PREPARATION OF 3- AND 3,5-SUBSTITUTED 1,2,4-TRIAZOLES

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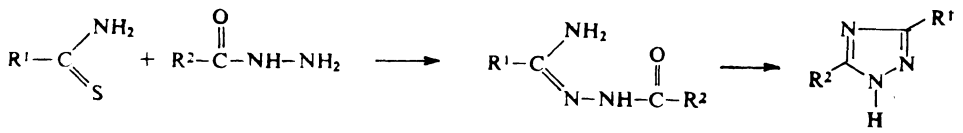
Ethyl 1,2,4-triazole-3-carboxylate (*V*), its 5-methyl and 5-phenyl derivatives (*V* and *VI*, respectively), 3-methyl-1,2,4-triazole (*VIII*), 3-phenyl-1,2,4-triazole (*IX*), 3,5-dimethyl-1,2,4-triazole(*X*), 3,5-diphenyl-1,2,4-triazole (*XI*) and 3-phenyl-5-methyl-1,2,4-triazole (*XII*) were prepared in 40–70% yields by thermal cyclization of acylamidrazones *III*.

In connection with studies of ribavirin (Virazol) analogues[1–3] we elaborated a simple synthesis of ethyl 1,2,4-triazole-3-carboxylate (*V*), a key intermediate in the ribavirin synthesis[4]. Our new synthesis[5], described in this communication, is more advantageous and shorter than the hitherto described syntheses of this compound[6,7] or its derivatives[8] and can be used as a general preparation of other 3- and 3,5-substituted 1,2,4-triazole derivatives.

The synthesis consists in thermal cyclization of N^1-acylamidrazones *III*. This method of 1,2,4-triazole synthesis was first used in the Pellizzaro reaction[9] in which acylamidrazones are formed as unisolated intermediates of thermal condensation of amides with acylhydrazides. However, the low reactivity of amides requires high reaction temperatures which leads to their partial dehydration and consequently low yields. Acylamidrazones *III* can be prepared by reaction of acylhydrazines *II* with nitriles, imino ethers or thioamides *I*. Our attempts to prepare N^1-acylamidrazones from nitriles have shown that, in accord with the literature[10], the reaction proceeds satisfactorily only with aromatic and heterocyclic nitriles and is thus not suitable for a general synthesis of 1,2,4-triazole derivatives. Although iminoethers have been used in the preparation of acylamidrazones and 1,2,4-triazoles[11,12], imidrazones, required for preparation of some compounds in this study (particularly *V*, *VI* and *VII*) are not easily accessible and are not very stable under the reaction conditions.

On the other hand, thioamides, which are easily accessible from nitriles[13,14], proved to be suitable starting compounds. When carried out in solvents, the condensation of thioamides *I* with acylhydrazines *II* does not lead to satisfactory results. It can, however, be performed by melting both components together. Usually, the formed acylamidrazone *III* crystallizes directly from the melt during the heating

or after cooling. Further heating of the acylamidrazones *III* above their melting point results in cyclization to the corresponding triazoles *IV*. In order to remove the arising water, cyclization of larger amounts should be performed by melting *in vacuo*. In several cases, the reactions $I + II \rightarrow III \rightarrow IV$ can be carried out without isolation of the intermediate *III*; however, its isolation naturally makes purification of the end product *IV* easier improving thus sometimes the yield.



I *II* *III* *IV*

The preparation of ethyl 1,2,4-triazole-3-carboxylate[5] (*V*) serves as an example of the mentioned synthesis. Its scope is illustrated by the preparation of some other derivatives with methyl, phenyl and ethoxycarbonyl groups. Monosubstituted triazoles are formed from the corresponding thioamides *I* and formylhydrazine (*II*, $R^2 = H$) whereas disubstituted derivatives can be prepared by two alternative procedures. Thus, *e.g.* 3-phenyl-5-methyl-1,2,4-triazole (*XII*) can be synthesized either from thioacetamide and benzhydrazide or from thiobenzamide and acetylhydrazine (Table I). In the synthesis of more complex disubstituted compounds we can thus choose the approach according to the accessibility of compounds *I* and *II*. Also for disubstituted derivatives in which one of the substituents is an alkoxycarbonyl

TABLE I

Synthesized 1,2,4-triazole derivatives

Compound	R^1	R^2	*T*, °C	Yield, %	Ref.
V	$COOC_2H_5$	H	165	75	6
	$COOC_2H_5$	CH_3	200	46	
VI	CH_3	$COOC_2H_5$	200	10	16
	$COOC_2H_5$	C_6H_5	180	51	
VII	C_6H_5	$COOC_2H_5$	180	9	—
VIII	CH_3	H	150	65	9
IX	C_6H_5	H	150	56	17
X	CH_3	CH_3	150	42	18
XI	C_6H_5	C_6H_5	190	74	19
XII	CH_3	C_6H_5	180	43	20
	C_6H_5	CH_3	180	64	

group (compound *VI* and *VII*) both pathways are possible, the more suitable way starting from the corresponding alkyl thioxamate and acylhydrazine (as used *e.g.* in the preparation of compound *V*). The alternative procedure, starting from an alkyl- or arylthioamide and oxalic acid ester-hydrazide, is mentioned[15] to give a negative result. We were able to prepare in this way compounds *VI* and *VII* but in substantially lower yields (Table I) caused probably by side-reactions of the relatively unstable oxalic acid ester-hydrazide.

EXPERIMENTAL

The melting points were determined on a Kofler block. Analytical samples were dried at room temperature and 13 Pa for 8 h.

Oxalic Acid Ethyl Ester Formamidrazone (*IV*)

A mixture of ethyl thioxamate (532 mg; 4 mmol) and formylhydrazine (240 mg; 4 mmol) was heated to 50–60°C for 15 min. After cooling, the crude melt was crystallized from ethanol to give 461 mg (74%) of the product, m.p. 159–160°C. For $C_5H_9N_3O_3$ (159·2) calculated: 37·73% C, 5·66% H, 26·42% N; found: 37·77% C, 5·51% H, 25·54% N.

Ethyl 1,2,4-Triazole-3-carboxylate (*V*)

Compound *IV* (318 mg; 0·5 mmol) was melted at 165°C for 20 min. Crystallization from ethanol afforded 232 mg (75%) of the product, m.p. 176–178°C (reported[6] m.p. 178°C).

Ethyl 5-Phenyl-1,2,4-triazole-3-carboxylate (*VII*)

A mixture of ethyl thioxamate (532 mg; 4 mmol) and benzoic acid hydrazide (544 mg; 4 mmol) was melted at 180°C for 1 h. Crystallization from ethyl acetate gave 440 mg (51%) of the product, melting at 168–169°C. For $C_{11}H_{11}N_3O_2$ (217·2) calculated: 60·82% C, 5·10% H, 19·34% N; found: 60·71% C, 5·31% H, 19·18% N.

Compounds *VI*, *VIII*–*XII* were prepared using the same procedure (*i.e.* without isolation of the amidrazone). The starting compounds, temperatures and yields are given in Table I.

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