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Simple and Convenient Routes to New Polyheterocycles Incorporating Pyrazole, Thiazole, Thiophene, and 1,3,4-Thiadiazole Moieties

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ABSTRACT: *The cyanothioacetanilide derivative* **3** *reacted readily with either α-halocarbonyl compounds* **4** *or α-halodicarbonyl compounds* **8** *to afford the same thiophene derivatives* **6**. *Compound* **3** *also reacted with hydrazonoyl chlorides* **12** *and* **16** *and furnished the new polyheterocyles* **14** *and* **17**, *respectively.* © 2002 Wiley Periodicals, Inc. Heteroatom Chem 13:248–251, 2002; Published online in Wiley Interscience (www.interscience.wiley.com). DOI 10.1002/hc.10024

INTRODUCTION

Recently, our research program has utilized some reactive-sulfur containing intermediates as versatile building blocks for the synthesis of several thiophene, thiazole, and 1,3,4-thiadiazole derivatives [1–3]. In this context, we report herein a convenient route to a variety of polyheterocyclic ring systems incorporating an antipyrin moiety via the reaction of the cyanothioacetanilide derivative **3** with some α-halocarbonyl compounds and halohydrazone derivatives.

Thus, reaction of cyanoacetamide derivative **1** [4] with phenyl isothiocyanate in potassium hydroxide solution afforded the non-isolable intermediate **2**, which was converted in situ into 2-cyano-2-*N*-[4-(1,2-dihydro-1,5-dimethyl-2-phenyl-3-oxo-3*H*-pyrazol-4-yl)thiazol-2-yl]carboxamidothioacetanilide (**3**) upon treatment with cold HCl solution (Scheme 1). The ^{1}H NMR spectrum of compound **3** revealed the presence of signals due to methyne and two NH protons at δ 4.43, 11.76, and 12.17, respectively. The reaction of the latter product with a variety of α-halocarbonyl compounds, as a key step for the synthesis of polysubstituted thiophene derivatives, was investigated. Thus, compound **3** reacted with ethyl chloroacetate (**4a**) in refluxing ethanol in the presence of triethylamine, to afford a single product identified as the thiophene derivative **6a**, rather than the expected dihydrothiazole derivative **7a** (Scheme 1) based on the elemental and spectral analyses of the isolated product (see Experimental).

When compound **3** was treated with ethyl α-chloroacetoacetate (**8a**) under the same reaction conditions, it afforded a product identical in all respects with **6a** (Scheme 1). A reasonable mechanism of the latter reaction is outlined in Scheme 2. A similar behavior was observed when compound **3** reacted with either chloroacetone (**4b**) or 3-chloropentan-2,4-dione (**8b**) under the same experimental conditions, where it afforded only one and the same product. The structure of the isolated product was assigned

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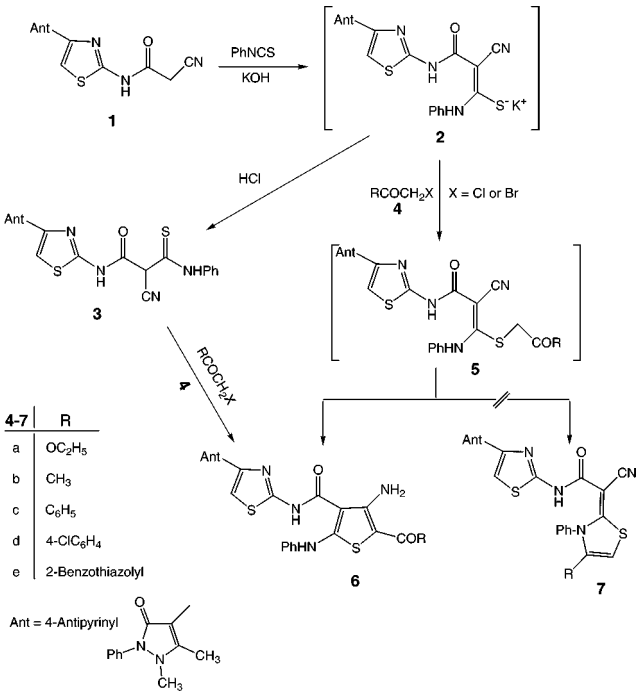


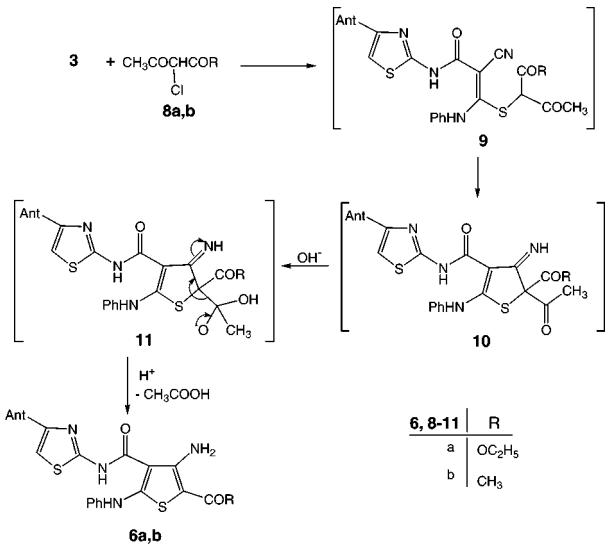
SCHEME 1

as 2-acetyl-3-amino-4-*N*-[4-(antipyrin-4-yl)thiazol-2-yl]carboxamido-5-*N*-phenylaminothiophene (**6b**) (Schemes 1 and 2). Both elemental analysis and spectroscopic data are in complete agreement with the assigned structure.

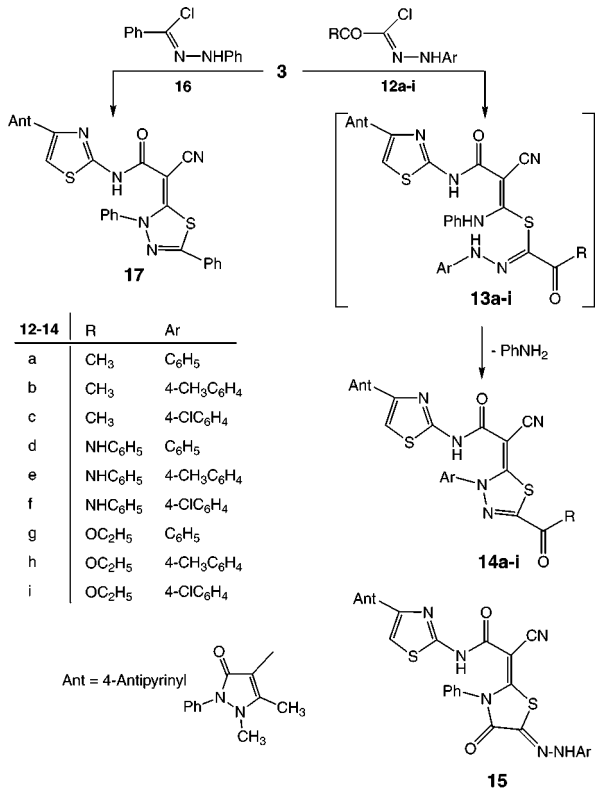
In addition, compound **3** reacted with other α-haloketones **4c–e** under similar reaction conditions to afford the polysubstituted thiophene derivatives **6c–e**, respectively (Scheme 1). The structures of the latter products were confirmed on the basis of their elemental analyses and spectral data. For example, the IR spectra of all products **6a–e** were free from a nitrile absorption band near 2200 cm^{-1}.

It is noteworthy to report that all the products **6a–e** were alternatively synthesized by the treatment of the precursors of intermediate **2** with the corresponding α-halocarbonyl compounds **4a–e**, respectively, (Scheme 1).

The behavior of compound **3** towards a variety of hydrazonoyl chlorides was also examined. Thus, treatment of compound **3** with (*C*-acetyl-, *C*-acetanilido-, or *C*-ethoxycarbonyl)-*N*-arylhydrazonoyl chlorides **12a–i**, in ethanolic triethylamine solution under refluxing conditions, furnished, in each case, only one isolable product. The structures of the isolated products were assigned as the dihydrothiadiazole derivatives **14a–i** (Scheme 3) on the basis of their elemental analyses and spectral data. For example, the ^1H NMR spectrum of **14b** revealed four singlet signals at δ 2.58, 2.62, 3.18, and 3.28 corresponding to four CH_3 protons in addition to a multiplet in the region δ 7.11–7.77 and a broad signal at δ 11.08 due to aromatic and amide-NH protons, respectively. The IR spectra of the products **14a–i** exhibited, in all cases, the presence of nitrile, amide-NH, and carbonyl stretching



SCHEME 2



SCHEME 3

bands near 3390, 2200, and 1680 cm^{-1}, respectively. Formation of the 2,3-dihydrothiadiazole structures **14a–i** is assumed to proceed via a mechanism analogous to that reported previously [3] (Scheme 3). Although loss of an ethanol molecule from the intermediates **13g–i** leading to the formation of compounds **15** would seem to be easier than the loss of aniline leading to the formation of compounds **14**; however the obtained results showed that reaction of the thioacetanilide derivative **3** with α-ketohydrazonoyl halides **12a–i** proceeds in the same manner, regardless of the type of hydrazonoyl halide used. This finding was supported by the reaction of *C*-phenyl-*N*-phenylmethanehydrazonoyl chloride (**16**) with compound **3**, where the reaction product was assigned as 2-*N*-[4-(antipyrin-4-yl)thiazol-2-ylcarboxamido]-cyanomethylene-3,4-diphenyl-2,3-dihydro-1,3,4-thiadiazole (**17**) on the basis of its elemental analysis and spectral data (Scheme 3).

EXPERIMENTAL

2-(Bromoacetyl)benzothiazole (**4e**) [5] and hydrazonoyl chlorides **12a–c** [6], **12d–f** [7], **12g–i** [8], and **16** [9] were prepared according to the procedures reported in the given references.

*2-Cyano-2-N-[4-(antipyrin-4-yl)thiazol-2-yl]-carboxamidothioacetanilide (**3**)*

To a stirred solution of potassium hydroxide (0.11 g, 2 mmol) in dimethylformamide (DMF) (20 ml) was added 2-cyano-*N*-[4-(antipyrin-4-yl)thiazol-2-yl]acetamide (**1**) [4]. After the mixture had been stirred for 30 min, phenyl isothiocyanate (0.27 g, 2 mmol) was added to the mixture. Stirring was continued for 6 h, then the mixture was poured over crushed ice containing hydrochloric acid. The solid product so formed was filtered off, washed with water, dried, and finally recrystallized from DMF/water to afford **3** in 90% yield, mp 201–202°C, ν_{max}/cm^{-1} (KBr) 3446 (NH), 2199 (C≡N), 1623, 1697 (2C=O), 1610, 1589 (2C=N); δ_H ($CDC1_3$) 2.43 (s, 3H), 3.47 (s, 3H), 4.43 (s, 1H), 7.28–7.86 (m, 11H), 11.76 (s, 1H), 12.17 (s, 1H); *m/z* 488 (M^+) (Found: C, 58.8; H, 4.4; N, 17.4; S, 12.9. $C_{24}H_{20}N_6S_2O_2$ requires C, 59.00; H, 4.13; N, 17.20; S, 13.13%).

Reaction of **3** *with α-Halocarbonyl Compounds* **4a–e**. *General Procedure*

To a solution of **3** (0.976 g, 2 mmol) in ethanol (20 ml) and the appropriate α-halocarbonyl compound **4a–e** (2 mmol), 0.2 ml of triethylamine was added. The reaction mixture was refluxed for 1 h, then allowed to cool. The formed solid product was filtered off, washed with ethanol, and recrystallized from DMF/water to afford the corresponding thiophene derivatives **6a–e** in 74–81% yield.

6a: (76%) mp 246–248°C; ν_{max}/cm^{-1} (KBr) 3437 (broad), 3319 (2NH, NH_2), 1641 (broad), 1620 (3C=O), 1589 (C=N); δ_H ($CDCl_3$) 1.29 (t, 3H), 2.43 (s, 3H), 3.2 (s, 3H), 4.24 (g, 2H), 6.39 (br. s, 2H, NH_2), 7.07–7.56 (m, 11H), 11.82 (br. s, 1H), 12.21 (br. s, 1H); *m/z* 574 (M^+) (Found: C, 58.7; H, 4.8; N, 14.9; S, 10.9. $C_{28}H_{26}N_6O_4S_2$ requires C, 58.52; H, 4.56; N, 14.62; S, 11.16%).

6b: (81%) mp 230–232°C ν_{max}/cm^{-1} (KBr) 3383, 3267, 3222 (2NH, NH_2), 1650 (broad), 1633 (3C=O); δ_H (DMSO-d_6), 2.44 (s, 3H), 2.47 (s, 3H), 3.27 (s, 3H), 7.37–7.61 (m, 11H), 8.45 (br. s, 2H, NH_2), 11.80 (br. s, 1H, NH), 12.10 (br. s, 1H, NH); *m/z* 544 (M^+) (Found: C, 59.3; H, 4.5; N, 15.7; S, 11.9. $C_{27}H_{24}N_6O_3S_2$ requires C, 59.54; H, 4.44; N, 15.43; S, 11.77%).

6c: (74%) mp 241–242°C, ν_{max}/cm^{-1} (KBr) 3406 (broad), 3296 (2NH, NH_2), 1647 (broad), 1620 (3C=O), 1589 (C=N); δ_H ($CDCl_3$) 2.45 (s, 3H), 3.23 (s, 3H), 6.37 (s, 1H, thiazole-5-CH), 7.12–7.70 (m, 15H, ArH), 8.95 (br. s, 2H, NH_2), 12.05 (s, 1H, NH), 12.38 (s, 1H, NH); *m/z* 606 (M^+) (Found: C, 63.6; H, 4.0; N, 14.0; S, 10.7. $C_{32}H_{26}N_6O_3S_2$ requires C, 63.35; H, 4.32; N, 13.85; S, 10.57%).

6d: (78%) mp 258–260°C; ν_{max}/cm^{-1} (KBr) 3405, 3371, 3255, (2NH and NH_2), 1656 (broad), 1630 (3C=O), 1594 (C=N); *m/z* 641 (M^+) (Found: C, 60.2; H, 3.7; N, 13.0; S, 9.8. $C_{32}H_{25}ClN_6O_3S_2$ requires C, 59.94; H, 3.93; N, 13.11; S, 10.00%).

6e: (79%) mp 260–262°C; ν_{max}/cm^{-1} (KBr) 3405, 3367, 3251 (2NH and NH_2), 1649 (broad), 1622 (3C=O); δ_H ($CDCl_3$) 2.47 (s, 3H), 3.28 (s, 3H), 6.97 (s, 1H thiazole-5-CH), 7.32–7.59 (m, 10H), 8.05–8.22 (m, 4H), 9.40 (br. s, 2H, NH_2), 12.10 (br. s, 1H, NH), 13.15 (br. s, 1H, NH); (Found: C, 60.0; H, 3.7; N, 14.9; S, 14.6. $C_{33}H_{25}N_7O_3S_3$ requires C, 59.71; H, 3.80; N, 14.77; S, 14.49%).

Reaction of **3** *with α-Chlorodicarbonyl Compounds* **8a,b**

A mixture of the cyanothioacetanilide derivative **3** (0.7 g, 2 mmol) and the appropriate α-chlorodiketone (**8a**) or α-chloroketoester (**8b)** (2 mmol) in absolute ethanol (20 ml), in the presence of triethylamine (0.2 ml), was refluxed for 2 h, then left to cool. The resulting reaction mixture was poured into a cold solution of 0.5 N HC1. The precipitated product was filtered off, washed with water followed by ethanol, dried, and finally recrystallized from DMF/water to afford products identical in all respects with those

obtained from the reaction of **3** with chloroacetone and with ethyl chloroacetate.

Reaction of **3** *with Hydrazonoyl Chlorides* **12a–i** *and* **16**

These reactions were carried out by the same procedure described above for the syntheses of thiophene derivatives **6a–e** using the appropriate hydrazonoyl chloride **12a–i** or **16** instead of the α-halocarbonyl compounds **4a–e**.

14a: (82%) mp 209–210°C; ν_{max}/cm^{-1} (KBr) 3387 (NH), 2210 (C≡N), 1680, 1659, 1645 (3C=O), 1602 (C=N); δ_H(DMSO-d_6) 2.61 (s, 3H), 3.18 (s, 3H), 3.26 (s, 3H), 7.12–7.74 (m, 11H, ArH and thiazole-5-CH), 11.15 (br. s, 1H); *m/z* 555 (M^+) (Found: C, 58.6; H, 3.6; N, 17.2; S, 11.3. $C_{27}H_{21}N_7O_3S_2$ requires C, 58.36; H, 3.81; N, 17.65; S, 11.54%).

14b: (83%); mp 204–205°C; ν_{max}/cm^{-1} (KBr) 3393 (NH), 2189 (C≡N), 1697, 1640 (broad) (3C=O), 1611, 1589 (2C=N); δ_H (DMSO-d_6) 2.58 (s, 3H), 2.62 (s, 3H), 3.18 (s, 3H), 3.28 (s, 3H), 7.12–7.77 (m, 10H), 11.08 (br. s, 1H); (Found: C, 59.1; H, 4.2; N, 17.5; S, 11.3. $C_{28}H_{23}N_7O_3S_2$ requires C, 59.04; H, 4.07; N, 17.21; S, 11.26%).

14c: (88%) mp 220–222°C; ν_{max}/cm^{-1} (KBr) 3393 (NH), 2189 (C≡N), 1693, 1650 (broad) (3C=O), 1610, 1590 (2C=N) *m/z* 591 ($M^+ + 1$), 590 (M^+) (Found: C, 55.2; H, 3.6; N, 16.5; S, 10.6. $C_{27}H_{20}N_7S_2O_3C1$ requires C, 54.96; H, 3.42; N, 16.62; S, 10.87%).

14d: (85%) mp 212–213°C; ν_{max}/cm^{-1} (KBr) 3476, 3402 (2NH), 2190 (C≡N), 1650 (broad), 1630 (3C=O), 1608, 1590 (2C=N); δ_H (DMSO-d_6) 2.61 (s, 3H), 3.18 (s, 3H), 7.10–7.81 (m, 16H), 11.05 (br. s, 1H), 12.40 (br. s, 1H); *m/z* 632 (M^+) (Found: C, 60.9; H, 3.6; N, 17.4; S, 10.0. $C_{32}H_{24}N_8O_3S_2$ requires C, 60.74; H, 3.82; N, 17.71; S, 10.14%).

14e: (87%) mp 289–291°C; ν_{max}/cm^{-1} (KBr) 3404, 3271 (2NH), 2207 (C≡N), 1679, 1658, 1645 (3C=O), 1603 (C=N); δ_H (DMSO-d_6) 2.46 (s, 3H), 2.73 (s, 3H), 3.16 (s, 3H), 7.35–7.81 (m, 15H), 11.02 (br. s, 1H), 11.18 (br. s, 1H) (Found: C, 61.4; H, 3.8; N, 17.5; S, 10.1. $C_{33}H_{26}N_8O_3S_2$ requires C, 61.28, H, 4.05; N, 17.33; S, 9.92%).

14f: (90%) mp > 300°C; ν_{max}/cm^{-1} (KBr) 3400, 3261 (2NH), 2204 (C≡N), 1661, 1634, 1620 (3C=O), 1603 (C=N); δ_H (insoluble in the common NMR solvents); (Found: C, 57.4; H, 3.6; N, 17.1; S, 9.5. $C_{32}H_{23}C1N_8O_3S_2$ requires C, 57.61; H, 3.47; N, 16.80; S, 9.61%).

14g: (80%) mp 270–271°C; ν_{max}/cm^{-1} (KBr) 3440 (NH), 2187 (C≡N), 1709, 1640 (2C=O), 1611, 1587 (2C=N); δ_H (DMSO-d_6) 1.45 (t, 3H), 2.71 (s, 3H), 3.19 (s, 3H), 4.53 (q, 2H), 7.42–7.67 (m, 11H), 9.15 (br. s, 1H); *m/z* 585 (M^+) (Found: C, 57.1; H, 4.1; N, 16.5; S, 11.2. $C_{28}H_{23}N_7O_4S_2$ requires C, 57.42; H, 3.96; N, 16.74; S, 10.95%).

14h: (80%) mp 242–243°C; ν_{max}/cm^{-1} (KBr) 3383(NH), 2189 (C≡N), 1719, 1645 (2C=O); δ_H (DMSO-d_6) 1.35 (t, 3H), 2.72 (s, 3H), 2.90 (s, 3H), 3.17 (s, 3H), 4.49 (q, 2H), 7.37–7.58 (m, 10H), 12.4 (br. s, 1H); *m/z* 599 (M^+) (Found: C, 58.2; H, 4.0; N, 16.6; S, 10.4. $C_{29}H_{25}N_7O_4S_2$ requires C, 58.08; H, 4.20; N, 16.35; S, 10.69%).

14i: (76%) mp 278–280°C; ν_{max}/cm^{-1} (KBr) 3404 (NH), 2191 (C≡N), 1709, 1636 (2C=O), 1589 (C=N); *m/z* 620 (M^+) (Found: C, 54.0; H, 3.7; N, 15.6; S, 10.0. $C_{28}H_{22}N_7O_4S_2Cl$ requires C, 54.23; H, 3.58; N, 15.81; S, 10.34%).

17: (75%) mp 272–274°C; ν_{max}/cm^{-1} (KBr) 3444 (NH), 2189 (C≡N), 1670, 1645 (2C=O), 1610 (C=N); δ_H (DMSO-d_6) 2.74 (s, 3H), 3.16 (s, 3H), 7.38–7.98 (m, 16H), 11.08 (br. s, 1H); *m/z* 589 (M^+) (Found: C, 63.4; H, 4.2; N, 16.8; S, 10.9. $C_{31}H_{23}N_7O_2S_2$ requires C, 63.14; H, 3.93; N, 16.63; S, 10.88%).

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