (40 ml) dried by passage through an alumina column and introduced directly from the column into the reaction flask. After stirring for 10 hours, water (100 ml) was added. The organic layer was separated, dried over anhydrous sodium sulfate, filtered, and the solvent was evaporated. The solid left was collected and crystallization from methanol gave **5** in 80% yield.

Compound **5** had mp 87°, ^{1}H nmr (deuteriochloroform): δ 8.40 (s, NH), 6.8-7.8 (m, ArH, and Het-H) ppm; ir (potassium bromide): 3300 (NH), 1595 (C = N) cm^{-1}.

Anal. Calcd. for $C_{11}H_9ClN_2S$: C, 55.81; H, 3.83; N, 11.83; S, 13.54. Found: C, 55.70; H, 3.67; N, 11.81; S, 13.41.

Reaction of *N*-Phenyl-*C*-(2-thienyl)nitrilimine (**7**) with Dipolarophiles.

General Procedure.

To a solution of the hydrazidoyl chloride **5** (1.2 g, 5 mmoles) and the appropriate dipolarophile (5 mmoles) in chloroform (30 ml) was added triethylamine (0.7 ml, 5 mmoles) at room temperature. The mixture was refluxed for 12-14 hours and then cooled. The mixture was then extracted with water, the organic layer was dried (anhydrous sodium sulfate), then filtered. The solvent was evaporated and trituration of the residue with little methanol precipitated the crude cycloadduct. The latter was collected and crystallized from the suitable solvent. The results are summarized in Tables 1 and 2.

1-Phenyl-3-(2-thienyl)-3,4-disubstituted pyrazoles **23a-e**.

General Method.

To an ethanolic sodium ethoxide solution [prepared from sodium metal (0.1 g, 0.005 g-atom) and absolute ethanol (20 ml)] was added the appropriate active methylene compound **20** (5 mmoles) with stirring. To the resulting solution the hydrazidoyl chloride **5** (1.2 g, 5 mmoles) was added at room temperature and the mixture was stirred for 4 hours. During this period, the chloride **5** dissolved and the crude pyrazole product precipitated. The latter was collected, washed with methanol and crystallized from the appropriate solvent to give **23** in 75-85% yield. The compounds **23a-e** prepared together with their physical constants are given in Tables 1 and 3.

Dehydrogenation of 1,4-diphenyl-3-(2-thienyl)-5-benzoyl-2-pyrazoline (**16a**).

A solution of **16a** (0.82 g, 2 mmoles) in xylene (25 ml) was refluxed with chloranil (0.54 g, 2.2 mmoles) for 65 hours. The reaction mixture was cooled and then extracted with aqueous sodium hydroxide solution (5%). The organic layer was collected, dried (anhydrous sodium sulfate) and the solvent was evaporated *in vacuo*. The solid left was collected and crystallized from ethanol to give 1,4-diphenyl-3-(2-thienyl)-5-benzoylpyrazole (**18a**) in 70% yield.

Compound **18a** had mp 155°; ir (potassium bromide): 1665 (C=O), 1595 (C=N) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 6.8-8.0 (m, ArH) ppm.

Anal. Calcd. for $C_{26}H_{18}N_2OS$: C, 76.82; H, 4.46; N, 6.89. Found: C, 77.05; H, 4.32; N, 7.08.

REFERENCES AND NOTES

[1] Author to whom correspondence would be addressed. Present address. Department of Chemistry, Faculty of Science, King Abdulaziz University, P. O. Box 9028, Jeddah 21413, Saudi Arabia.

[2] For review see: [a] A. S. Shawali and C. Parkanyi, *J. Heterocyclic Chem.*, **17**, 833 (1980); [b] A. S. Shawali, *Heterocycles*, **20**, 2239 (1983); [c] P. Caramella and P. Grunanger, "1,3-Dipolar Cycloaddition Chemistry", A. Padwa, ed, Wiley-Interscience, New York, 1984, Vol **I**, Chapter 3.

[3] L. C. Behr, R. Fusco and C. H. Jarboe, "Pyrazoles, Pyrazolines, Pyrazolidines, Indazoles and Condensed Rings", R. H. Wiley, ed, Interscience, New York, 1967.

[4] P. Wolkoff, *Can. J. Chem.*, **53**, 1333 (1975).

[5] W. Fliege, R. Huisgen, J. S. Clovis and H. Knupfer, *Chem. Ber.*, **116**, 3039 (1983).

[6] G. Butt, J. Cilmi, P. M. Hooben and R. D. Topson, *Spectrochim. Acta*, **36A**, 521 (1980).

[7] J. P. Jessen and H. W. Thompson, *Spectrochim. Acta*, **13**, 217 (1958).

[8a] R. Huisgen, M. Seidel, G. Wallbillich and H. Knupfer, *Tetrahedron*, **17**, 3 (1962); [b] T. Oida, T. Shimizu, Y. Hayashi and K. Teramura, *Bull. Chem. Soc. Japan*, **54**, 1429 (1981).

[9] R. Fusco and P. D. Croce, *Tetrahedron Letters*, 3061 (1970).

[10] G. Bianchi, R. Gandolfi and C. DeMichelli, *J. Chem. Res.* (S), 6 (1981); *ibid.*, (M) 0135 (1981).

[11] P. Caramella and K. N. Houk, *J. Am. Chem. Soc.*, **98**, 6397 (1976).