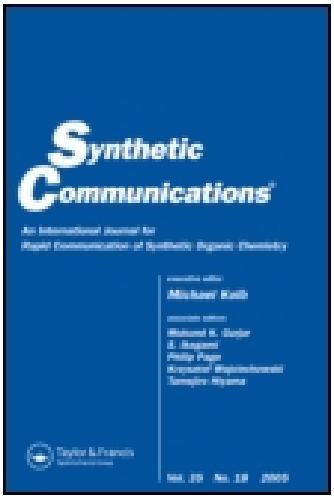

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Published online: 09 Dec 2009.

To cite this article: Guaili Wu , Ruirui Liang , Yongjiang Chen & Longmin Wu (2009) Thiocyanation on N-Benzene Rings of 1,3,5-Trisubstituted Pyrazolines with Oxone, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 40:1, 129-134, DOI: 10.1080/00397910902957415

To link to this article: http://dx.doi.org/10.1080/00397910902957415

Synthetic Communications®, 40: 129–134, 2010

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910902957415

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THIOCYANATION ON *N*-BENZENE RINGS OF 1,3,5-TRISUBSTITUTED PYRAZOLINES WITH OXONE

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An efficient aromatic thiocyanation of 1,3,5-trisubstituted pyrazolines occurred regioselectively at the para position of N-benzene rings using ammonium thiocyanate as a thiocyanation reagent and oxone as an oxidant.

Keywords: Ammonium thiocyanate; oxone; pyrazolines; thiocyanation

Because of the current interest in the application of oxone in organic synthesis,[1] we have explored some of its applications in forming carbon–heteroatom bonds. These reactions were involved in oxone-mediated addition of thiocyanate to aromatic/heteroaromatic compounds and 1,1-disubstituted olefins.[2] Afterward, further study was carried out to extend the substrate scope for 1,3,5-trisubstituted pyrazolines (**1**). Pyrazolines **1** not only are a kind of important structural unit present in biologically active natural products but also are a kind of building block for the synthesis of medicinally interesting compounds.[3] As such, the introduction of a thiocyano group to the framework of **1** will be of significance. The thiocyanato group is available for further chemical manipulations, including transformation of various sulfur functional groups and sulfur-containing heterocycles.[4,5] The thiocyanato group also plays a special role in several biologically active natural products.[6,7] In the present work, we disclose the results of aromatic thiocyanation of 1,3,5-trisubstituted pyrazolines (Scheme 1).

We started with 1,3,5-triphenyl pyrazoline **1a**. The treatment of **1a** with ammonium thiocyanate and oxone in methanol gave a monothiocyanated product, 1-(*para*-thiocyano)phenyl-3,5-diphenyl pyrazoline **2a** (Scheme 1) in 97% yield. The thiocyanation occurred at the *para* position of *N*-benzene ring of **1a** rather than at the pyrazoline ring. No side product was detected. Extension to other 1,3,5-trisubstituted pyrazolines also gave encouraging results (Table 1).

Received January 16, 2009.

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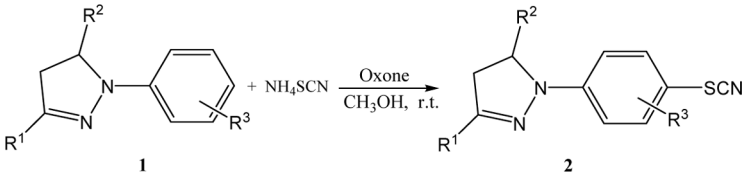

1 2

Scheme 1. Thiocyanation of 1,3,5-trisubstituted pyrazolines with oxone.

Table 1 clearly indicates that the thiocyanation regioselectively occurred at the para position of *N*-benzene rings. No reaction occurred within 1 h, on 1-(2′,4′-dinitro)phenyl-3,5-diphenyl pyrazoline where the *para* position on *N*-benzene ring was occupied, and no reaction took place at the *ortho* position. This might prove that the reaction regiospecifically occurred at the *para* position of benzene rings. 1,3,5-Trisubstituted pyrazole **1i** was examined accordingly. It took much time and gave a poor yield. Phenylhydrazine **1j** was overoxidized, and no desired thiocyanated product was obtained.

The effects of solvent were examined in various solvents, such as CCl_4, CH_2Cl_2 (DCM), ethyl ether, and acetonitrile. Methanol was found to be highly favorable for the thiocyanation under consideration.

It can be concluded that (a) the thiocyanation on *N*-benzene rings of both 1,3,5-trisubstituted pyrazolines and pyrazoles is achieved using oxone and ammonium thiocyanate, (b) the thiocyanation of 1,3,5-trisubstituted pyrazolines is more rapid and favorable than that of 1,3,5-trisubstituted pyrazoles under the same reaction conditions, (c) this approach provides an alternate way to introduce a thiocyanato group to these substrates,[8] and (d) this entry offers several advantages such as commercially available reagents, mild reaction conditions, and good yields of products.

Table 1. Thiocyanation of 1,3,5-trisubstituted pyrazolines using oxone and ammonium thiocyanate in methanol

	Substrate				
Entry	R^1	R^2	R^3	Time (h)	Yield of **2** (%)
1a	Ph	Ph	H	0.50	97
1b	(p)–OCH_3–Ph	Ph	H	0.67	93
1c	(p)–Cl–Ph	Ph	H	0.42	98
1d	(p)–Me–Ph	Ph	H	0.50	97
1e	(p)–Br–Ph	Ph	H	0.83	96
1f	(p)–OCH_3-Ph	(p)–Cl–Ph	H	0.50	93
1g	Ph	(p)–MeO–Ph	H	0.67	95
1h	Ph	Ph	2,4-Dinitro	24	NR
1i[a]	Ph	(p)–MeO–Ph	H	24	35
1j[b]		$PhNH_2NH_2$		24	—

[a]1,3,5-Trisubstituted pyrazoles.
[b]Overoxidized by oxone; no product was formed.

EXPERIMENTAL

Melting points were measured on a Yanagimoto melting-point apparatus and are uncorrected. IR spectra (KBr) were recorded on a Nicolet Nexus 670 Fourier transform (FT)–IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury Plus 300/400 NMR spectrometer. Chemical shifts (δ) are reported relative to tetramethylsilane (TMS) (^{1}H) or $CDCl_3$ (^{13}C) as internal standards. Mass spectrometry–electron impact (MS-EI) (70 eV) determinations were conducted on an HP 5985A spectrometer. High-resolution mass spectrometry–electrospray ionization (HRMS-ESI) detections were run on a Bruker Daltonics Apex II 47e spectrometer with ESI. Chemicals were the highest grade commercially available and used as received. All reagents were weighed and handled in air at room temperature.

Typical Procedure for the Preparation of 1a

A mixture of 5 mmol of chalcone and 10 mmol of phenylhydrazine in 30 mL of glacial acetic acid was refluxed on an oil bath at 110–120°C until completion of the reaction, monitored by thin-layer chromatography (TLC). It was then cooled and poured in ice water. The resulting solid was washed with water and recrystallized from 95% ethanol, giving **1a**.

Typical Procedure for the Reaction of 2a with Oxone and Ammonium Thiocyanate

A solution of 1.0 mmol of **1a** and 1.5 mmol of ammonium thiocyanate in 10 mL of methanol was treated with 1.5 mmol of oxone and allowed to stir at room temperature until completion of the reaction, monitored by TLC. Consequently, it was diluted with water and extracted with 4×15 mL of DCM. The DCM solution was dried over Na_2SO_4, and DCM was evaporated. The residue was purified by column chromatography on aluminium oxide neutral gel (200–300 mesh, ethyl acetate/hexane) to afford the product as colorless crystal. It was recrystallized from DCM/hexane or ethyl acetate/hexane, providing pure **2a**. All products were identified by ^{1}H and ^{13}C NMR, MS, IR, and HRMS-ESI.

Characterization Data for Products

1-(4′-Thiocyano)phenyl-3,5-diphenyl Pyrazoline (2a). Yellow solid, mp 142–143°C. IR (KBr, cm^{-1}) *v*: 3061, 3031, 2152, 589, 1496, 1398, 1330, 1132, 759. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.74 (dd, 2H, $J = 1.2$ Hz, $J = 6.6$ Hz, arom), 7.25 (m, 10H, arom), 6.80 (dd, 2H, $J = 3.0$ Hz, $J = 6.9$ Hz, arom), 5.28 (dd, 1H, $J = 6.9$ Hz, $J = 12.3$ Hz, CH), 3.85 and 3.16 (dd, 2H, $J = 12.3$ Hz, $J = 17.1$ Hz, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 148.7, 145.8, 141.3, 133.8, 131.9, 129.3, 129.2, 128.6, 127.9, 125.9, 125.6, 114.4, 112.2, 109.9, 63.7, 43.6. MS-EI *m/z*: 355 (M^+), 355, 297, 278, 148, 104; HRMS-ESI *m/z*: calcd. for $C_{22}H_{17}N_3S + H$: 356.1216; found: 356.1219.

1-(4′-Thiocyano)phenyl-3(4′-methoxyl)phenyl-5-phenyl Pyrazoline (2b). Yellow solid, mp 153–154°C. IR (KBr, cm^{-1}) *v*: 3033, 2922, 2152, 1590, 1497, 1396, 1252, 1178, 831, 701. ^1H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.67 (d, 2H, $J = 8.7$ Hz, arom), 7.31 (m, 7H, $J = 3.3$ Hz, $J = 4.8$ Hz, $J = 6.9$ Hz, arom), 7.04 (d, 2H, $J = 9.3$ Hz, arom), 6.93 (d, 2H, $J = 9.0$ Hz, arom), 5.25 (dd, 1H, $J = 5.7$ Hz, $J = 6.3$ Hz, $J = 12$ Hz, CH), 3.84 (s, 3H, OCH_3), 3.83 and 3.15 (dd, 2H, $J = 6.3$ Hz, $J = 6.6$ Hz, $J = 16.9$ Hz, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 160.5, 148.7, 146.1, 141.5, 133.9, 129.3, 127.9, 127.5, 125.6, 124.7, 114.2, 114.0, 112.3, 109.3, 63.5, 55.3, 43.8. MS-EI *m/z*: 385 (M^+), 385, 328, 251, 148, 77. HRMS-ESI *m/z*: calcd. for $C_{23}H_{19}N_3SO + H$: 386.1322; found: 386.1327.

1-(4′-Thiocyano)phenyl-3(4′-chloro)phenyl-5-phenyl Pyrazoline (2c). Yellow solid, mp 160–161°C. IR (KBr, cm^{-1}) *v*: 3059, 2923, 2153, 1589, 1493, 1389, 1331, 1131, 1092, 824, 732. ^1H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.73 (m, 2H, arom), 7.38 (m, 7H, arom), 7.19 (dd, 2H, $J = 1.8$ Hz, $J = 2.1$ Hz, $J = 5.3$ Hz, arom), 7.05 (dd, 2H, $J = 6.6$ Hz, $J = 6.9$ Hz, $J = 8.0$ Hz, arom), 5.27 (dd, 1H, $J = 5.7$ Hz, $J = 6.3$ Hz, $J = 12$ Hz, CH), 3.87 and 3.15 (dd, 2H, $J = 1.2$ Hz, $J = 1.8$ Hz $J = 5.4$ Hz, $J = 6.6$ Hz, $J = 16.2$ Hz, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 148.6, 145.6, 139.8, 133.9, 133.7, 131.7, 129.5, 129.4, 128.7, 127.0, 125.9, 114.4, 112.1, 110.3, 62.9, 43.5. MS-EI *m/z*: 389 (M^+), 389, 330, 278, 148, 77. HRMS-ESI *m/z*: calcd. for $C_{22}H_{16}N_3SCl + Na$: 412.0646; found: 412.0640.

1-(4′-Thiocyano)phenyl-3(4′-methyl)phenyl-5-phenyl Pyrazoline (2d). Yellow solid, mp 143–144°C. IR (KBr, cm^{-1}) *v*: 3061, 3031, 2918, 2153, 1590, 1497, 1394, 1327, 1131, 1094, 819, 701. ^1H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.62 (d, 2H, $J = 1.2$ Hz, $J = 8.1$ Hz, arom), 7.28 (m, 9H, arom), 7.06 (dd, 2H, $J = 1.8$ Hz, $J = 2.4$ Hz, $J = 7.5$ Hz, arom), 5.28 (dd, 1H, $J = 6.3$ Hz, $J = 18.3$ Hz, CH), 3.87 and 3.18 (dd, 2H, $J = 1.5$ Hz, $J = 1.8$ Hz, $J = 6.9$ Hz, $J = 7.5$ Hz, CH_2), 2.39 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 148.9, 145.9, 141.4, 139.4, 133.8, 129.3, 129.2, 129.1, 127.9, 125.9, 125.6, 114.3, 112.2, 109.5, 63.5, 43.7, 21.4. MS-EI *m/z*: 369 (M^+), 369, 292, 220, 148, 90, 77. HRMS-ESI *m/z*: calcd. for $C_{23}H_{19}N_3S + H$: 370.1372; found: 370.1367.

1-(4′-Thiocyano)phenyl-3(4′-bromo)phenyl-5-phenyl Pyrazoline (2e). Yellow solid, mp 163–164°C. IR (KBr, cm^{-1}) *v*: 3063, 3032, 2921, 2153, 1590, 1496, 1387, 1325, 1133, 1072, 823, 701. ^1H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.55 (m, 4H, $J = 7.9$ Hz, $J = 8.7$ Hz, $J = 18.3$ Hz, arom), 7.35 (m, 7H, arom), 7.06 (d, 2H, $J = 9.0$ Hz, arom), 5.29 (dd, 1H, $J = 6.0$ Hz, $J = 12.3$ Hz, CH), 3.83 and 3.14 (dd, 2H, $J = 6.3$ Hz, $J = 6.6$ Hz, $J = 17.6$ Hz, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 147.5, 145.6, 141.0, 133.8, 131.7, 130.9, 129.3, 128.0, 127.3, 125.5, 123.2, 114.5, 112.1, 110.3, 63.8, 43.4. MS-EI *m/z*: 433 (M^+), 433, 375, 277, 192, 148, 90. HRMS-ESI *m/z*: calcd. for $C_{22}H_{16}N_3SBr + H$: 434.0321; found: 434.0328.

1-(4′-Thiocyano)phenyl-3(4′-methoxyl)phenyl-5(4′-chloro)phenyl Pyrazoline (2f). Yellow solid, mp 107–108°C. IR (KBr, cm^{-1}) *v*: 3045, 2959, 2933, 2153, 1591, 1496, 1396, 1252, 1091, 829, 732. ^1H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.66 (d, 2H, $J = 8.7$ Hz, arom), 7.31 (m, 4H, $J = 2.7$ Hz, $J = 10.4$ Hz, $J = 10.5$ Hz, arom), 7.19 (d, 2H, $J = 8.4$ Hz, arom), 6.97 (m, 4H, $J = 9.0$ Hz, $J = 24.0$ Hz, arom), 5.21 (dd, 1H, $J = 6.0$ Hz, $J = 6.6$ Hz, CH), 3.82 (s, 3H, $J = 8.7$ Hz, OCH_3), 3.80

and 3.10 (dd, 2H, $J = 5.7$ Hz, $J = 6.6$ Hz, $J = 17.3$ Hz, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 160.9, 148.9, 146.2, 140.3, 134.2, 133.9, 129.8, 127.8, 127.4, 124.8, 114.6, 114.4, 112.5, 110.1, 63.3, 55.6, 44.0. MS-EI m/z: 419 (M^+), 308, 271, 178, 148, 84. HRMS-ESI m/z: calcd. for $C_{23}H_{18}N_3SClO$ +H: 420.0932; found: 420.0924.

1-(4′-Thiocyano)phenyl-3-phenyl-5(4′-methoxyl)phenyl Pyrazoline (2g). Yellow solid, mp 121–122°C. IR (KBr, cm^{-1}) v: 3060, 3002, 2836, 2153, 1588, 1508, 1496, 1398, 1248, 1178, 827, 732, 692. ^1H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.74 (dd, 2H, $J = 1.8$ Hz, $J = 7.5$ Hz, arom), 7.40 (m, 5H, arom), 7.18 (d, 2H, $J = 8.7$ Hz, arom), 7.08 (dd, 2H, $J = 2.4$ Hz, $J = 8.7$ Hz, arom), 6.88 (d, 2H, $J = 8.7$ Hz, arom), 5.24 (dd, 1H, $J = 5.7$ Hz, $J = 6.3$ Hz, $J = 9.6$ Hz, CH), 3.83 (s, 3H, $J = 8.7$ Hz, OCH_3), 3.82 and 3.16 (dd, 2H, $J = 6.3$ Hz, $J = 6.6$ Hz, $J = 17.6$ Hz, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 159.1, 148.7, 145.8, 133.8, 133.3, 132.0, 129.1, 128.6, 126.8, 125.9, 114.6, 114.4, 112.2, 109.7, 63.1, 55.2, 43.6. MS-EI m/z: 385 (M^+), 278, 251, 236, 193, 148, 90. HRMS-ESI m/z: calcd. for $C_{23}H_{19}N_3SO + H$: 386.1322; found: 386.1327.

1-(4′-Thiocyano)phenyl-3-phenyl-5(4′-methoxyl)phenyl Pyrazole (2i). White solid, mp 154–155°C. IR (KBr, cm^{-1}) v: 2956, 2924, 2854, 2155, 1610, 1490, 1453, 1255, 1029, 836, 735, 693. ^1H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.98 (m, 2H, $J = 1.2$ Hz, $J = 7.5$ Hz, arom), 7.51 (m, 3H, arom), 7.31 (m, 8H, arom), 6.97 (s, 1H, CH), 3.86 (s 3H, OCH_3). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 160.5, 154.2, 148.5, 139.3, 131.5, 131.0, 129.1, 129.0, 128.7, 128.4, 128.1, 124.9, 119.7, 114.3, 112.0, 55.3, 29.7. MS-EI m/z: 383 (M^+), 382, 280, 210, 149. HRMS-ESI m/z: calcd. for $C_{23}H_{17}N_3SO$ +H: 384.1165; found: 384.1156.

ACKNOWLEDGMENT

Project 20572040 was supported by the National Natural Science Foundation of China.

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