

Reactions with 3-Amino-5-trifluoromethyl[1,2,4]-triazole: A Convenient Route to Fluorinated Triazolo[1,5-c]thiadiazine, Triazolo[1,5-a]triazine, Thiazoles and Thiadiazoles

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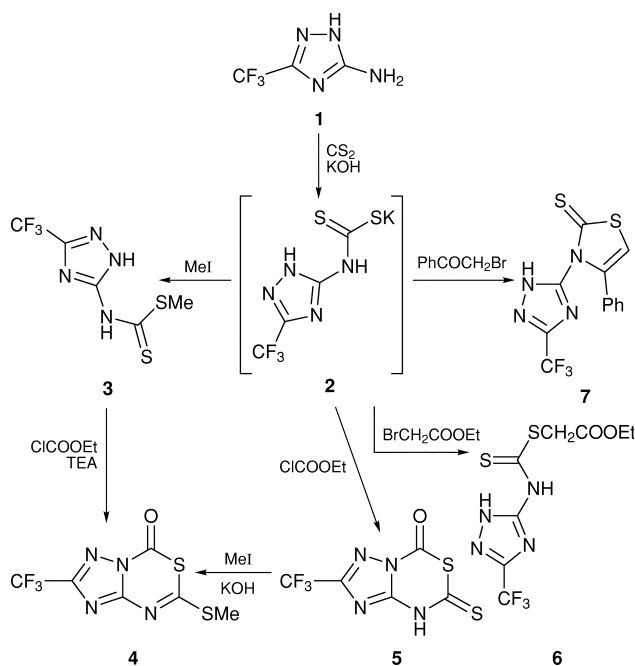
The reaction of 3-amino-5-trifluoromethyl[1,2,4]triazole with carbon disulfide or phenyl isothiocyanate followed by heterocyclization with haloketones, haloesters and hydrazonoyl halides has been utilized for the synthesis of the title compounds; chemical and spectroscopic evidence for the suggested structures of the new compounds and a sequence leading to their formation are discussed.

Considerable interest has been shown in heterocyclic compounds containing a trifluoromethyl group. In addition, the importance of thiazoles and 2,3-dihydrothiadiazoles which arises from their diverse biological potential^{3,4} has led us to embark on a program to investigate the scope of the reaction of carbon disulfide and phenyl isothiocyanate with different reagents.^{5–7} Therefore, in continuation of our interest in the synthesis of heterocycles bearing the trifluoromethyl group^{8–11} we report herein the utility of the reaction of 3-amino-5-trifluoromethyl[1,2,4]triazole with carbon disulfide and phenyl isothiocyanate for the synthesis of several new substituted 2-trifluoromethyl[1,2,4]triazolo[1,5-c]-[1,3,5]thiadiazine, 2-trifluoromethyl[1,2,4]triazolo[5,1-a]-[1,3,5]triazine, thiazoles and thiadiazoles required for a medicinal chemistry programme.

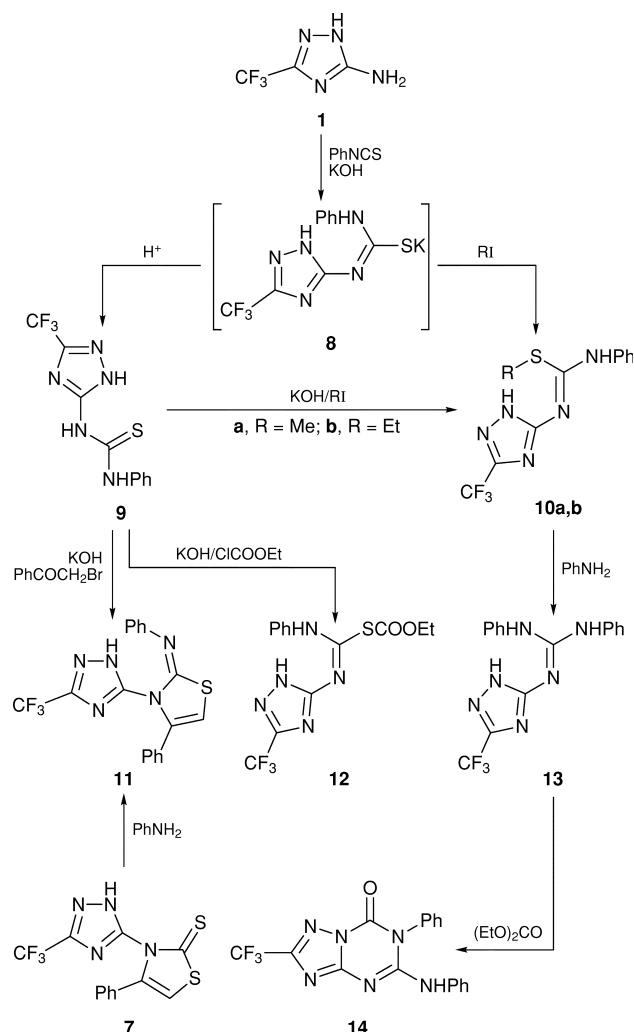
The reaction of 3-amino-5-trifluoromethyl[1,2,4]triazole (**1**) with CS₂, in dry dimethylformamide containing equimolar amounts of KOH at room temperature afforded the non-isolable potassium dithiocarbamate derivative **2**. Treatment of **2** with MeI gave methyl 5-trifluoromethyl[1,2,4]triazol-3-ylidithiocarbamate (**3**) which was cyclized to yield 7-methylthio-2-trifluoromethyl[1,2,4]triazolo[1,5-c][1,3,5]thiadiazin-5-one (**4**) upon treatment with ethyl chloroformate. Evidence for the assigned structure was provided

by analytical and spectroscopic data and by alternative synthetic routes. Also, treatment of **2** with ethyl chloroformate afforded 7-thioxo-2-trifluoromethyl-7,8-dihydro[1,2,4]triazolo[1,5-c][1,3,5]thiadiazin-5-one (**5**). The latter reacted with MeI, in the presence of KOH, to yield a product identical in all respects with compound **4** (Scheme 1). Treatment of **2** with ethyl bromoacetate afforded the 5-trifluoromethyl[1,2,4]triazol-3-ylidithiocarbamate derivative **6**. Furthermore, the reaction of **2** with *o*-bromoacetophenone yielded 4-phenyl-3-(5-trifluoromethyl[1,2,4]triazol-3-yl)thiazole-2(3*H*)-thione (**7**).

The reaction of **1** with equimolar amounts of phenyl isothiocyanate and KOH, afforded the non-isolable potass-

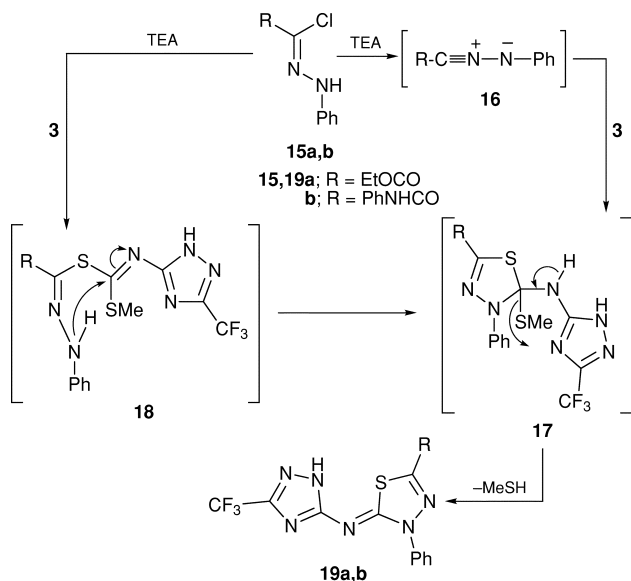


Scheme 1



Scheme 2

*(E-mail: zohdi@main-scc.cairo.eun.eg).



Scheme 3

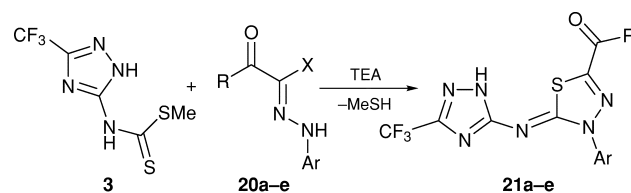
ium sulfide **8**, which was converted into the thiourea derivative **9** by treatment with acetic acid. Compound **8** also reacted with MeI and EtI to afford the S-methyl- and S-ethyl derivatives **10a,b**, respectively (Scheme 2). Treatment of **9** with ω -bromoacetophenone and with ethyl chloroformate, afforded compounds **11** and **12**, respectively. Compound **11** was also obtained by heating compound **7** with aniline.

However, treatment of compound **10a** (or **10b**) with boiling aniline afforded a sulfur-free compound which was assigned structure **13**. The formation of 1,3-diphenyl-2-(5-trifluoromethyl[1,2,4]triazol-3-yl)guanidine (**13**) took place *via* loss of methane- (or ethane-) thiol. Treatment of **13** with diethyl carbonate, at reflux, gave 6-phenyl-7-phenylamino-2-trifluoromethyl[1,2,4]triazolo[1,5-*a*][1,3,5]triazin-5(6*H*)-one (**14**).

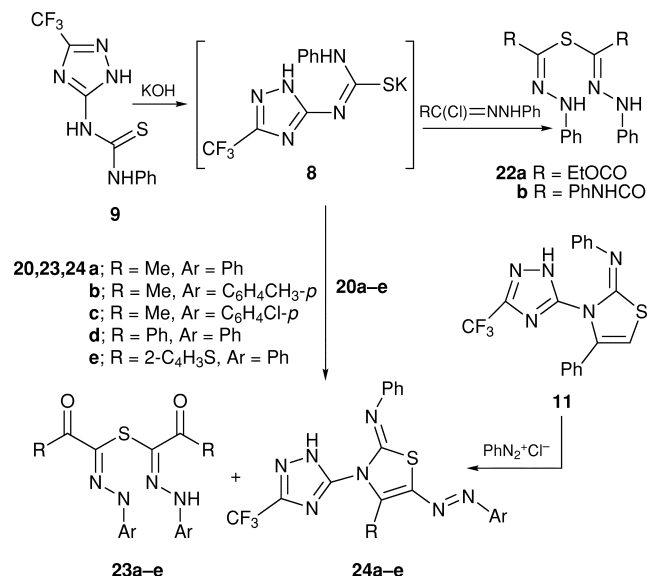
Reaction of **3** with ethyl chloro(2-phenylhydrazono)acetate (**15a**), in the presence of triethylamine at room temperature, gave 2,3-dihydro-5-ethoxycarbonyl-3-phenyl-2-(5-trifluoromethyl[1,2,4]triazol-3-ylimino)[1,3,4]thiadiazole (**19a**) (Scheme 3). Similarly, compound **15b** reacted with **3** to give 2,3-dihydro-3-phenyl-5-phenylcarbamoyl-2-(5-trifluoromethyl[1,2,4]triazol-3-ylimino)[1,3,4]thiadiazole (**19b**). The products **19a,b** are assumed to be formed *via* elimination of methanethiol from the corresponding cyclo-adduct **17**, formed from 1,3-dipolar cycloaddition of the nitrile imide intermediate **16** to the C=S of the methyl dithiocarbamate **3** (Scheme 3). The formation of **19a,b** can also be explained by a stepwise path involving substitution to afford the acyclic hydrazone **18** which readily cyclizes to give the intermediate **17** which subsequently eliminates methanethiol to give the final product **19a,b**.

The reaction of α -oxohydrazone halides **20a–e** with **3**, in the presence of triethylamine at room temperature, was investigated and found to give the corresponding thiadiazolines **21a–e** (Scheme 4).

In contrast, the reaction of hydrazone chlorides **15a,b** and **20a–e** with the thiourea derivative **9** afforded the sulfides



Scheme 4



Scheme 5

22 and **23** and thiazoles **24**. Thus, treatment of **9** with **15a**, in the presence of KOH at room temperature, furnished a single isolable product which analysed correctly for $C_{20}H_{22}N_4O_4S$. The structure of the product was elucidated, on the basis of its elemental analysis, spectral data and alternative synthesis,¹³ as the ethoxycarbonyl hydrazone sulfide **22a**. Similarly, the reaction of **9** and **15b** afforded a single product, identified as the phenylcarbamoyl hydrazone sulfide **22b**.

The reaction of α -oxohydrazone halides **20a–e** with **9** gave, in each case, two isolable products (Scheme 5). The products obtained from the reaction of **20a** with **9**, for example, were found to have the molecular formulae $C_{18}H_{18}N_4O_2S$ and $C_{19}H_{14}F_3N_7S$, respectively. The first product was assigned structure **23**, which was further confirmed by the independent synthesis of **23a**.¹³ The second product was formulated as 2,3-dihydro-4-methyl-5-phenylazo-2-phenylimino-3-(5-trifluoromethyl[1,2,4]triazol-3-yl)thiazole (**24a**) on the basis of its spectroscopic data. Similarly, the reactions of **20b–e** with **9** were found to produce two isolable products, in each case, which were similarly identified as the hydrazone sulfides **23b–e**^{13,14} and the thiazole derivatives **24b–e**. Further support for structure **24** was provided by reacting **11** with benzenediazonium chloride to give a product identical in all respects to **24d**.

Techniques used: IR, 1H NMR, mass spectrometry

References: 14 Schemes: 5

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