TRIAZOLES
1,2,4

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THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

A SERIES OF MONOGRAPHS

ARNOLD WEISSBERGER and EDWARD C. TAYLOR

Editors

TRIAZOLES

1,2,4

This is the Thirty-Seventh Volume in the Series

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

The Chemistry of Heterocyclic Compounds

The chemistry of heterocyclic compounds is one of the most complex branches of organic chemistry. It is equally interesting for its theoretical implications, for the diversity of its synthetic procedures, and for the physiological and industrial significance of heterocyclic compounds.

A field of such importance and intrinsic difficulty should be made as readily accessible as possible, and the lack of a modern detailed and comprehensive presentation of heterocyclic chemistry is therefore keenly felt. It is the intention of the present series to fill this gap by expert presentations of the various branches of heterocyclic chemistry. The subdivisions have been designed to cover the field in its entirety by monographs which reflect the importance and the interrelations of the various compounds, and accommodate the specific interests of the authors.

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Note to the Reader

The text and tables of this volume on 1,2,4-triazoles, triazolines, and triazolidines have been comprehensively compiled through the use of *Chemical Abstracts*. The text was composed from abstracts and references present in volumes 51–85 (1957–1976) of *Chemical Abstracts*, which covers the period from the reviews of K. T. Potts (1961) and J. H. Boyer (1961). The tables list the compounds indexed by *Chemical Abstracts* for the period of time from the Second Supplement of Beilstein (1929) through 1975 and also the majority of compounds for 1976. Because of the large number of compounds, only a small number of 1,2,4-triazoles, triazolines, and triazolidines are listed individually in the Subject Index, which, however, will refer to the text for a particular group of compounds. Also a particular group of compounds can be located readily by inspection of the Contents. For convenience in cross-checking, the sections of the text and the tables are denoted by the same title and number. The arrangement of the sections of text and tables has been classified according to the nature of the atom connecting the substituent to the ring, which follows the order of carbon (alkyl, aryl, carboxylic acid, acyl), nitrogen (amino, azo, nitro, etc.), oxygen (alkoxy, aroxy, etc.), sulfur (alkyl- and aryl- thio, sulfinyl, etc.), and halogen. Those compounds that contain more than one representative function are discussed and assembled, respectively, in the appropriate sections and tables. In the text, references are indicated by arabic numbers, which refer to *Chemical Abstracts* numbers listed at the end of each section. Also, the reference for a compound listed in the tables is denoted by a *Chemical Abstracts* number. The latter, listed numerically in the master reference section, will identify either the patent or journal reference. Prior to volume 66 (1967), *Chemical Abstracts* denoted the position of compounds within an abstract by a page number and a letter, either one or both of which might not correspond exactly to the *Chemical Abstracts* number that identifies the journal reference. For patents or journals that might not be readily available, *Chemical Abstracts* can be consulted. In the text, footnotes are used for those journal references that appeared prior to *Chemical Abstracts*.

Compounds described by the title of the table are listed as *parent*. *N*-alkoxy-, *N*-hydroxy-, *N*-, *P*-, and *S*-oxides, and organometallic radicals substituted on either carbon or nitrogen are not considered a representative function, and these compounds are listed with the parent triazole. All compounds are listed alphabetically. When isomeric compounds are listed, the isomer with the lowest number appears first. The tables containing the alkyl or aryl compounds include the substituted alkyl or aryl derivatives; for example, triazole-3-acetic acid is listed under alkyl rather than carboxylic acid derivatives. Also, the tables containing the amino compounds include

alkyl- or arylamino, acylamino, and hydrazino type compounds. The names of compounds that are derivatives of another class have been changed and listed in the tables as triazoles. For example, *triazolyl*pyridine has been listed as *pyridyl*triazole; (triazolyl)-2-propanone as acetonyltriazole. Further, the names of imides and derivatives of guanazine have been changed, when possible, and listed as the corresponding aminotriazoles. In contrast, hydroxytriazoles, triazolol, and triazolones are listed as triazolinones; mercaptotriazoles, triazolethiol, and triazolethione as triazolinethiones. Similar considerations as described above apply to the triazolines and triazolidines. Compounds containing conjunctive names are listed alphabetically. For compounds with conjunctive names of mixed function, the chief function is determined by the grouping.

CARROLL TEMPLE, JR.

Birmingham, Alabama
June 1980

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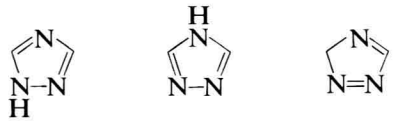
C. T.

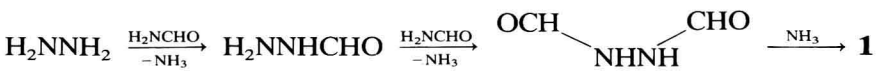
Contents

Introduction

The heteroaromatic triazole ring system is composed of five atoms, two carbons, and the three nitrogens, which can be arranged in two combinations to give either 1,2,3-triazole or 1,2,4-triazole. Although two NH (**1** and **2**) and one CH_2 (**3**) tautomeric forms are possible for 1,2,4-triazole, this



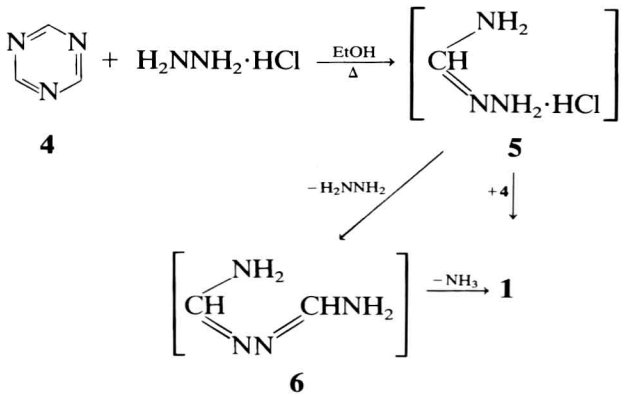
1 **2** **3**



structure is best represented as a positively charged hydrogen associated with the resonance stabilized triazole anion.[1] In *Chemical Abstracts* 3-substituted and 3,5-disubstituted 1,2,4-triazoles are usually indexed as *s*-triazoles. The 1,2,4-1H-triazole notation is used to describe a 1*N*-substituted triazole, whereas 1,2,4-4H-triazole is used to describe a 4*N*-substituted triazole. Trivial names such as guanazole(3,5-diamino-*s*-triazole), guanazine(3,4,5-triamino-1,2,4-4H-triazole), and either bicarbamimide or urazole(1,2,4-triazolidine-3,5-dione) have been replaced by systematic names throughout this chapter. Additional information on nomenclature is described in the introduction to the tables. In addition to reviews by Potts[1] and Boyer,[2] the relationship of the 1,2,4-triazoles in regard to other small-ring azoles has been reviewed recently by Schofield, Grimmett, and Keene.[3]

Bladin reported the preparation of derivatives of *s*-triazole (**1**) in 1885,[4] and soon thereafter Pellizzari obtained the parent ring system from the reaction of formylhydrazine with formamide.[5] This and related reactions, which gave low and variable yields of *s*-triazole (**1**), have been reviewed.[1] Later the condensation of hydrazine sulfate with formamide was reported to give a 53% yield of *s*-triazole (**1**).[6] Ainsworth and Jones observed that a large quantity of ammonia was evolved in the reaction of hydrazine with

formamide, and to prevent the loss of ammonia, the intermediate *N,N'*-diformylhydrazine was reacted with excess ammonia in a pressure vessel to give a 70 to 80% yield of *s*-triazole (**1**).[7] A further improvement in the yield of *s*-triazole (**1**) resulted from the work of Grundmann and Rätz, who obtained a 95% yield of *s*-triazole (**1**) from the interaction of *s*-triazine (**4**) with hydrazine hydrochloride.[8] Apparently, the intermediate amidrazone (**5**) was initially formed, which was postulated to react with another molecule of *s*-triazine (**4**) to give *s*-triazole (**1**). However, the acid-catalyzed self-condensation of amidrazones is well documented,[9–11] and *s*-triazole (**1**)



might be formed via intermediate **6**. With hydrazine rather than its hydrochloride, *s*-triazine (**4**) reacted to give 1,2-diformylhydrazine dihydrazone.[12]

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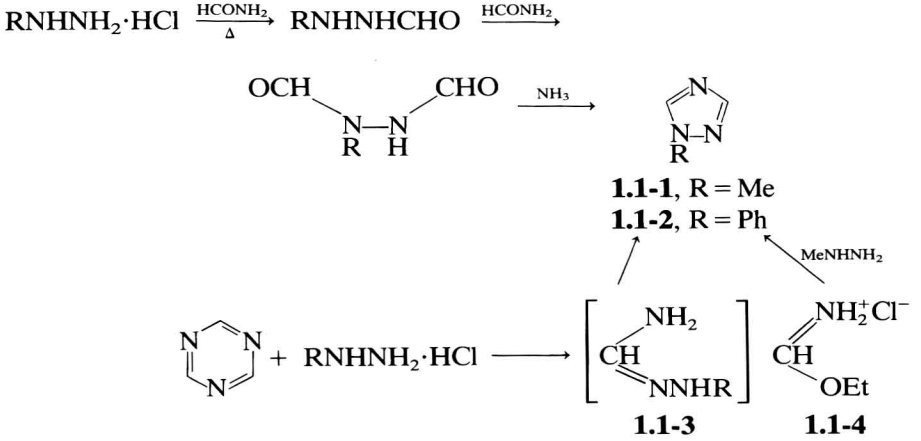
CHAPTER 1

Alkyl- or Aryl-Monosubstituted 1,2,4-Triazoles

1.1. 1-Alkyl- or Aryl-Substituted 1H-1,2,4-Triazoles

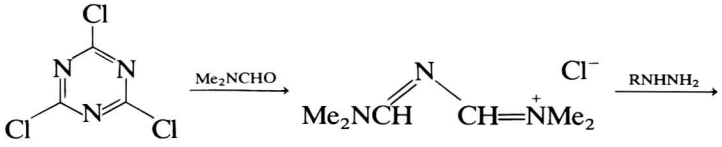
The reaction of either 1-substituted hydrazines or the corresponding formyl derivatives with formamide (Pellizzari reaction) at high temperatures (>200°) produced both 1-alkyl- and 1-aryl-1,2,4-triazoles (**1.1-1**, **-2**). The products are generally isolated in low yields because the separation of by-products is often difficult.*,[1] Both 1-methyl- and 1-phenyltriazole are formed in high yields (>80%) via an amidrazone intermediate (**1.1-3**) in the acid-catalyzed condensation of the appropriate hydrazine with *s*-triazine in refluxing ethanol.[2] An amidrazone intermediate was also involved in the reaction of the imino ether (**1.1-4**) with methyl hydrazine in ether to give a



mixture of a dihydrotetrazine (38%) and 1-methyl-1,2,4-triazole (**1.1-1**) (27%).[3] In a related reaction, treatment of 2,4,6-trichloro-*s*-triazine (**1.1-5**)

* G. Pellizzari and A. Soldi, *Gazz. Chim. Ital.*, **35,** 373 (1905).

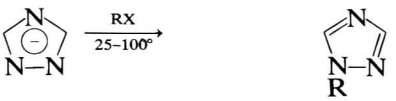
with dimethylformamide gave the reactive [(dimethylaminomethylene)-amino]dimethylammonium intermediate (**1.1-6**), which was condensed with substituted hydrazines to give good yields of triazoles (e.g., **1.1-2**, **1.1-7**, **1.1-8**).[4,5]



1.1-5 **1.1-6**

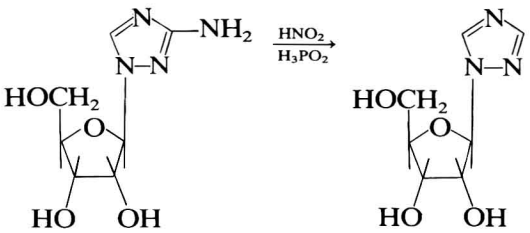
1.1-2, R = Ph (77%)
1.1-7, R = $HOCH_2CH_2$ (62%)
1.1-8, R = $Et_2NCH_2CH_2$ (50%)

Another important method, the alkylation of the anion of *s*-triazole, can be used with a variety of both simple and complex alkyl halides to give 1-alkyl-1,2,4-triazoles (e.g., **1.1-1**, **1.1-9**, **1.1-10**).[6,7] In addition, the silver salt



1.1-1, R = Me (78%)
1.1-9, R = $PhtNCH_2$ (41%)
1.1-10, R = EtO_2CCH_2 (81%)

of *s*-triazole was alkylated with butyl iodide in refluxing benzene to give 1-butyl-1,2,4-triazole,[8] and the condensation of the trimethylsilyl derivative of *s*-triazole with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide in acetonitrile gave the *O*-benzoyl derivative of 1-(β-D-ribofuranosyl)-1,2,4-triazole (**1.1-12**).[9] The latter was also prepared by the reductive deamination of 3-amino-1-(β-D-ribofuranosyl)-1,2,4-triazole (**1.1-11**) with nitrous acid in the



1.1-11 **1.1-12**