Polyheterocyclic systems incorporating pyrazole, thiophene, thiazole, and thiadiazole moieties†

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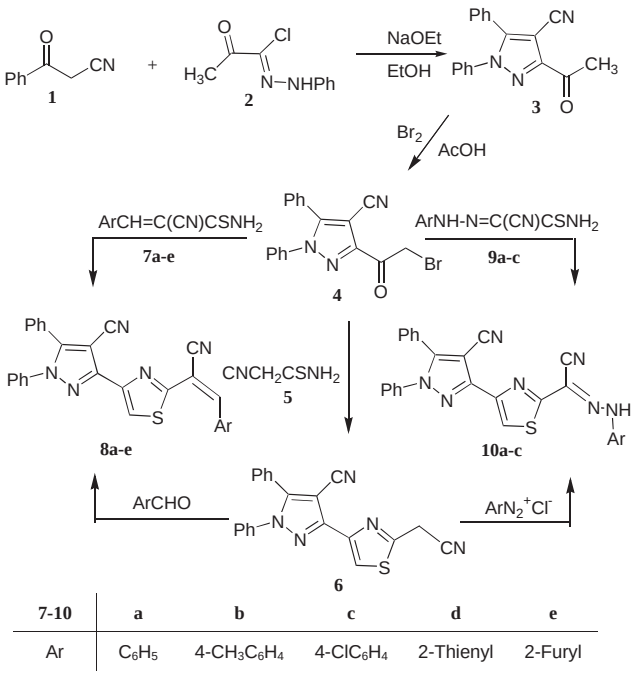
A variety of polyheterocyclic ring systems having pyrazole, thiophene, thiazole and thiadiazole moieties are synthesised utilising the reaction of sulfur functionalised substrates with α-halocarbonyl compounds and hydrazonyl chlorides.

Keywords: pyrazoles, 2-thiazoleacetonitriles, 1,3,4-thiadiazoles, 2-cyanothioacetanilide, aminothiophenes

Owing to their considerable pharmacological importance,[1] pyrazole derivatives have attracted a great deal of attention. The synthesis of combinatorial libraries of heterocyclic compounds permits the testing of the biological properties of a vast array of compounds. Routes to novel skeletons, which could be synthesised using combinatorial methods, are presently a major research objective. In continuation of our recent work aiming at the synthesis of polyheterocyclic systems,[2-5] we here describe a general route to novel polycyclic skeletons having pyrazole, thiophene, thiazole and thiadiazole moieties, which probably could be adapted to the synthesis of libraries.

In the course of our investigation, we have found that 3-bromoacetyl-1,5-diphenyl-1*H*-pyrazole-4-carbonitrile (**4**) is an excellent building block for the synthesis of polyheterocyclic ring systems. Compound **4** was obtained by bromination of 3-acetyl-1,5-diphenyl-1*H*-pyrazole-4-carbonitrile (**3**) in acetic acid (Scheme 1).

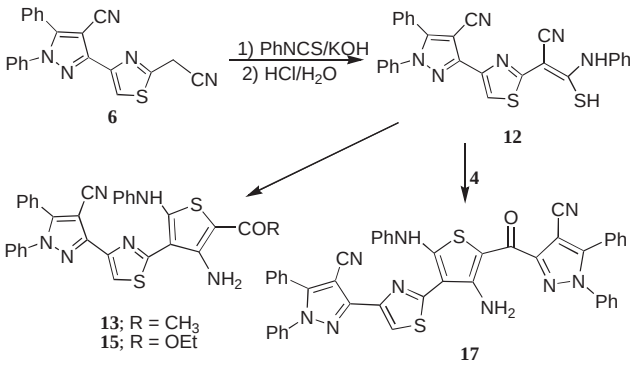


Scheme 1 Formation of thiazole products 6, 8, 10.

Treatment of the pyrazolecarbonitrile **4** with 2-cyano-ethanethioamide (**5**), in refluxing ethanol and in the presence of a catalytic amount of triethylamine, afforded a single product identified as 4-(4-cyano-1,5-diphenyl-1*H*-pyrazol-3-yl)-2-thiazoleacetonitrile (**6**). Its ^{1}H NMR spectrum revealed a singlet signal at δ 4.27 characteristic for the methylene protons. Its mass spectrum showed the molecular ion peak at *m/z* 367. The assigned structure of **6** was further supported by its chemical transformations outlined in Scheme 1. Thus, when compound **6** was treated with aromatic or heteroaromatic aldehydes, in refluxing ethanol and in the presence of catalytic piperidine, it afforded products identified as 4-(4-cyano-1,5-diphenyl-1*H*-pyrazol-3-yl)-α-(aryl-/heteroaryl-methylene)-2-thiazoleacetonitrile derivatives **8a–e**. Their structures were established on the basis of elemental analysis and spectral data. Their IR spectra showed, in each case, two nitrile absorption bands in the region 2209–2230 cm^{-1}, and their ^{1}H NMR spectra revealed lack of signals due to methylene protons. The structures **8a–e** were further confirmed by their alternative synthesis from reaction of 3-bromoacetylpyrazole **4** with 3-aryl/heteroaryl-2-cyanothioacrylamides **7a–e** in refluxing ethanol in the presence of catalytic triethylamine (Scheme 1).

Treatment of compound **6** with aromatic diazonium salts in pyridine afforded the 4-(4-cyano-1,5-diphenyl-1*H*-pyrazol-3-yl)-α-(arylhydrazono)-2-thiazoleacetonitriles **10a–c** (Scheme 1). The structures of the latter products were supported by the nitrile and hydrazone NH absorption bands at *ca* 2209–2230 and 3210 cm^{-1}, respectively, in their IR spectra and the lack of the methylene proton signals in their ^{1}H NMR spectra. Compounds **10a–c** were further substantiated by their independent synthesis from the reaction of compound **4** with 2-arylhydrazono-2-cyanoethanethioamides **9** in refluxing ethanol and in the presence of catalytic triethylamine.

Next, when compound **6** was treated with phenyl isothiocyanate in dimethylformamide, in the presence of potassium hydroxide at room temperature, it afforded the corresponding potassium salt which was converted into the cyanothioacetanilide derivative **12** upon treatment with dilute hydrochloric acid (Scheme 2). The structure of the latter product was established on the basis of its elemental analysis and spectral data. Its IR spectrum showed an NH band at 3263 cm^{-1} and two strong nitrile absorptions at 2232 and 2185 cm^{-1} Moreover, the mass spectrum of the product **12** exhibited a molecular ion peak at *m/z* 502.



Scheme 2 Formation of aminothiophene products 13, 15, and 17.

Treatment of the cyanothioacetanilide derivative **12** with chloroacetone afforded 2-acetyl-3-amino-4-[4-(4-cyano-1,5-diphenyl-1*H*-pyrazol-3-yl)thiazol-2-yl]-5-(*N*-pheny-lamino)

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thiophene (**13**) (Scheme 2). Its IR spectrum revealed three bands in the region 3440–3310 cm^{-1} due to NH_2 and NH groups and one nitrile absorption at 2216 cm^{-1}. Its ^1H NMR spectrum revealed two signals at δ 8.26 and 9.83 (exchangeable with D_2O) due to NH_2 and NH protons, respectively and a singlet signal at δ 2.19 due to $COCH_3$ protons, in addition to a multiplet signals at δ 7.30–7.48 corresponding to the aromatic protons.

When compound **12** was treated with ethyl chloroacetate it afforded a single product, ethyl 3-amino-4-[4-(4-cyano-1, 5-diphenyl-1*H*-pyrazol-3-yl)thiazol-2-yl]-5-phenylamino-thiophene-2-carboxylate (**15**) (Scheme 2). The ^1H NMR spectrum revealed signals characteristic of the ethoxy group. Its IR spectrum showed bands in the region 3410–3312 cm^{-1} due to NH and NH_2. Moreover, the mass spectrum of the same product revealed a peak at *m/z* 588 corresponding to its molecular ion.

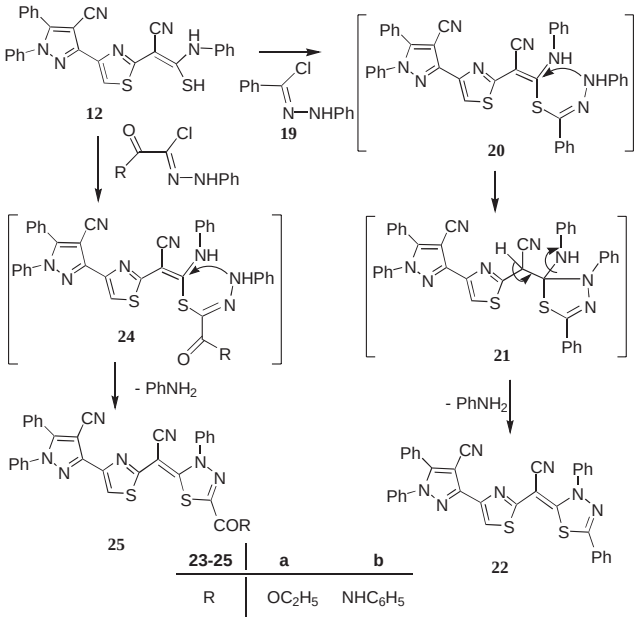
Treatment of the cyanothioacetanilide derivative **12** with bromoacetylpyrazole **4** also afforded a single product. The elemental analysis and spectral data were compatible with the thiophene structure **17**. This assignment was supported by the appearance of NH, NH_2 and carbonyl absorption bands at 3400, 3320 and 1675 cm^{-1}, respectively, in the IR spectrum of the isolated product.

When the cyanothioacetanilide derivative **12** was treated with the hydrazonoyl chlorides **19** and **23**, it afforded, in each case, a single product (as examined by TLC). The reaction products were identified as 2,3-dihydro-1,3,4-thiadiazole derivatives **22** and **25a**,**b** (Scheme 3). For example, their IR spectra showed two strong absorption bands in the region 2230–2181 cm^{-1} corresponding to two nitrile functions. A carbonyl absorption peak in the region 1680–1740 cm^{-1} supported the structures of the thiadiazole derivatives **25a**,**b** and ruled out isomeric phenylazo-oxathiole derivatives.

In conclusion, we have established routes from a simple monopyrazole via a bicyclic 2-(pyrazol-3-yl)thiazole to give novel tricyclic and tetracyclic skeletons. The methodology is likely to be applicable to the synthesis of libraries of polycyclic heterocycles.

Techniques used: ^1H NMR, IR spectroscopy, MS

References: 11



Scheme 3 Formation of thiadiazole products 22, 25.

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