Synthesis and Reactivity of 3-Alkylthio-5-cyanomethyl-4-phenyl-1,2,4-triazoles

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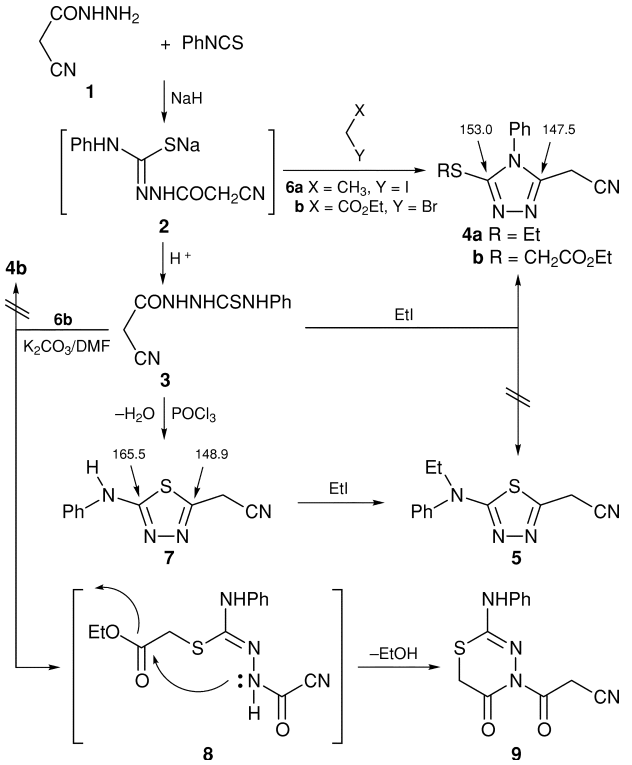
Phenyl isothiocyanate reacts with 2-cyanoacetohydrazide (**1**) to yield the corresponding 1-cyanoacetyl-4-phenyl-thiosemicarbazide (**3**), *via* acid hydrolysis of the intermediate **2** whereas cyclization of **3** gave the 1,2,4-triazoles **4**, 1,3,4-thiadiazoles **7** and 1,3,4-thiadiazine-5-ones **9**; compound **4a** was reacted with phenyl isothiocyanate, dicyandiamide, sulfanylacetic acid and benzaldehyde to afford **11**, **13**, **14** and **15**, respectively.

1,2,4-Triazoles are considered to be very interesting heterocyclic ring systems because of their therapeutic importance. For example, derivatives of 1,2,4-triazole have been found, recently, to have significant antiseptic[1] and analgesic[2] activity and there are drugs that contain a 1,2,4-triazole group, *e.g.* triazolam,[3] alprazolam,[4] etizolam[5] and furacrylin.[6] Additionally, several of the *S*-substituted thiotriazoles have shown biological activity aganist tuberculosis,[7,8] as anticoccidal agents in chicken[9] and in cephalosporins as antibacterial agents.[10] Prompted by the aforesaid biological and pharmaceutical activities, and in continuation of our previous work aimed at developing new approaches for the synthesis of polyfunctionally substituted heterocyclic compounds of expected biological activity,[11–15] we report here the synthesis of the versatile, hitherto unreported, 3-alkylthio-5-cyanomethyl-4-phenyl-1,2,4-triazoles **4** and their utility as building blocks in the synthesis of several new heterocycles in which the triazole moiety is incorporated. Mohareb and co-workers[16] have examined the reaction of phenyl isothiocyanate with 2-cyanoacetohydrazide, under basic conditions, which proceeds to give 3-amino-1-(phenylaminothiocarbonyl)-pyrazol-5-one. In our hands, the reaction of phenyl isothiocyanate with 2-cyanoacetohydrazide (**1**) in DMF and in the presence of sodium hydride gave the non-isolable intermediate **2**, and this was converted into 1-cyanoacetyl-4-phenyl-thiosemicarbazide **3** by treatment with concentrated HCl. Structure **3** was assigned to this product on the basis of elemental analysis and spectral data (experimental details are given in the full text). The reaction of **3** with ethyl iodide in DMF at room temperature and in the presence of anhydrous potassium carbonate gave a solid product of molecular formula $C_{12}H_{12}N_4S$ ($M^+ = 244$) which may be formulated as **4a** or its isomer **5** (Scheme 1). Structure **4a** was indicated by the ^{13}C NMR spectra which gave conclusive evidence for the triazole structure. The spectrum reveals low-field signals at 153.0 ppm (triazole C-3) and 147.5 ppm (triazole C-5) in addition to a signal at 115.3 ppm for a cyano function. The methylene and ethyl signals also appeared at the expected fields (see Experimental in the full text). If this product was the isomeric thiadiazole **5**, the C-2 and C-5 thiadiazole signals should have appeared at a higher field.[17,18] The structure of triazole **4a** was proven by an independent synthesis involving the treatment of **2** with **6a** to yield **4a** (Scheme 1). This product was identical in all aspects to the compound obtained by reaction of **3** with ethyl iodide. In addition, the structure of **4a** was confirmed further by an alternative synthesis of its isomer **5** through the known 2-anilino-5-cyanomethyl-1,3,4-thiadiazole (**7**).[19] Thus, compound **3** reacted with phosphoryl chloride at reflux to give **7**. Reacting compound **7** with ethyl iodide in DMF at 60–65 °C gave *N*-ethyl-*N*-(5-cyanomethyl-1,3,4-thiadiazol-2-yl)aniline (**5**). Comparison of the data of **5** with those of **4a** showed differences in mp, IR and ^1H NMR data which indicated the structure of **5** for our product (see Experimental in the full text). Compound **4b** was also prepared by reacting **2** with **6b** under the same conditions as before (Scheme 1).



Scheme 1

Reacting compound **3** with **6b** in a DMF solution containing potassium carbonate, at room temperature, did not afford the expected triazoles **4b**, but rather the new heterocyclic 2-anilino-4-(cyanoacetyl)-5,6-dihydro-1,3,4-thiadiazine-5-one (**9**). Formation of **9** is assumed to take place through intermediate **8** which undergoes cyclization and loss of ethanol (Scheme 1). Structure **9** was established for the reaction product based on its analytical and spectral data (see Experimental in the full text).

Compound **4a** reacted with phenyl isothiocyanate in absolute ethanol containing potassium *t*-butoxide to give the non-isolable potassium salt **10**. Treatment of **10** with **6b** gave a single product whose structure was assumed to be **11** or **12** (Scheme 2). However, structure of **12** was excluded by the presence of a CN stretching band in the IR spectra of the reaction product and by the ^1H NMR spectra which showed a sharp singlet signal at $\delta = 4.15$ ppm, assignable to the methylene protons at C-5 of a 1,3-thiazole ring. Amino and ester protons were missing as well (see Experimental, full text).

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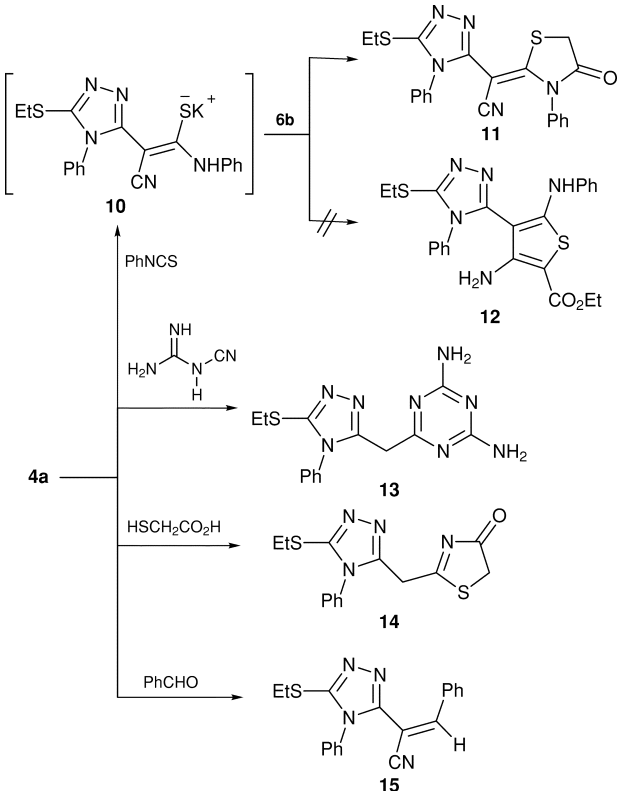

Scheme 2

Refluxing **4a** with dicyandiamide in alcoholic KOH gave 5-[(2,4-diamino-triazin-6-yl)methyl]-3-ethylthio-4-phenyl-1,2,4-triazole (**13**) (Scheme 2). Its structure was confirmed on the basis of elemental analysis and spectral data. The IR spectrum of **13** had no cyano band, its mass was compatible with the molecular formula $C_{14}H_{16}N_8S$ (M^+: 328), while the ^1H NMR spectrum showed the presence of two amino groups at 6.62 ppm (see Experimental, full text).

On the other hand, the thiazole derivative **14** was formed by heating **4a** with sulfanylacetic acid in pyridine at the reflux temperature while the condensation of **4a** with benzaldehyde yielded the benzylidene derivatives **15** (Scheme 2). Structures **14** and **15** were confirmed on the basis of their analytical and spectral data (see Experimental full text).

Techniques used: IR, ^1H and ^{13}C NMR, elemental analysis, TLC and mass spectrometry

References: 19

Schemes: 2

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