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Review

5-Substituted-1*H*-tetrazoles as Carboxylic Acid Isosteres: Medicinal Chemistry and Synthetic Methods

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Abstract—5-Substituted-1*H*-tetrazoles (RCN_4H) are often used as metabolism-resistant isosteric replacements for carboxylic acids (RCO_2H) in SAR-driven medicinal chemistry analogue syntheses. This review provides a brief summary of the medicinal chemistry of tetrazolic acids and highlights some examples of tetrazole-containing drug substances in the current literature. A survey of representative literature procedures for the preparation of 5-substituted-1*H*-tetrazoles, focusing on preparations from aryl and alkyl nitriles, is presented in sections by generalized synthetic methods.

Contents

Introduction

This review provides a summary of the medicinal chemistry aspects of 5-substituted-1*H*-tetrazoles, which have found common usage as an isosteric replacement for the carboxylic acid moiety in recent years. A discussion of the structural features of the tetrazolyl group which make it a suitable substitution for a carboxyl functionality in drug design will be presented, as well as a description of some of the metabolic liabilities of this surrogate moiety. An examination of some prominent examples of tetrazolic acid-containing drug substances from the literature will also be presented, focusing on

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two aryl and one aliphatic compound. Practicing medicinal chemists who may be interested in an evaluation of more comprehensive tabular surveys may also consult some of the review materials listed in this bibliography.[1–5] Some representative literature procedures for the preparation of 5-substituted-1*H*-tetrazoles from aryl and alkyl nitriles will be presented, as well as some highlights from the very recent literature which involve carbon–carbon bond formations with 1-substituted-5-lithiotetrazoles.

Chemical and Pharmacological Properties

It has been long held that 5-substituted-1*H*-tetrazoles (RCN_4H) may serve as a non-classical isostere for the carboxylic acid moiety (RCO_2H) in biologically active molecules.[1–7] The term non-classical isosterism (used interchangeably with the term bioisosterism) refers to the concept in which functional groups that have similar physicochemical properties may be interchangeable, resulting in similar biological properties. Furthermore, a non-classical isostere may or may not have the same steric or electronic characteristics, nor even the number of atoms, as the substituent for which it is used as a replacement.[5,7–9] Other simple carboxylic acid surrogates include carboxamides, sulfonamides, acyl sulfonamides, sulfamides, sulfonates and phosphates. More complicated isosteres include isoxazol-3-ols, hydroxy-2-methylpyran-4-ones, 4*H*-[1,2,4]oxadiazol-5-ones, 4*H*-[1,2,4]thiadiazol-5-ones and 2,4-dihydro-[1,2,4]triazol-3-ones, to name a few.

5-Substituted tetrazoles that contain a free N–H bond are also frequently referred to as tetrazolic acids, and exist as a nearly 1:1 ratio of 1*H*- and 2*H*-tautomeric forms (Fig. 1, **1** and **2**, respectively), although it is sometimes also convenient to describe them as imidoyl azides **3**. It should be stated that tetrazolic acid structures that appear throughout this article are assumed to be mixtures of both 1*H*- and 2*H*-tautomers. Previous studies have shown that the two positional isomers **1** and **2** may be differentiated on the NMR timescale.[10] Recently, Sadlej-Sosnowska has applied calculated natural bond orbital analysis to a series of 5-substituted tetrazoles and determined that 2*H*-tautomers **2** are the more stable isomers, although they were found to have a larger degree of electron delocalization than 1*H* tautomers **1**.[11] This consideration, in combination with steric factors, may have some bearing on the observation that *N*-alkylation of tetrazolic acids often places the substituent on the N2 position.[12]

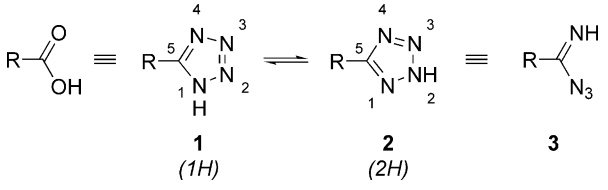


Figure 1. Tetrazolic acids are bioisosteres of carboxylic acids.

The free N–H bond of tetrazoles makes them acidic molecules, and not surprisingly it has been shown that both the aliphatic and aromatic heterocycles have pK_a values that are similar to corresponding carboxylic acids (4.5–4.9 vs 4.2–4.4, respectively), due to the ability of the moiety to stabilize a negative charge by electron delocalization.[6,12–16] In general, tetrazolic acids exhibit physical characteristics similar to carboxylic acids and are strongly influenced by the effect of substituents at the C5-position.[6] For example, many 5-aryl tetrazoles are highly soluble in water and are best crystallized from aqueous alcoholic solvents. However 5-aliphatic analogues, while still often soluble in water, are best crystallized from solvents such as ethyl acetate or toluene/pentane mixtures.[6] The corresponding tetrazolate anionic species (RCN_4Na or RCN_4Li), which have a higher capacity for hydrogen bonding than the protic species,[17] are easily generated in hot alcohol or aqueous solutions and these intermediates are more reactive than the corresponding neutral species toward a variety of electrophiles and alkylating agents.[6] A recent review on the *N*-substitution of tetrazoles has appeared, which focuses on alkylation and electrophilic reactions at tetrazole nitrogen atoms.[12] A recent review of transformations of heterocycles into tetrazoles, and conversions of tetrazoles into other ring systems, also takes into consideration the physical properties of tetrazoles.[18]

Like their carboxylic acid counterparts, tetrazoles are ionized at physiological pH (7.4), and both exhibit a planar structure. However, Hansch has shown that anionic tetrazoles are almost 10 times more lipophilic than the corresponding carboxylates,[19] which is an important factor to bear in mind when designing a drug molecule to pass through cell membranes. Another important factor when considering a tetrazole as a replacement is the effect of delocalization of the negative charge around the tetrazole ring. The distribution of charge over a greater molecular surface area may be favorable for a receptor–substrate interaction, or may complicate the contact, depending on the local charge density available at the interface.[20] The larger size of the heterocycle (vs a carboxyl group) may also reduce the binding affinity at the active site, either by less favorable orientation of functional groups, or by steric hindering of an active conformational change of the receptor complex.[21] An interesting comparison between the effective 'length' of carboxylic acid versus tetrazole pharmacophores was recently reported by Pellicciari and coworkers (Fig. 2).[22] In a study designed to explore the SAR of propellane-derived analogues of L-glutamic acid as mGlu1 receptor agonists, the authors prepared the amino acids **4** and **5**, which contained distal carboxylic

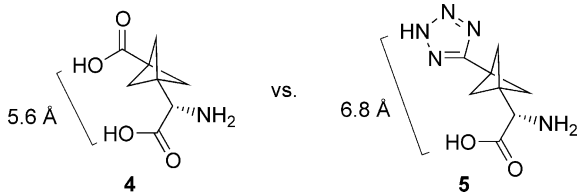


Figure 2. The size of tetrazole **5** extends the distance between the two acidic pharmacophores relative to the analogous dicarboxylic acid **4**.

acid and tetrazole units, respectively. Models suggested that the distance between the acidic functional groups were such that the 2*H*-tetrazole moiety increases the distance between the pharmacophores by about 1 Å. In vitro evaluation revealed that the tetrazole **5** was 2.5-fold less potent versus **4**, which was attributed to the increased distance between the two acidic sites, indicating an unfavorable fit between two important synergistic positions.

Hydrogen bonding capability of tetrazolic anions with receptor recognition sites has recently been shown to be the key interaction for enhanced binding affinity. The finding that tetrazole substrates may form two hydrogen bonds with peptide residues in a biological target site may well explain the stronger binding interaction. For example, mutagenesis studies have indicated that the tetrazolate moiety of several nonpeptide antagonists interact with a protonated lysine and a histidine in the active site of the angiotensin II receptor.[23] A short time ago an X-ray crystal structure has revealed the ionic interaction of the N1 and N2 tetrazole nitrogens of an HIV-1 integrase inhibitor with two lysine residues within the enzyme active site.[24] Lately it has been shown that a tetrazole can form two hydrogen bonds to an *N,N'*-disubstituted benzamidine, although with a considerably smaller association constant versus the corresponding carboxylate-amidine interaction.[25]

In the design of drug molecules, one advantage of tetrazolic acids over carboxylic acids is that they are resistant to many biological metabolic degradation pathways. Some of the earliest findings showed that tetrazole-derived nicotinic acid analogues that were administered to dogs were excreted essentially unchanged over a 24-h period, whereas nicotinic acid itself was rapidly metabolized.[26] As in these cases, it is often seen that the resistance of tetrazolic drug substances to metabolism may result in a longer duration of action versus carboxylic acids, although just as often a corresponding lack of potency is also observed.

When drug substances enter the body, a host of processes take action in order to render these xenobiotics into more polar substrates for elimination. While both carboxylic acids and tetrazoles may act as ligand binding functionality for CYP450-derived oxidative metabolic processes, tetrazoles may exhibit an advantage over carboxylic acids in terms of escaping most biotransformations by Phase II (a.k.a. conjugation) reaction pathways. Benzoic acid substrates often undergo covalent bond formation with transferase enzymes such as Coenzyme-A to form activated acyl (thio)esters, which then undergo subsequent conjugation transformations by a variety of pathways.[8] However, the analogous activation process does not occur with aromatic or aliphatic tetrazoles,[7] and so this moiety will not undergo glycine conjugation, incorporation into lipids, or degradation by β-oxidation.[27]

On the other hand, tetrazolic acids have been shown to undergo conjugation reactions to form β-*N*-glucuronides, a metabolic fate that often befalls aliphatic carboxylic acids to form *O*-β-glucuronic acid conjugates (Fig. 3).[28] Glucuronidation of xenobiotics is an important pathway for the biological clearance of drug compounds, and involves the transfer of the glucuronic acid functionality of the cofactor uridine-5′-diphospho-α-D-glucuronic acid (UDPGA) to the nucleophilic atom of a substrate (e.g., carboxylate or tetrazolic anion). This transformation is mediated by an isoform of the enzyme UDP-glucuronosyltransferase (UDPGT), and the resultant inversion of the α-stereochemistry at the pyranose anomeric center by a nucleophile results in a β-product.[8] Both tetrazole tautomers may serve as substrates for *N*-glucuronidation, and indeed both structural variations are known. In 1980, Nohara identified the first tetrazole N1 glucuronide **8** in the urine stream of several animals orally dosed with a chromone-derived tetrazole,[29] which was identified as the exclusive isomer by synthesis and NMR studies. Several more recent studies have shown that the N2-product **7** is the preferred metabolite of biphenyltetrazole substrates, as determined by NMR and X-ray crystal structures,[30,31] and the N2-glucuronide of an aliphatic drug candidate has also recently been reported.[32] Some authors have attributed the long half-life of a number of orally administered tetrazolic acid drugs to enterohepatic recirculation mechanisms.[31] While *N*-glucuronide formation and subsequent biliary excretion of a tetrazolic acid may remove the drug from circulation, reabsorption of the metabolite may result in hydrolysis by microflora in the intestinal mucosa, thereby allowing additional assimilation of the parent drug in a second pass. Indeed similar reprocessing phenomena have long been implicated as a mechanism for unexpectedly long drug half-lives of other drug substances.

Tetrazole compounds which also contain an additional basic functionality in the molecule may exist as zwitterions, which can result in poor absorption properties for a potential drug candidate. In some cases a prodrug approach has been developed, similar to the strategy developed for carboxylic acids to enhance oral bioavailability.[33] Derivatization of polar molecules into compounds in which the acidic tetrazole N–H bond has been masked (protected by a moiety that can be removed under physiological conditions) results in a more lipophilic molecule of neutral charge that can exhibit greater biomembrane transport ability. This tactic has been used to improve the physicochemical

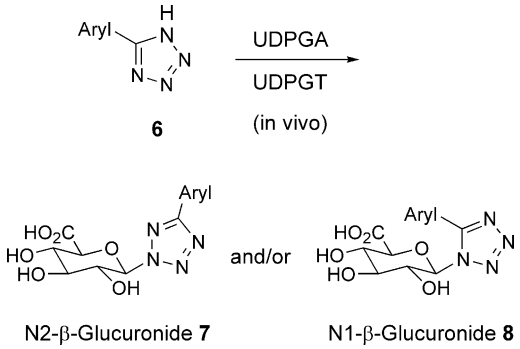


Figure 3. *N*-Glucuronidation is the major metabolic pathway for physiological clearance of aryl tetrazolic acids.

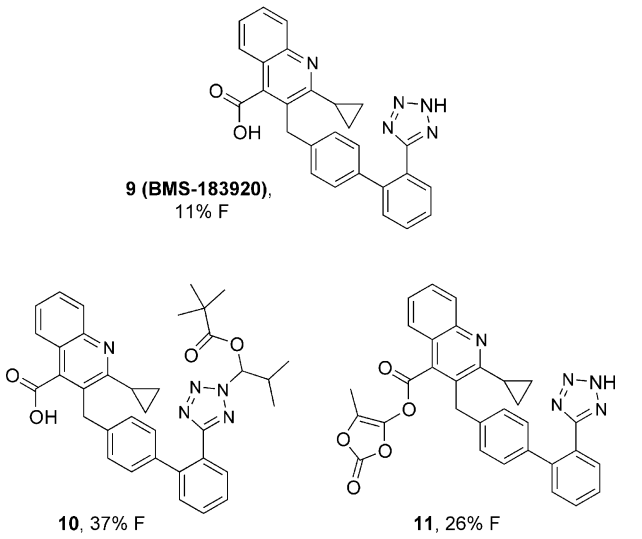


Figure 4. A tetrazole prodrug approach to mask BMS-183920 (**9**) as **10** increased bioavailability (% F) by better than 3-fold.

properties of the angiotensin II receptor antagonist BMS-183920 (diacidic structure **9**) as the prodrug **10** (Fig. 4).[34] By *N*-'bioreversible' protection of the poorly absorbed tetrazole with a pivaloylisobutyl moiety, the bioavailability in rats was increased from 11% for **9** to 37% for **10**. Interestingly, prodrug protection of the carboxylic acid instead of the tetrazole moiety (**11**) did not increase oral availability to better than 26%.

A word of caution: the pharmacological effects of bioisosteric replacement of carboxylates with tetrazoles in a potential drug candidate are not necessarily predictable, as the wealth of medicinal chemistry literature points out. In fact, diverse examples from the literature show that the pharmacological effects can be enhanced, reduced or eliminated completely when compared to carboxylic acid analogues. The next section will showcase a few examples in which the application of the surrogate strategy has advanced research toward both aromatic and aliphatic tetrazole-containing commercial drugs and drug contenders.

Before moving onto some case histories, it is also worth noting that an emerging field of research has begun to accumulate evidence that 1,5-disubstituted tetrazoles are effective bioisosteres for *cis*-amide bonds in peptidomimetics (Fig. 5). Marshall and Zabrocki have shown that peptides which contain a 1,5-disubstituted tetrazole unit, as in **13**, may be effective conformational mimics for the corresponding peptides that prefer to adopt a *cis*-amide bond conformation, or which need to preorganize the amide bonds to act as enzyme substrates, as in **12**.[35,36] A synthetic probe of this type can be important when investigating the role of peptide bond *cis–trans* isomerism in the geometry of molecular recognition. Through synthesis and conformational study of an analogue of bradykinin, it was shown that peptides containing a tetrazole in place of an amide bond were able to adopt most of the conformations available to the parent compound.[35,36] This applies to peptides that contain a free N–H bond, as well as for

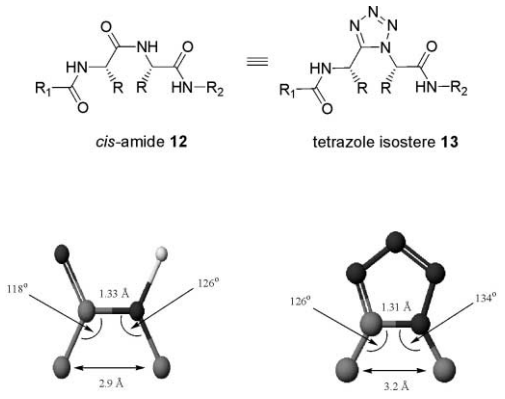


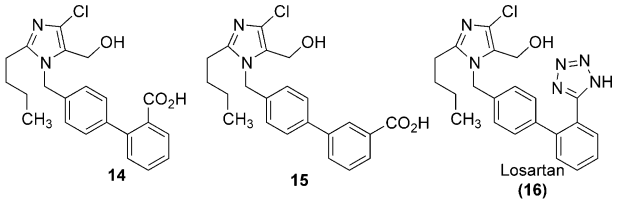
Figure 5. 1,5-Disubstituted tetrazoles as *cis*-amide surrogates.

N-methyl amino acids. In a recent report, Rodziewicz-Motowidlo and coworkers conducted a two-dimensional NMR study of the conformational constraint imparted to scyliorhinin I when a 1,5-tetrazole ring was introduced between positions 7 and 8.[37] Much more can be said of this interesting field of study, and readers should refer to the citations listed here.

Three Medicinal Chemistry Case Histories

The following examples were taken from the literature to represent the various classes of aryl and aliphatic tetrazole-containing analogues that emerged from research efforts. Often clinically advanced or commercial tetrazolic acid drugs were identified as isosteres prepared to investigate the binding energy of carboxylic acid lead compounds. In addition to these examples, several reviews have appeared which evaluate tetrazolic acid by disease state in tabular formats.[1–5] Readers are also encouraged to peruse publications of other current research efforts[38] as well as to review some lead articles for the preparation of tetrazole analogues of amino acids and peptides.[39]

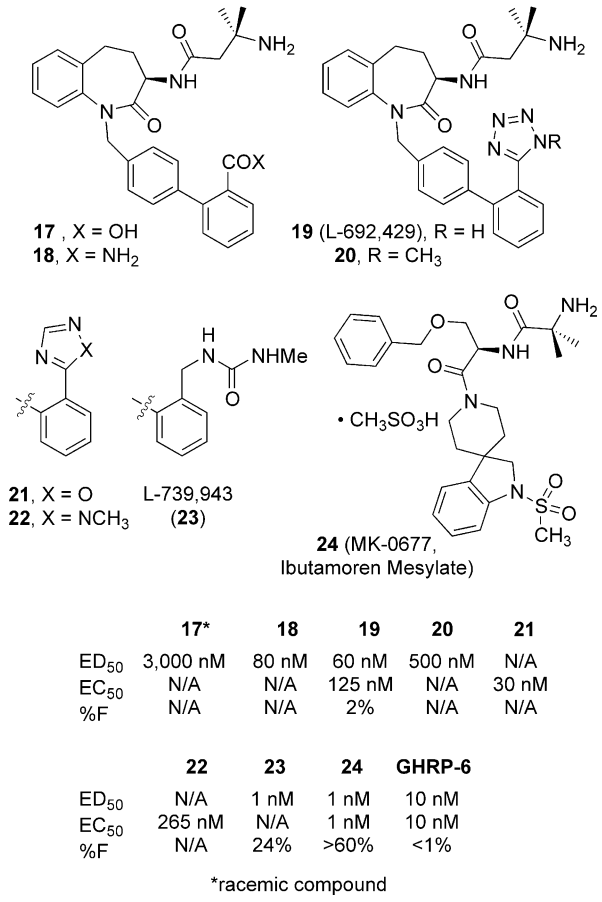
A comprehensive search of the patent literature shows that the majority of tetrazolic acid-based drug substances are aryl tetrazoles. In fact, a great part of these structures contain the biphenyl tetrazole motif, many of which are structural derivations of DuPont's non-peptidic selective angiotensin II receptor antagonist Losartan (**16**, Fig. 6), a drug launched in 1994 to treat



IC_{50}	0.23 μM	0.49 μM	0.02 μM
EC_{30} iv	3 mg/kg	45 mg/kg	0.8 mg/kg
EC_{30} po	11 mg/kg	(inactive)	0.6 mg/kg
pKa	4.5	4.5	5.0
logP	1.2	1.4	4.5

Figure 6. Comparison of Losartan (**16**) data with early 2- and 3-carboxybiphenyl analogue leads.

hypertension.[40–42] While investigating a new series of analogues derived from a biphenyl scaffold, it was found that compound isomers **14** and **15** were both active by intravenous injection into renal hypertensive rats. Unfortunately, the effect was minimized upon oral administration. In an effort by the research team to find compounds of greater potency and bioavailability, a series of carboxylic acid isosteres were prepared. Interestingly, no carboxamide or sulfonamide compounds were found to improve the oral activity, but when tetrazole was introduced at the C2-position, a dramatic enhancement in binding affinity and oral potency were observed. The authors felt that the increase in receptor binding was due to the greater ability of the heterocycle to distribute a negative charge at physiological pH, allowing for better interaction (vs carboxylate) with the positive charge at the receptor.[23a] This early hypothesis has more recently been borne out by conformational analysis utilizing theoretical calculations and NMR spectroscopy.[43] As well, the longer spatial distance of the N–H bond into the receptor may be the optimal depth for receptor binding. Better oral bioavailability (33% for Losartan) may be due to the greater lipophilicity of tetrazole **16** versus **14** and **15**, a property which can be evaluated by a comparison of log *P* values. The major metabolite of Losartan has been identified as the N2-glucuronide,[30] which has also been implicated in the long duration of action, perhaps by an enterohepatic reprocessing mechanism.[31] Since the introduction of Losartan to the literature, a great number of papers have been published regarding potential analogues of Losartan (**16**), as well as a variety of other biphenyl tetrazolic acid structures for other indications.[23a,44]



	17*	18	19	20	21
ED_{50}	3,000 nM	80 nM	60 nM	500 nM	N/A
EC_{50}	N/A	N/A	125 nM	N/A	30 nM
%F	N/A	N/A	2%	N/A	N/A

	22	23	24	GHRP-6
ED_{50}	N/A	1 nM	1 nM	10 nM
EC_{50}	265 nM	N/A	1 nM	10 nM
%F	N/A	24%	>60%	<1%

*racemic compound

Figure 7. The role of L-692,429 (**19**) as a mid-stream success early in the development of MK-0677 (**24**).

An interesting tetrazole semi-success story can be told about Merck & Company's non-peptidyl growth hormone secretagogue L-692,429 (**19**, Fig. 7). In 1988, a program was started to identify small molecule peptidomimetics of the growth hormone releasing hexapeptide His-D-Trp-Ala-Trp-D-Phe-Lys-NH_2 (GHRP-6), from which the biphenyltetrazole **17** was designated as a lead compound.[45] Replacement of the 2′-carboxylic acid group with a series of isosteric replacements singled out primary carboxamide **18** and tetrazole **19** (L-692,429), which provided an increased in vitro potency from the micromolar range to low nanomolar concentrations. On the other hand, acidic isosteres such as sulfonamides and acyl sulfonamides were found to be only micromolar in potency.[46] At this point L-692,429 (**19**) was nominated for participation in clinical trial studies, and has progressed as far as Phase I.[47] (Note: ED_{50} is defined as the effective dose at which a 50% maximal growth hormone response was achieved in vitro. EC_{50} is defined as the effective concentration at which 50% of maximal growth hormone release was induced.) A short time later, SAR studies conducted by chemists at Novo-Nordisk determined that other heterocycles without an acidic functionality were even more potent than **19** (e.g., **21**, **22** and *N*-methyltetrazole **20**), leading the researchers to conclude that the relevant ionic interaction with the receptor involved a hydrogen bond acceptor functionality on the drug molecule.[48] This makes intuitive sense that tetrazole **19**, being slightly less acidic than carboxylic functionality of **17**, would conversely be a better hydrogen bond acceptor. It was around this time that Merck researchers became aware of some serious problems with the oral bioavailability of candidate **19**, which was determined to be about 2% as studied in beagle dogs.[49] The acidic tetrazolic functionality in presence of a basic primary amine causes **19** to be zwitterionic in nature, resulting in poor oral absorption properties that contribute to low oral efficacy. Based on this complicating factor, ongoing work to develop appropriate functional group compatibility had concurrently identified the *N*-methylurea candidate **23** (L-739,943). This neutral compound was even more potent at 1 nM (GHRP-6 has a potency of 10 nM) and was found to have a greatly enhanced oral bioavailability of 24% (hexapeptide GHPR-6 has an availability by oral dose at less than 1%).[50] Ultimately, however, Merck has progressed the candidate MK-0677 (**24**; L-163,191; Ibutamoren Mesylate) into Phase II clinical studies for the treatment of growth hormone deficiency.[51] Based on the 'privileged structure' approach[52] to discover leads for G-protein coupled receptors, the researchers grafted the spiroindane moiety onto the peptide portion of **19**, resulting in the potent growth hormone secretagogue **24**. Oral dosing with MK-0677 was shown to elevate levels of growth hormone in dogs as low as 0.125 mg/kg, and its oral bioavailability was

estimated to be greater than 60%. Merck researchers attributed the excellent oral absorption of **24** to its lipophilicity (log $P = 3.0$ for **24** vs 2.5 for **19**) in combination with the good aqueous solubility of the mesylate salt.[53]

The next example will serve to showcase a representative pharmaceutical substance that contains an aliphatic tetrazolic acid. In the early 1970s, the pharmaceutical division of Fisons Limited published the discovery of FPL 55712 (**25**, Fig. 8),[54] a prototypical selective cysteinyl leukotriene D_4 (LTD_4) receptor antagonist. While the short half-life and poor bioavailability of **25** kept it from reaching clinical trials, it nevertheless set the stage for the ensuing flood of research efforts focused on the development of peptidomimetic antagonists as anti-asthmatic agents.[55] In the late 1980s, the then-ICI Pharmaceuticals group proposed the similarity between the endogenous ligand LTD_4 (**26**) and FPL 55712 was such that the chromone acid portion of **25** corresponded to the glycine terminus of **26** (rather than the aliphatic C1 carboxyl group),[56] an assertion which has more recently been confirmed experimentally.[57] This led to the development of several leukotriene antagonist analogues in which the hydroxyacetophenone moiety was tethered to terminal carboxylic acids, including **27**, which exhibited a much longer duration of action in vivo versus **25**. Researchers at the Lilly Research Labs synthesized **27** and had come to the same finding independently,[58] and took their SAR one step further to examine carboxylic isosteres, eventually identifying tetrazole L-171883 (**28**) as a potent antagonist in vitro and with excellent oral activity in vivo with guinea pigs.[59] The authors attributed the better activity of **28** in vitro (30 times more potent than **27**) to the better ability of the delocalized tetrazolic anion to interact with the arginine residue in the LTD_4 active site (vs the carboxylate). It is also interesting to compare the lipophilicities of the isosteric analogues, in which the log P of tetrazole **28** (2.8) is higher than the corresponding carboxylic acid **27** (2.4). This may have some bearing when keeping in mind that the pharmacophoric models built over the last decade have reflected both the importance of the acidic component of LTD_4 antagonists as well as the need for an overall lipophilic character.[57,60] Ultimately L-171883 (**28**) was chosen for clinical evaluation, and under the drug name Tomelukast it is currently in Phase III studies as an anti-asthmatic.[61,62] It is worth mentioning that the tetrazolic replacement approach has also been successful in at least one other LTD_4 antagonist research effort.[63]

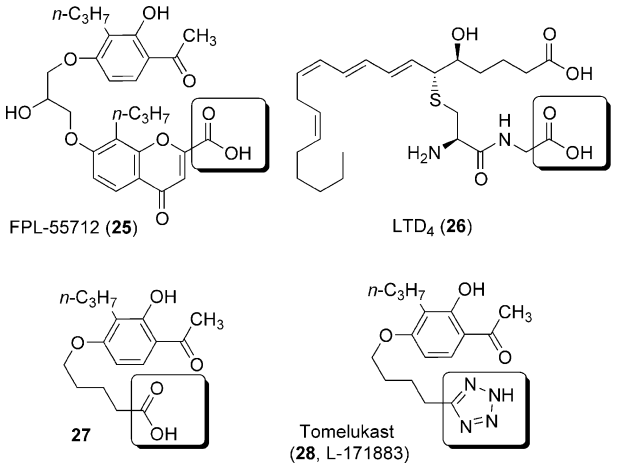


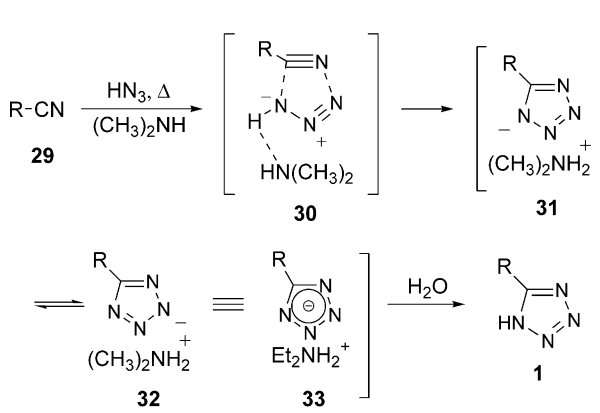
Figure 8. The tetrazole moiety of Tomelukast (**28**) mimics the cysteinylglycine terminus of growth hormone LTD_4 (**26**).

The text throughout the rest of this review will attempt to provide a representative survey of the most often-used literature procedures for the preparation of 5-substituted-1*H*-tetrazoles, focusing on preparations of tetrazolic acids from aryl and alkyl nitriles. A few other synthetic methods will be presented, including some very recent procedures involving carbon–carbon bond formations with 1-substituted 5-lithiotetrazoles, which show useful alternatives to the standard cycloaddition chemistry protocols.

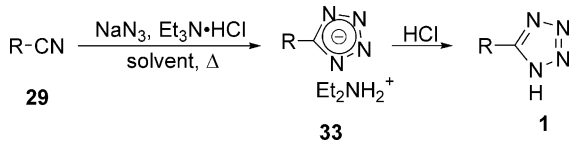
Early Synthetic Procedures Using Hydrazoic Acid

The earliest published methods for the preparation of 5-substituted tetrazoles were reactions of nitriles with azides.[64] In fact, the first method to appear in the literature was the reaction of hydrazoic acid (HN_3) with organic cyanides in 1932 (Scheme 1).[65] This process is generally thought to occur by a concerted 1,3-dipolar cycloaddition mechanism, in which nitrile **29** acts as the dipolarophile toward the azide, which serves as the 1,3-dipolar species (which may or may not be hydrogen-bonded with the amine).[66] Cycloaddition through **30** leads to the tautomeric tetrazolium anions **31** and **32**, which can simply be drawn as the delocalized resonance form **33**. Protonation of **33** upon workup provides the tetrazolic acid **1**. It should be mentioned that some evidence to support a two-step mechanism has also been reported.[67]

A great disadvantage to this procedure is that hydrazoic acid in organic solution is toxic and extremely explosive. Not many organic solvents are stable at the high temperatures that are necessary for this cycloaddition (sometimes as high as 130 °C), and for this reason DMF is most commonly used for this purpose.[4,6,66]



Scheme 1.

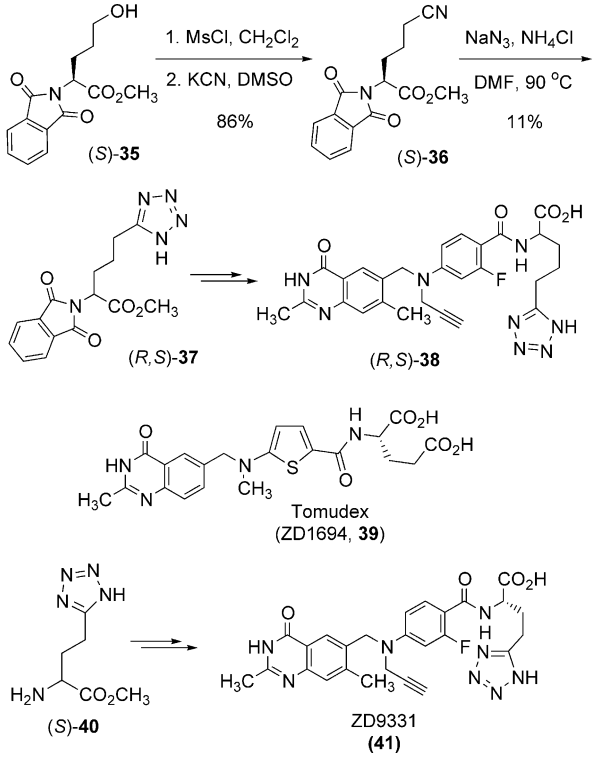


Scheme 2.

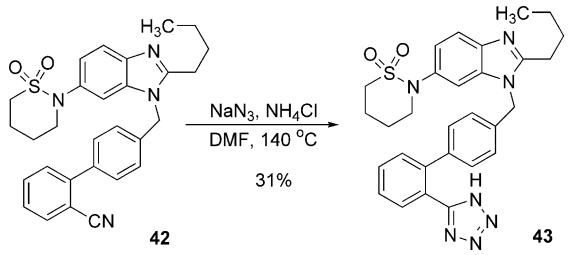
Metal Salt Methods Using Sodium Azide

Although many groups reported improved syntheses of 5-substituted tetrazolic acids from nitriles, it was really the work of Robert Lofquist that led to a practical procedure by in situ generation of hydrazoic acid from ammonium chloride and sodium azide (Scheme 2).[68] A process chemistry approach to the problem led these US Navy chemists to find that DMF and DMSO were the best solvents for the cyclization reaction. A host of other amine salts were investigated, leading the researchers to conclude that reaction temperatures lower than 130 °C at atmospheric pressure could be achieved when hydrazoic acid was generated from an ammonium azide. This 'gentle' acidic media procedure was more efficient than the older methods in which hydrazoic acid was used directly, and where high-pressure equipment or heating from four to seven days to reach completion were common.[68]

More recently, Bernstein and Vacek showed that a combination of sodium azide and triethylamine hydrochloride is useful when *N*-methylpyrrolidinone is used as a solvent.[69] Use of this higher-boiling solvent allowed the cycloaddition reaction for one particular substrate to be complete in 76% isolated yield after 3 h at 150 °C.



Scheme 3.



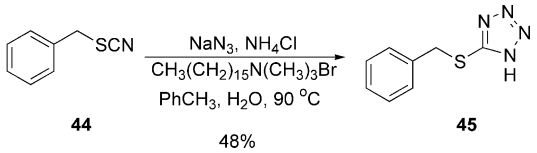
Scheme 4.

This is in comparison to the use of ammonium chloride in DMF, which provided only a 35% yield of the same product after heating at 125 °C for 96 h. A very recent paper has shown that aqueous micellar media may also serve as a method for preparation of aryl tetrazoles.[70]

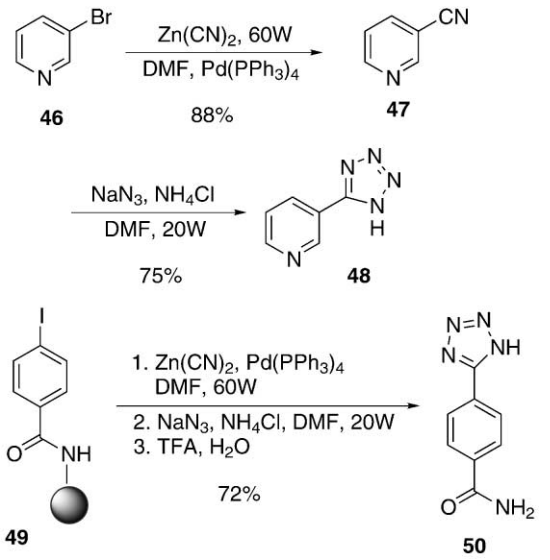
Recent examples of the ammonium azide method for the preparation of drug targets include the synthesis of **38** and **41**, which are analogues of AstraZeneca's Tomudex (**39**, Scheme 3).[71] These compounds were prepared in a program effort to identify peptide-based inhibitors of thymidylate synthase, and include replacement of the γ-carboxylic acid of the L-glutamate portion of **39** by a tetrazolic acid moiety (Scheme 3).[71] In this case, the conditions described by Grzonka and coworkers for tetrazole formation from nitrile **36** (90 °C in DMF for 16 h)[39c] were responsible for the complete racemization of the α-amino acid stereochemistry leading to a mixture of enantiomers **37**. In the end, the biological activity of this homologue was not interesting enough to justify a chiral resynthesis of **38**, or even to optimize the reaction yield. The L-glutamate-derived (*S*)-tetrazole analogue **40** was prepared by a similar method, but in this case the conditions used for tetrazole formation (reflux in THF for 72 h) did not racemize the amino acid stereochemistry. It is interesting to note that the enantiopure analogue ZD9331 (**41**), prepared from (*S*)-amino acid **40**, was found to have increased potency versus Tomudex (**39**) and is currently undergoing Phase II clinical development trials. The epimeric analogue of **41**, prepared from the antipode of **40**, was found to have diminished activity versus **39** and **41**.

Another example of the metal azide/ammonium salt combination method was published by chemists at the Dr. Karl Thomae GmbH in Germany. This synthesis required heating of the aryl nitrile **42** in DMF at 140 °C to provide synthetically useful amounts of the benzimidazole-based Losartan derivative **43** (Scheme 4).[72]

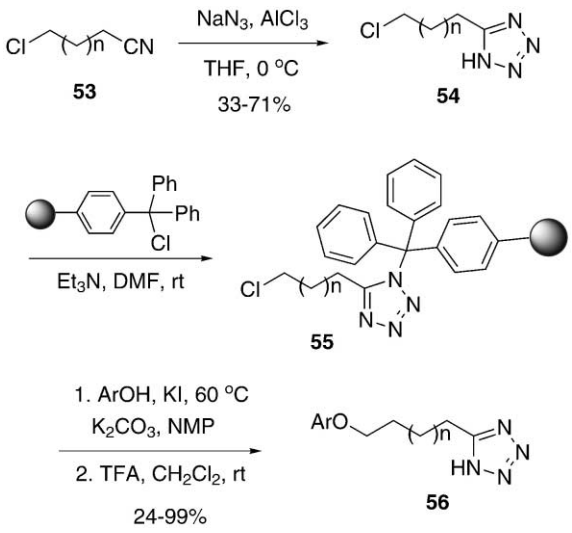
A recent paper by Jursic and LeBlanc has shown that the addition of a phase transfer catalyst improves the synthesis of 5-benzylthiotetrazoles **45** from benzyl thiocyanates **44** (Scheme 5).[73] In this case, hexadecyltrimethylammonium



Scheme 5.



Scheme 6.

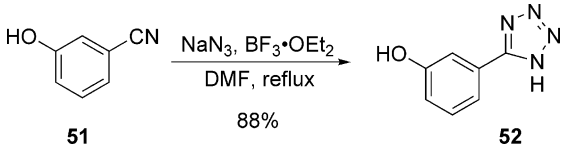


Scheme 8.

bromide was found to be the most useful catalyst. The authors point out that 5-alkylthio- and 5-arylthiotetrazoles are significantly better activators for RNA and DNA synthesis than the corresponding 5-aryltetrazoles, presumably due to the fact that the alkylsulfur moiety increases the acidity of the tetrazole proton.[74]

Alterman and Hallberg recently disclosed a report in which aryl and vinyl tetrazoles were prepared from nitriles using ammonium azide conditions in which microwaves were used as the energy source (Scheme 6).[75] A microwave-assisted palladium-catalyzed cross-coupling reaction between several aryl bromides and an organozinc reagent provided a series of aryl nitriles. Cycloaddition using sodium azide and ammonium chloride smoothly converted all of the aryl nitriles to the corresponding tetrazoles, most requiring no more than fifteen min of microwave irradiation time. Conversion of cyanopyridine **47** to the tetrazole **48** was achieved in 15 min in the same good yield as when the reaction mixture was heated at 90 °C for 7 h. A one-pot transformation of the solid support-bound 4-iodobenzamide **49** to the aryl tetrazole **50** was accomplished in good overall yield, with minimal decomposition of the resin.

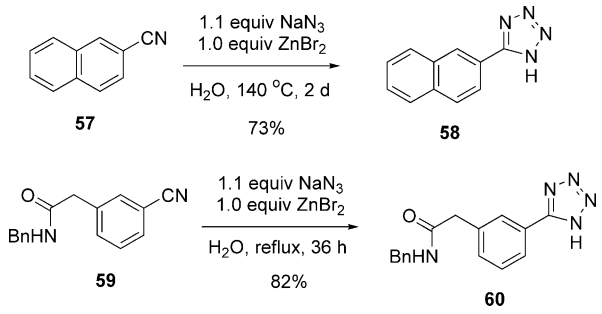
An interesting report by Shechter and coworkers described the preparation of a few simple 5-(hydroxyphenyl)tetrazoles by the reaction of aryl nitriles with sodium azide in the presence of boron trifluoride (Scheme 7).[76] This is one of the few examples in the literature by which a Lewis acid was used to generate a hydrazoic acid species in situ. In this example, 3-hydroxyphenylnitrile (**51**) was transformed into the 5-(3-hydroxy)phenyltetrazole (**52**) in excellent yield, as was the case for the 2- and 4-hydroxyphenyl precursors.



Scheme 7.

A recent publication described the use of aluminum chloride as a Lewis acid catalyst for the generation of aliphatic tetrazoles **54** from a series of nitriles **53** (Scheme 8).[77] The crude products were protected as resin-bound trityl derivatives **55**, which were subjected to alkylation followed by cleavage from the solid support to generate pure alkyl tetrazole derivatives **56**. This parallel synthesis method was then extended to assemble a sample library of 5 × 6 compounds.

One of the most notable contemporary advances in tetrazolic acid synthesis was published by Demko and Sharpless at the end of 2001, in which a method was described for the assembly of tetrazoles from nitriles in water as a solvent (Scheme 9).[78] This method utilizes a 1:1 ratio of sodium azide and zinc(II) bromide as reagents, and is run at temperatures ranging from reflux to 170 °C. Electron poor aromatic nitriles reach completion at reflux after a few days, whereas electron-rich aromatic species and unactivated aliphatic nitriles require higher temperatures with the use of a sealed glass pressure reactor. Nevertheless, the protocol minimizes the risk of liberating hydrazoic acid, and usually a simple acidification is all that is necessary to provide the pure tetrazole products. The

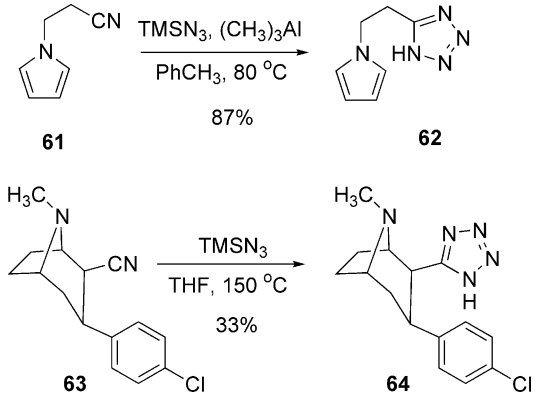


Scheme 9.

authors are hopeful that the ease of use will make this method amenable to both laboratory and industrial scales.

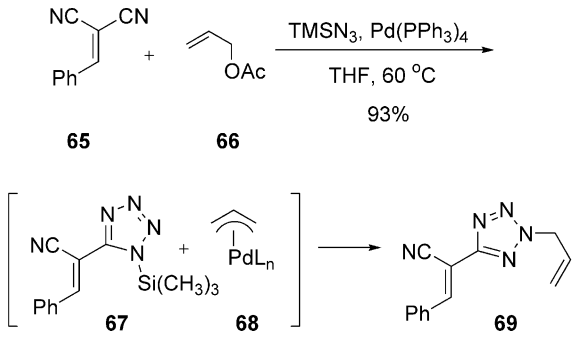
Tin- and Silicon-Mediated Methods

Some of the newer methods for the preparation of 5-substituted tetrazolic acids involve the reaction of alkyl- or arylnitriles with safer organic soluble azide reagents such as trialkyltin azide or trimethylsilyl azide.[4,6] A method using trimethylsilyl azide was recently described by Lilly chemists Huff and Staszak, who showed that an equimolar mixture of trimethylaluminum and trimethylsilyl azide in hot toluene was very effective at producing 5-substituted tetrazole **62** from nitrile **61** in a yield comparable to the sodium azide phase-transfer method (Scheme 10).[79] Carroll and coworkers used azidotrimethylsilane for their preparation of heterocyclic tropane **64** in a synthetically useful amount at 150 °C in a sealed container.[80]

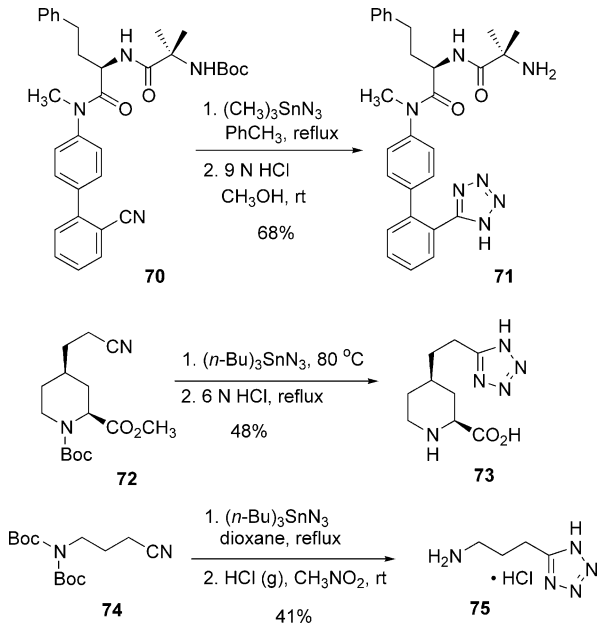


Scheme 10.

Yamamoto and coworkers recently published a method for the regioselective preparation of 2,5-disubstituted tetrazole **69** from the reaction of nitrile **65** with allylic acetate (**66**) in the presence of azidotrimethylsilane with a palladium(0) catalyst (Scheme 11).[81] Presumably the intermediate *N*-silyl tetrazole **67**, derived from the reaction between nitrile **65** and azide, was reacted in situ with the π-allylpalladium species **68** to provide the *N*-allylated product **69**. Although the relative 2,5-substitution of **69** was confirmed by X-ray crystallographic analysis, an explanation for this exclusive regioselectivity was not proposed by the authors.

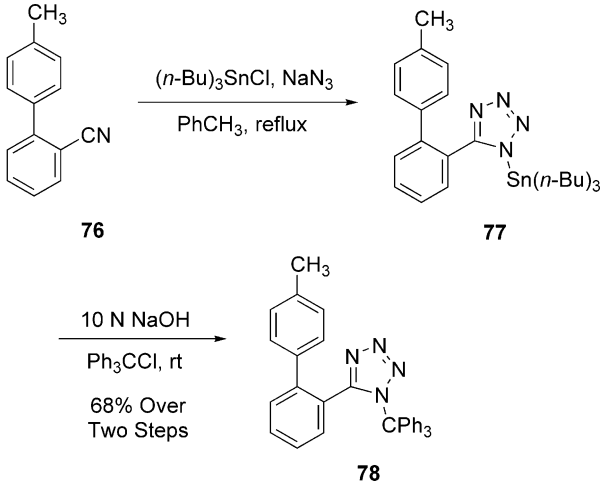


Scheme 11.



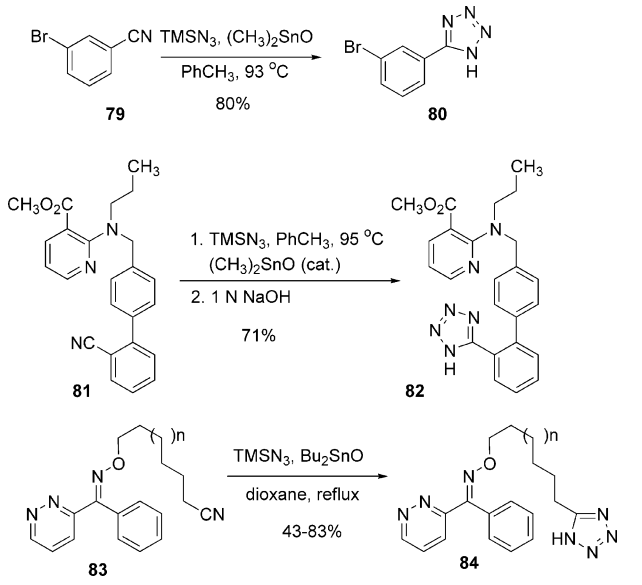
Scheme 12.

Methods for tetrazole formation from organic nitriles using the organic-soluble reagents trimethylstannyl azide[82] or tri-*n*-butylstannyl azide[83] seem to be more commonly utilized than the sodium azide/amine salt protocols (Scheme 12). While this procedure generates one molar equivalent of hazardous tin byproduct (which may present purification problems later on), better yields are generally found when directly compared to silicon-based azide reagents. The conditions typically require the use of one equivalent of trialkyltin azide in refluxing THF, toluene, 1,4-dioxane or xylenes. A separate acidic hydrolysis step is then required to remove the tin group from the tetrazole ring.

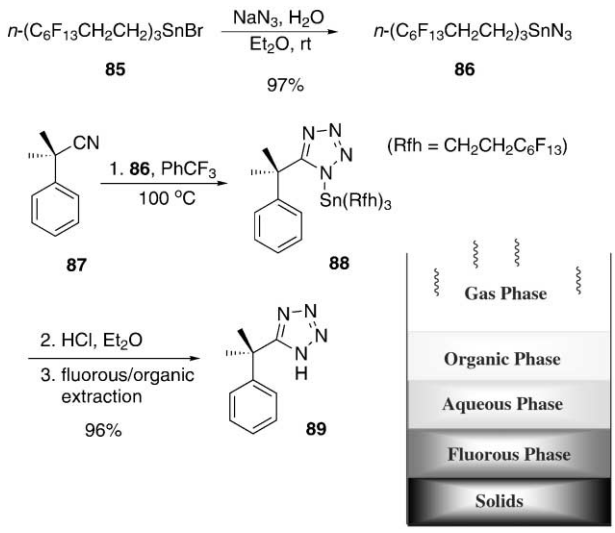


Scheme 13.

DuPont chemists Carini and Duncia have also shown that trialkylstannyl azide reagents may be generated in situ by the reaction of trialkyltin chlorides with sodium azide (Scheme 13).[40b] These reagents in refluxing toluene with biphenyl nitrile **76** provided the



Scheme 14.



Scheme 15.

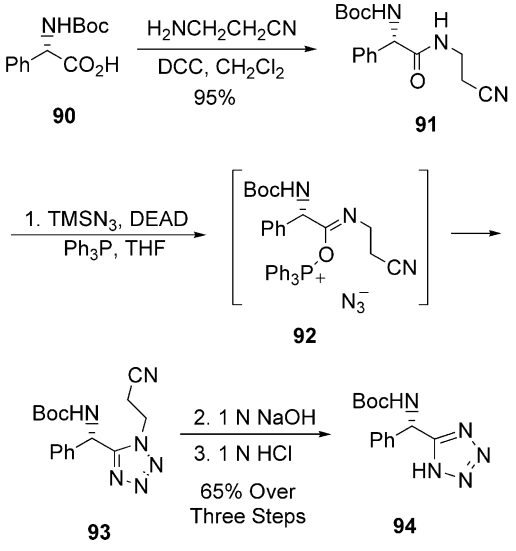
N-stannyl tetrazole **77**, which was subjected to aqueous sodium hydroxide in a separate step to remove the tin moiety. When the hydrolysis was done in the presence of triphenylmethyl chloride, the resulting tetrazole was isolated as the trityl adduct **78**, which was more easily purified than the free tetrazolic acid. This protected intermediate **78** was then used for further chemistry and unmasked at later stages, leading to a separate series of novel Losartan derivatives. (It should be noted that the *N*-substituted tetrazole structures **77** and **78** are representations of equimolar mixtures of N-1 and N-2 regioisomers.)

Abbott Laboratories chemists Wittenberger and Donner showed that azidotrimethylsilane with a catalytic amount of dimethyltin oxide was useful for the transformation of nitriles to tetrazoles, as in the example of **79** to **80** (Scheme 14).[84] This mixture generates small amounts of the more reactive trialkyltin species in situ, eliminating the need to use an equimolar amount of the volatile and toxic reagent azidotrimethylstannane. This process chemistry team then applied their method toward the preparation of multi-gram quantities of the biphenyl tetrazole **82** (from the biphenyl substrate **81**), a precursor to an angiotensin II antagonist, in excellent yield.[85] The research groups of Rakowitz and Costantiono have recently reported the use of this method to prepare a series of aliphatic tetrazoles **84** as inhibitors of aldose reductase.[86]

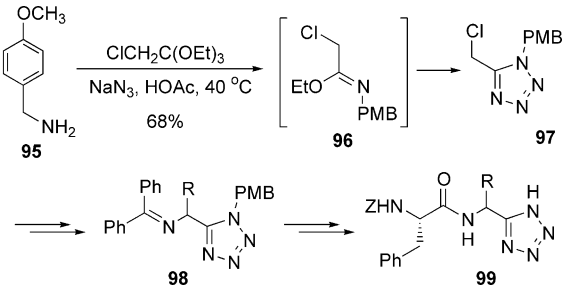
Curran and coworkers have recently applied fluorous technology to the preparation of 5-substituted tetrazoles such as **89** (Scheme 15).[87] The new tin reagent Tris(2-perfluorohexylethyl)tin azide (**86**) was readily prepared from the stannyl bromide **85** and was subjected to cyclization reactions with an organic nitrile such as **87**. Following acidic hydrolysis of the stannyl tetrazole **88** (actually a mixture of N-1 and N-2 regioisomers), a fluorous/organic (liquid/liquid) extraction purification was used to isolate the pure organic tetrazole **89**, leaving the fluorous tin chloride byproduct in the fluorous solvent layer for later recovery and reuse.

Other Methods

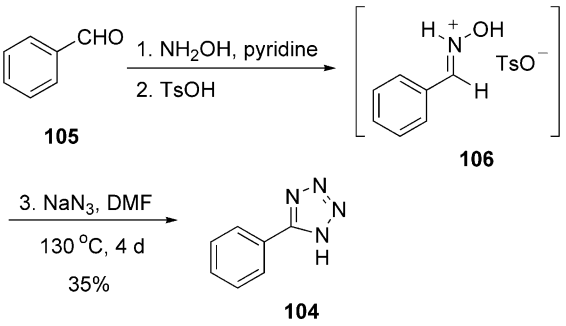
Several reports have appeared which make use of precursors other than nitriles to prepare 5-substituted-1*H*-tetrazoles. One procedure utilized the Mitsunobu protocol to affect the formation of phosphonium imidate **92** from *N*-(cyanoethyl)amide **91**, which then underwent reaction with azidotrimethylsilane to provide *N*-protected tetrazole **93** (Scheme 16).[88] In this case, only the N-1 regioisomer is obtained. A novel component of this transformation is that the nitrile-containing protecting group does not seem to react with the azide under these conditions. Removal of the *N*-cyanoethyl moiety of **93** with aqueous sodium hydroxide, followed by acidification, led to the free tetrazole **94** in good overall yield. The authors also pointed out that no racemization at the chiral center was observed. In a similar case the deprotection step was achieved as part of the aqueous workup of the reaction, leading to a one-



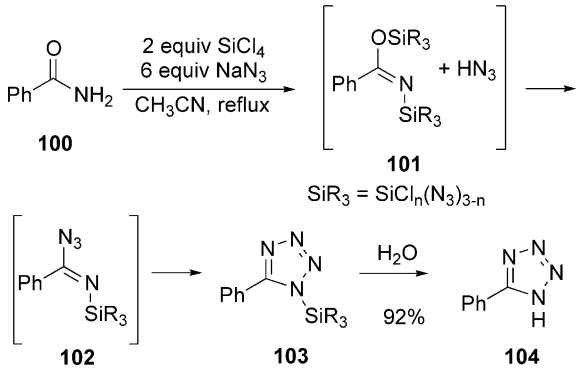
Scheme 16.



Scheme 17.



Scheme 19.



Scheme 18.

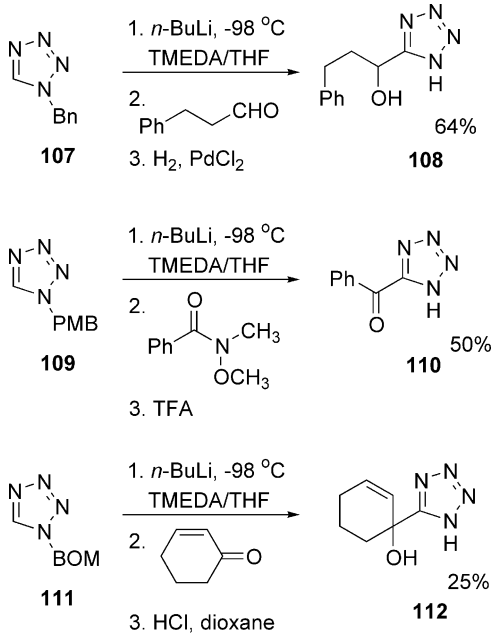
pot preparation of the tetrazole from the *N*-(cyanoethyl)amide.[40d]

Novartis chemists Satoh and coworkers recently published a method for the preparation of a useful chloromethyl tetrazole synthon **97**, which was ultimately utilized for the synthesis of tetrazole analogues of amino acid **99** (Scheme 17).[89] Formation of imidate **96** by the condensation of *p*-methoxybenzylamine (**95**) with 2-chloro-1,1,1-triethoxyethane in hot acetic acid was followed by in situ cycloaddition with sodium azide to form the *N*-protected tetrazole **97** in good yield. This reagent was used for the preparation of the racemic N-terminal protected amino acid **99** after removal of the *p*-methoxybenzyl moiety.

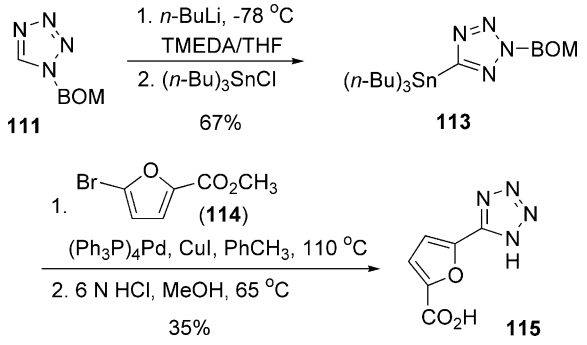
Mansoura University researchers in Egypt have recently shown that simple benzamides such as **100** may be converted to 5-substituted-1*H*-tetrazolic acids using triazidochlorosilane (Scheme 18).[90] The authors believe this transformation may be explained by the in situ formation of an azidochlorosilane species, represented as $SiCl_n(N_3)_{3-n}$, from tetrachlorosilane and sodium azide in a 1:3 ratio, respectively. In this example the azidosilane reagent forms *N,O*-bis silyl imidate **101**, which in turn reacts with an equivalent of hydrazoic acid that is generated in the process. The intermediate imidoyl azide **102** tautomerizes to *N*-silyl tetrazole **103** (presumably as this N-1 regioisomer), which is hydrolyzed in the workup to provide **104**. It is interesting to note that this reagent apparently does not react with the acetonitrile solvent.

A useful process for the preparation of 5-substituted-1*H*-tetrazole **104** from sodium azide and oxime salt **106** was developed by Antonowa and Hauptmann (Scheme 19).[91] In this fashion, benzaldehyde (**105**) may be directly transformed into the corresponding aryl tetrazole **104**, albeit under somewhat forcing conditions.[92]

The two final methods to be described take advantage of the reactivity of the unsubstituted C-5 carbon when the tetrazolic acid functionality is protected (Scheme 20). Novartis chemists Satoh and coworkers reported a process in which lithiation of *N*-benzyl tetrazole (**107**) or *N*-(*p*-methoxybenzyl)tetrazole (**109**) at −98 °C with *n*-butyllithium was followed by a quench with an electrophile. The homologated intermediate was then deprotected by either hydrogenolysis, by treatment with trifluoroacetic acid or by ceric ammonium nitrate oxidation to provide a 5-substituted-1*H*-tetrazole (e.g., **108** and **110**).[93] This transformation could also be achieved with lithiation of *N*-benzyloxymethyltetrazole (**111**) to provide homologated tetrazole **112** after deprotection by hydrogenolysis.[94] The benzyloxymethyl protecting group may also be removed by treatment with anhydrous hydrochloric acid.



Scheme 20.



Scheme 21.

Bookser more recently expanded on this idea by quenching 5-lithiated **111** with tri-*n*-butyltin chloride to provide the stannyl tetrazole **113** (Scheme 21).[95] This synthon was then coupled with a variety of aryl halides under copper-catalyzed Stille conditions to provide several aryl tetrazoles, after hydrolytic removal of the benzyloxymethyl group. In this case, palladium-catalyzed cross coupling reaction of **113** with methyl 5-bromo-2-furoate (**114**) was followed by treatment with anhydrous acid to provide the carboxylic acid **115** in good yield for the two-step process.

Conclusion

This review has provided a summary of the physicochemical and pharmacological aspects of 5-substituted-1*H*-tetrazoles, which have found common usage as an isosteric replacement for the carboxylic acid moiety in recent years. Tetrazoles are metabolically resistant to many of the biological transformations that the carboxylic acid functionality is susceptible to in the liver, although recent research studies (including two reviews[28]) show that the main mode of biological clearance of tetrazoles follows from *N*-glucuronidation and biliary excretion. Some prodrug approaches to tetrazole drugs have been implemented to improve oral bioavailability, a practice which may find more applications in the future. Three examples were chosen from the literature to showcase the development of drug substances which have resulted from the use of this non-classical isosteric replacement tactic in a few drug discovery programs. While some successes have been shown, one should exercise caution when making an analogue substitution of this type, as this seemingly subtle change can have a dramatic but unpredictable effect on biological activity.

A survey of representative literature procedures for the synthesis of 5-substituted-1*H*-tetrazoles has been offered, concentrating on preparations of tetrazolic acids from aryl and alkyl nitriles. Overall, organic chemists have tended toward procedures utilizing trialkyltin azides, which consistently seem to provide higher yields in comparison to ammonium chloride/sodium azide combination methods. Some of the more recent adaptations that use catalytic amounts of tin reagents with azidotrimethylsilane should probably gain favor within process chemistry arenas for concerns of safety and toxic waste minimization. The protocol recently described by Demko and Sharpless for making tetrazoles in water is especially notable for the same reason. Other synthetic methods have also been described, including some very recent procedures involving carbon–carbon bond formations with 1-substituted-5-lithiotetrazoles, which show that useful alternatives to cycloaddition chemistry are available.

Acknowledgements

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