***SHORT PAPER***

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# A facile and rapid method for the synthesis of novel pyrazolyl thiosemicarbazones†

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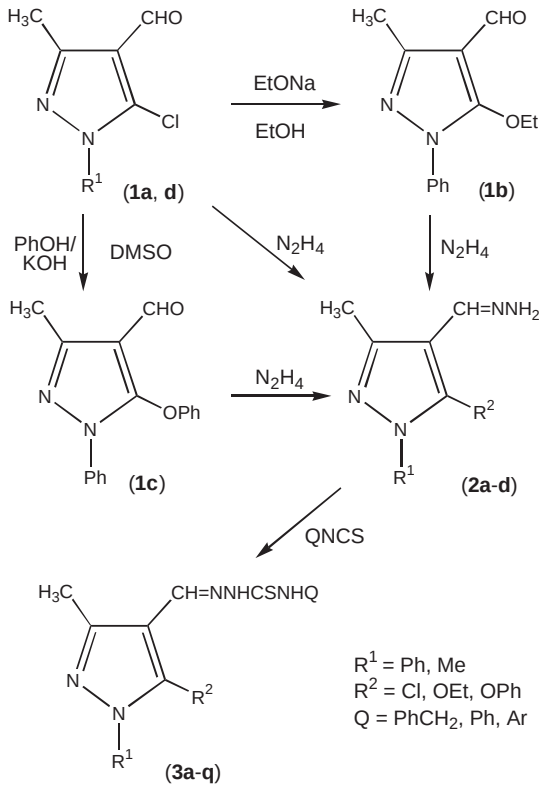
Sixteen novel thiosemicarbazone compounds **3a–q** were obtained under mild conditions by a simple route. Their structures were confirmed by IR, $^1$H NMR, MS and elemental analysis. Bioassay showed some of the products to have fungicidal activity.

**Keywords:** pyrazolecarboxaldehydes, hydrazones, thiosemicarbazones, fungicides

Thiosemicarbazone derivatives are known to exhibit a wide range of biological activities: antitumor[1], anticancer[2], anticonvulsant[3], insecticidal[4], and herbicidal[5]. In order to obtain compounds possessing better bioactivity, we synthesised pyrazolyl thiosemicarbazone compounds. Pyrazole derivatives represent one of the most attractive classes of compounds for their good bioactivities and structural option, and have widely been used as pharmaceuticals [6, 7]and agrochemicals[8]. The traditional synthetic route to thiosemicarbazones is by the addition-elimination reaction of carbonyl compounds with thiosemicarbazide.[1, 2] Herein we report an efficient method for the synthesis of pyrazolyl thiosemicarbazone compounds by reaction of hydrazones **2a–d** with isothiocyanates under mild conditions, as shown in Scheme 1.




**Scheme 1** Preparation of pyrazole thiosemicarbazones

Starting materials were 5-chloro-3-methyl-1-phenyl-*1H*-pyrazole-4-carboxaldehyde (**1a**) and 5-chloro-1,3-dimethyl-*1H*-pyrazole-4-carboxaldehyde (**1d**) which were prepared by a Vilameier-Haack reaction.[9] **1a** reacted with EtONa to afford **1b,** and **1c** was prepared by reaction of **1a** with potassium phenoxide.[10] When aldehydes **1** were heated with 85% hydrazine hydrate for several hours, hydrazones **2a–d** were obtained. The hydrazones on treatment with isothiocyanates in dry ethanol at room temperature formed the sixteen novel pyrazolyl thiosemicarbazones **3a–q** in 75–94 % yields. Evidently, this methodology can be extended to the synthesis of other heterocyclic compounds which may possess higher biological activity.

The elemental analyses and spectral data of compounds **3a–q** were consistent with their assigned structures. Their IR spectra showed characteristic strong absorptions at ~3420cm$^{-1}$ and ~3250cm$^{-1}$ due to N-H stretching vibration of the two imino groups. The presence of an absorption band in the range 1238–1284 cm$^{-1}$ corresponded to the C=S stretching vibrations. The important bands due to C=N, C=C and benzene ring stretching vibrations appeared at 1590, 1540, and 1510cm$^{-1}$, these were present in all of the pyrazolyl thiosemicarbazone compounds. In $^1$H NMR spectra of **3a–q**, the peaks of 3-methyl protons of pyrazole are singlets at 2.37–2.53 ppm. The –C*H*= proton absorbs as singlets in the range 7.80 - 8.27 ppm. The imino protons of –CH=NN*H*– showed as broad absorptions above 9.57 ppm. The imino protons of ArN*H* took up values between 8.1 and 9.6 ppm. Benzene ring protons showed as multiplets, 6.7 – 8.1 ppm. Their mass spectra showed the expected molecular peaks. The molecular ion of **3e** is at *m/z* 437 (8%), with *m/z* 439 :437 = 3 : 8, as expected for one chloride atom in the molecule.

The bioactivities of some of the products were evaluated *in vivo* at a concentration of 500 ppm in a greenhouse. Preliminary bioassays indicate that compounds **3d, 3g** and **3k** have moderate inhibitory activity against *Rhizoctonia solani* (>50%), and **3g** also has inhibitory activity against TMV (60%). Further study of structure and activity relationship is under way.

## Experimental

Elemental analyses were carried out on a Yanaco MT-3 instrument. Melting points were determined with a Yanaco MP-500 apparatus. Mass spectra were obtained on an HP 5989 mass spectrometer (EI). IR spectra were recorded on a Shimadzu-435 spectrometer in KBr pellets. $^1$H NMR spectra were recorded on a Bruker AC-200Q spectrometer with TMS as internal standard. Exchangeable protons were detected by addition of $D_2O$. The solvents were available commercially and were purified according to conventional methods.

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† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

**Table 1** Physical constants and elemental analyses of compounds **3a–q**

| No | Formula | FW | $R_1$ | $R_2$ | Q | M.p. (°C) | Yield /% | Elemental analyses (calc.) % C | H | N |
|---|---|---|---|---|---|---|---|---|---|---|
| **3a** | $C_{18}H_{16}ClN_5S$ | 369.87 | Ph | Cl | Ph | 187–188 | 92 | 58.35 (58.46) | 4.47 (4.36) | 18.68 (18.94) |
| **3b** | $C_{19}H_{18}ClN_5S$ | 383.89 | Ph | Cl | $CH_2Ph$ | 154–155 | 78 | 59.42 (59.44) | 4.70 (4.73) | 17.93 (18.24) |
| **3c** | $C_{19}H_{18}ClN_5OS$ | 399.89 | Ph | Cl | $C_6H_4OMe$-*p* | 184–185 | 93 | 56.99 (57.07) | 4.56 (4.54) | 17.72 (17.51) |
| **3d** | $C_{18}H_{15}Cl_2N_5S$ | 404.35 | Ph | Cl | $C_6H_4Cl$-*o* | 208–209 | 93 | 53.47 (53.47) | 3.76 (3.74) | 17.53 (17.31) |
| **3e** | $C_{19}H_{15}ClF_3N_5S$ | 437.93 | Ph | Cl | $C_6H_4CF_3$-*m* | 187–188 | 86 | 52.09 (52.12) | 3.54 (3.45) | 15.73 (15.99) |
| **3f** | $C_{25}H_{23}N_5OS$ | 441.56 | Ph | OPh | $CH_2Ph$ | 174–175 | 83 | 68.14 (68.00) | 5.31 (5.25) | 15.99 (15.86) |
| **3g** | $C_{24}H_{21}N_5OS$ | 427.53 | Ph | OPh | Ph | 178–179 | 94 | 67.12 (67.43) | 4.78 (4.95) | 16.04 (16.38) |
| **3i** | $C_{25}H_{23}N_5O_2S$ | 457.56 | Ph | OPh | $C_6H_4OMe$-*p* | 197–198 | 91 | 65.38 (65.63) | 5.29 (5.07) | 15.06 (15.31) |
| **3j** | $C_{25}H_{20}F_3N_5OS$ | 495.54 | Ph | OPh | $C_6H_4CF_3$-*m* | 170–171 | 87 | 60.63 (60.60) | 4.07 (4.07) | 13.95 (14.13) |
| **3k** | $C_{20}H_{21}N_5OS$ | 379.49 | Ph | OEt | Ph | 177–178 | 82 | 63.03 (63.30) | 5.56 (5.58) | 18.20 (18.45) |
| **3l** | $C_{21}H_{23}N_5O_2S$ | 409.52 | Ph | OEt | $C_6H_4OMe$-*p* | 174–175 | 85 | 61.68 (61.59) | 5.58 (5.66) | 17.30 (17.10) |
| **3m** | $C_{21}H_{20}F_3N_5OS$ | 447.43 | Ph | OEt | $C_6H_4CF_3$-*m* | 191–192 | 84 | 56.31 (56.37) | 4.45 (4.50) | 15.93 (15.65) |
| **3n** | $C_{13}H_{14}ClN_5S$ | 307.86 | $CH_3$ | Cl | Ph | 194–195 | 84 | 50.81 (50.73) | 4.55 (4.58) | 22.64 (22.75) |
| **3o** | $C_{14}H_{16}ClN_5OS$ | 337.88 | $CH_3$ | Cl | $C_6H_4OMe$-*p* | 203–204 | 75 | 49.67 (49.77) | 4.79 (4.77) | 20.76 (20.73) |
| **3p** | $C_{14}H_{13}ClF_3N_5S$ | 375.86 | $CH_3$ | Cl | $C_6H_4CF_3$-*m* | 201–202 | 90 | 44.61 (44.74) | 3.75 (3.49) | 18.61 (18.64) |
| **3q** | $C_{13}H_{13}Cl_2N_5S$ | 342.35 | $CH_3$ | Cl | $C_6H_4Cl$-*o* | 198–199 | 82 | 45.60 (45.62) | 3.87 (3.83) | 20.17 (20.46) |

**Table 2** $^1$H NMR and IR data of compounds **3a–q**

| No | $^1$H NMR data (δ / ppm) | NH | C=N, C=C, Ph | C=S |
|---|---|---|---|---|
| **3a** | 2.53 (s, 3H, 3-$CH_3$), 7.24–7.69 (m, 10H, 2Ph), 7.90 (s, 1H, -CH=), 9.15 (s, 1H, NHQ), 9.80 (s, 1H, =NNH) | 3413, 3145 | 1596, 1551, 1510 | 1263 |
| **3b** | 2.37 (s, 3H, 3-$CH_3$), 4.92 (d, 2H, $PhCH_2$), 7.24–7.48 (m, 10H, 2Ph), 7.89 (s, 1H, -CH=), 9.50 (s, 1H, NHQ) | 3405, 3129 | 1592, 1530, 1497 | 1241 |
| **3c** | 2.51 (s, 3H, 3-$CH_3$), 3.80 (s, 3H, $OCH_3$), 6.89–6.93, 7.44–7.51 (m, 9H, 2Ph), 7.95 (s, 1H, -CH=), 8.90 (s, 1H, NHQ), 10.10 (s, 1H, =NNH) | 3414, 3131 | 1595, 1546, 1507 | 1238 |
| **3d** | 2.56 (s, 3H, 3-$CH_3$), 8.69–8.73 (d), 7.24–7.51 (m, 9H, 2Ph), 7.90 (s, 1H, -CH=), 9.57 (s, 2H, 2NH) | 3415, 3140 | 1592, 1543, 1507 | 1271 |
| **3e** | 2.55 (s, 3H, 3-$CH_3$), 7.47–7.53 (m, 9H, 2Ph), 8.02 (s, 1H, -CH=), 9.19 (s, 1H, NHQ), 10.10 (s, 1H, =NNH) | 3410, 3126 | 1560, 1534, 1498 | 1253 |
| **3f** | 2.37 (s, 3H, 3-$CH_3$), 4.70 (d,2H, $PhCH_2$), 6.81–7.52 (m, 15H, 3Ph), 8.27 (s, 1H, -CH=), 9.74 (s, H, NHQ) | 3396, 3176 | 1593, 1533, 1501 | 1242 |
| **3g** | 2.49 (s, 3H, 3-$CH_3$), 6.94–7.56 (m, 15H, 3Ph), 8.27 (s, 1H, -CH=), 9.70 (s, 1H, NHQ) | 3407, 3126 | 1593, 1550, 1511 | 1260 |
| **3i** | 2.46 (s, 3H, 3-$CH_3$), 3.81 (s, 3H, $OCH_3$), 6.90–7.40 (m, 14H, 3Ph), 8.01 (s, 1H, -CH=), 9.90 (s, 1H, NHQ) | 3479, 3117 | 1558, 1532, 1502 | 1240 |
| **3j** | 2.49 (s, 3H, 3-$CH_3$), 6.96–7.54 (m, 14H, 3Ph), 8.27 (s, 1H, -CH=), 9.30 (s, 1H, NHQ) | 3409, 3124 | 1556, 1514, 1489 | 1258 |
| **3k** | 1.21-1.28 (t, 3H, $CH_3$), 2.50 (s, 3H, 3-$CH_3$), 4.05–4.08 (q, 2H, $OCH_2$), 7.22–7.67 (m, 10H, 2Ph), 8.06 (s, 1H,-CH=), 9.05 (s, H, NHQ), 10.10 (s, 1H, =NNH) | 3397, 3128 | 1613, 1550, 1503 | 1262 |
| **3l** | 1.26–1.33 (t, 3H, $CH_3$), 2.52 (s, 3H, 3-$CH_3$),3.91 (s, 3H, $OCH_3$), 3.98–4.26 (q, 2H, $OCH_2$), 7.24–7.67 (m, 9H, 2Ph), 7.70 (s, 1H, -CH=), 8.90 (s, 1H, NHQ), 10.20 (s, 1H, =NNH) | 3410, 3137 | 1594, 1548, 1508 | 1242 |
| **3m** | 1.21–1.28 (t, 3H, $CH_3$), 2.48 (s, 3H, 3-$CH_3$), 4.03–4.07 (q, 2H, $OCH_2$), 7.24–7.67 (m, 9H, 2Ph), 8.05 (s, 1H, -CH=), 9.05 (s, 1H, NHQ), 10.30 (s, 1H, =NNH) | 3401, 3140 | 1596, 1558, 1504 | 1250 |
| **3n** | 2.41 (s, 3H, 3-$CH_3$), 3.79 (s, 3H, 1-$CH_3$), 7.20–7.67 (m, 5H, Ph), 7.87 (s, 1H, -CH=), 9.09 (s, H, NHQ), 10.11 (s, 1H, =NNH) 2.39 | 3411, 3298 | 1616, 1551, 1500 | 1260 |
| **3o** | (s, 3H, 3-$CH_3$), 3.78 (s, 3H, $OCH_3$), 3.79 (s, 3H, 1-$CH_3$), 6.87–7.48 (d, 4H, Ph), 7.87 (s, H, -CH=), 8.90 (s, H, NHQ), 10.20 (s, H, =NNH) | 3401, 3142 | 1590, 1549, 1507 | 1236 |
| **3p** | 2.43 (s, 3H, 3-$CH_3$), 3.81 (s, 3H, 1-$CH_3$), 7.46, 7.85 (m, 4H), 7.99 (s, H, -CH=), 9.17 (s, H, NHQ), 9.89 (s, H, =NNH) | 3409, 3119 | 1598, 1543, 1505 | 1253 |
| **3q** | 2.46 (s, 3H, 3-$CH_3$), 3.82 (s, 3H, 1-$CH_3$), 8.64 (d), 7.11–7.41 (m, 4H, Ph), 7.86 (s, H,-CH=), 9.52 (s, 1H, NHQ), 9.81 (s, 1H, =NNH) | 3409, 3253 | 1591, 1543, 1502 | 1266 |

Compounds **1a**[9], **1b**[10], **1c**[10], and **1d**[9] were prepared according to the literature references indicated; **2a, 2b, 2c** and **2d** were prepared following Lock and Stach.[11]

*General procedure for the preparation of N$^1$-[(1-phenyl-3-methyl-5-chloro-1H-pyrazol-4-yl)methylene]-N$^4$-phenylthiosemicarbazide* (**3a**): Phenyl isothiocyanate (0.54 g, 4.0mmol) was added to **2a** (0.94g, 4.0mmol) in dry ethanol (20ml). The mixture was stirred at room temperature until compound **2a** was consumed (checked by TLC). The solvent was then evaporated to dryness and the residue was recrystallised from DMF-$C_2H_5OH$. Compound **3a** (1.16g, 92%) was obtained, m.p. 187–188°C.

Compounds **3b–q** were prepared analogously.

Physical constants and elemental analyses of compounds **3a–q** are shown in Table 1; $^1$H NMR and IR data are shown in Table 2.

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