Cycloaddition

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1,3-Dipolar Cycloaddition: Click Chemistry for the Synthesis of 5-Substituted Tetrazoles from Organoaluminum Azides and Nitriles**

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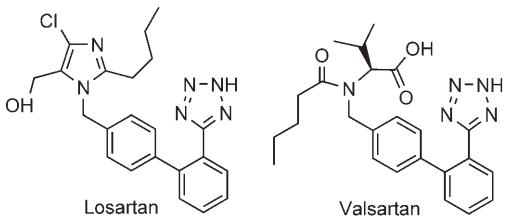
Dedicated to Professor Horst Prinzbach

Tetrazoles are a class of heterocycles with a wide range of applications that are receiving considerable attention.[1,2] This functional group has a role in coordination chemistry[3] as well as in various materials science applications, including photography,[1] and specialty explosives.[4] Moreover, extensive work has been carried out in the field of medicinal chemistry.[5] Tetrazoles are frequently used as metabolically stable surrogates for carboxylic acids,[6] as the tetrazoles generally offer a more favorable pharmacokinetic profile.[1,7] Driven in particular by the widespread incorporation of the tetrazole functionality into angiotensin II antagonist structures (sartans, Scheme 1), several methods have been described for the synthesis of tetrazoles.[8c,9]



Scheme 1. Sartans.

The first reported method to synthesize tetrazoles was the reaction of hydrazoic acid (HN_3) with organic cyanides in 1932.[10] However, this procedure has not found practical application on account of the high toxicity, explosive nature, and low boiling point (37 °C) of hydrazoic acid. Currently, 5-substituted tetrazoles are usually obtained by the addition of azide salts to nitriles (typically at 100–150 °C).[5,8,11] Unfortunately, all of these protocols have disadvantages, including the use of toxic metals, expensive reagents, and harsh reaction conditions; water sensitivity; and the presence of dangerous hydrazoic acid. In addition, the majority of methods use dipolar aprotic solvents such as DMF. One of the most common methods involves the use of sodium azide in the presence of ammonium chloride or tertiary ammonium chloride to form ammonium azide species in situ.[12–14] The reaction is accompanied by the sublimation of explosive NH_4N_3.[15] Trimethylsilyl and trialkyl tin azides are alternative general reagents.[5,8d,16] In some cases, full conversion can only be obtained with a large excess of azide and harsh reaction conditions. The major drawback of this method is the difficult removal of highly toxic residual organotin compounds at the end of the reaction.[17] Organostannane catalysts are also often used;[8d,17–19] however, it is difficult to completely separate the desired product from the stannane compounds. Aluminum azide was reported by Wiberg and Michaud in 1957.[20] However, during the workup, two moles of HN_3 are formed for every mole of product. Huff proposed a procedure in 1993 using equimolar amounts of trimethylsilyl azide activated by trimethylaluminum, but strongly hindered nitriles resulted in poor conversion.[8b,21] Sharpless and coworkers recently introduced the term "click chemistry" as a chemical philosophy that uses only the most practical and reliable chemical transformations.[22a] They have reported the preparation of tetrazoles in water requiring stoichiometric amounts of Zn^{II} salts.[22] In the case of sterically hindered aromatic or deactivated alkyl nitriles, high temperature (140–170 °C) and long reaction times are required.

During our investigation of alternative syntheses of sartan derivatives, we became interested in finding an alternative safe process for the preparation of tetrazoles on an industrial scale. We report herein the discovery and development of a novel process for the efficient transformation of a wide variety of nitriles into the corresponding tetrazoles using dialkyl aluminum azides. Diethylaluminum azide[23] is already known as an activated azide donor for the conversion of esters to acylazides,[24] ring opening of epoxyalcohols, and triazole formation from α′-amino-α,β-unsaturated ketones[25] but has never been employed in the synthesis of tetrazoles. We have now found that organic aluminum azides are effective reagents for the direct conversion of nitriles to tetrazoles (Scheme 2).[26]

The differential scanning calorimetry (DSC) scans of dialkyl aluminum azides are comparable to that of tributyltin azide in terms of safety margins.[27] The aluminum reagents can be prepared in a short time (Scheme 2) by addition of an equimolecular amount of dialkyl aluminum chloride to

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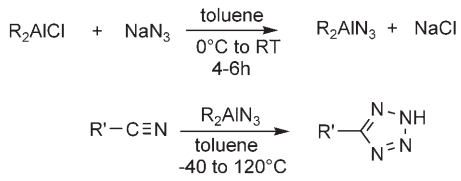
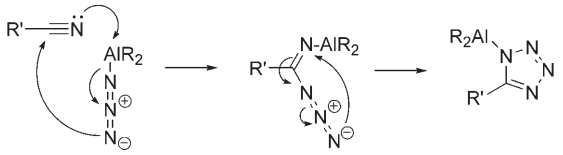


Scheme 2. [2+3] Cycloaddition route to tetrazoles.

sodium azide in an aprotic organic solvent, such as toluene, xylene, or hexane.[24,26] The alkyl residues (R) can be branched (isobutyl) or linear (methyl or ethyl). During the cycloaddition, no byproducts are observed; the reaction takes place rapidly and produces the desired tetrazole in excellent yield and with a simple workup procedure, and the product can easily be isolated in excellent purity. Although the mechanism is not yet established, we suggest that the aluminum center acts as a Lewis acid, activating the nitrile for azide addition (Scheme 3).

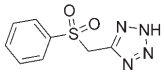
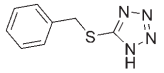
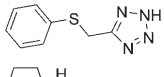
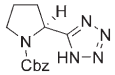
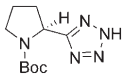
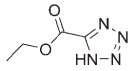
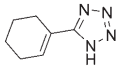
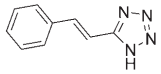
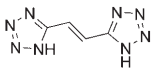
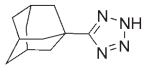
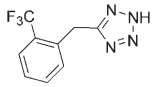
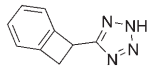
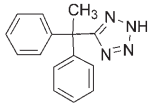
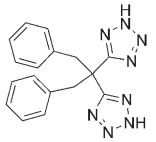
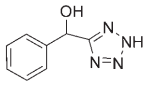
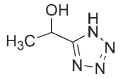


Scheme 3. Two-step mechanism for the formation of tetrazoles.

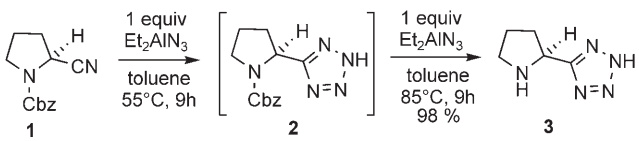
The reaction temperature can be selected from a wide range (−40–120 °C), depending on the reactivity of the substrates. An excess of dialkyl aluminum azide (1–3 equiv) is used, which is safely destroyed by quenching with sodium hydroxide and sodium nitrite and subsequent acidification with hydrochloric acid, which destroys the hydrazoic acid formed.[28] Acidification (pH 2) removes the aluminum salts, which are water-soluble. Basic extraction of the tetrazole derivative separates the starting nitrile, and re-acidification affords the pure product.

Deactivated and sterically hindered alkyl nitriles require relatively high temperatures and long reaction times (Table 1, entries 7, 10, 12, 13), but with electron-withdrawing substituents in the α-position, temperature and reaction time can be much lower (Table 1, entries 1, 2, 11, 15, 16). Alkyl nitriles with an α-hydroxy group react at a lower temperature, although it is necessary to protect the hydroxy group with triethylaluminum, which is removed during the conventional workup procedure (Table 1, entry 15, 16). α,β-unsaturated vinyl nitriles are relatively good substrates; the cyclohexene-1-carbonitrile (Table 1, entry 7) requires a higher temperature than cinnamonitrile (Table 1, entry 8). Fumaronitrile provides the corresponding tetrazole after just 90 min at room temperature (Table 1, entry 9). Protecting groups like *tert*-butoxycarbonyl (Boc) and benzyloxycarbonyl (Cbz) require mild reaction conditions (Table 1, entry 4, 5). Both enantiomers of **2** (see Scheme 4 and Table 1, entry 4) were prepared for the first time under very mild conditions in nine hours at 50 °C in excellent yield (96 %), and the preparation of the *R* enantiomer was scaled up to 1.5 kg with very good reprodu-

Table 1: Synthesis of 5-substituted tetrazoles.

Entry	*T* [°C]	*t* [h]	Product	Yield [%]
1[a]	55	3		76
2[a]	45	4.5		46
3[a]	55	30		86
4[b]	50	9		96
5[c]	40	30		57
6[a]	RT	1		94
7[a]	90	20		65
8[b]	50–70	18		97
9[b]	RT	1.5		49
10[a]	90–110	72		82
11[a,e]	65	17		80
12[d]	70	49		64
13[b]	85 to 120	18		45
14[b]	75	18		87
15[b,f]	45	1.3		82
16[b,f]	0 to RT	24		65

[a] Et_2AlN_3 in toluene (2.5 M). [b] Et_2AlN_3 in xylene (2.7 M). [c] Et_2AlN_3 in toluene (2.5 M), workup with $KHSO_4$ to pH 5. [d] Et_2AlN_3 in toluene (1.8 M). [e] Me_2AlN_3 in hexane (1 M). [f] i) Et_3Al in toluene (1.8 M) 0–RT, 2 h; ii) Et_2AlN_3 in toluene (2.5 M).



Scheme 4. One-pot reaction for the preparation of 1*H*-tetrazol-5-yl pyrrolidine.

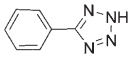
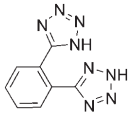
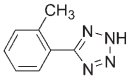
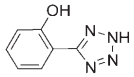
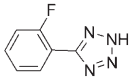
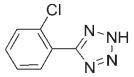
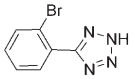
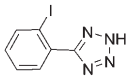
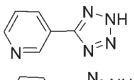
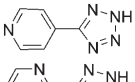
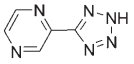
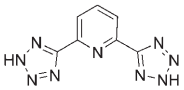
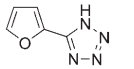
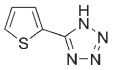
cibility.[26b] The Boc analogue (Table 1, entry 5) is formed with the same reaction conditions, but the acidic workup partially cleaves the Boc group to give the unprotected pyrrolidine tetrazole **3**. This 5-(pyrrolidin-2-yl)-tetrazole is an interesting alternative to proline[29] as an organocatalyst for a variety of reactions including aldol, Mannich, and Diels–Alder reactions as well as Michael additions.[30]

The pyrrolidine tetrazole **3**[31] can be directly obtained in a one-pot reaction with an excess of dialkyl aluminum azide to provide first the cycloaddition and then the cleavage product by warming the reaction mixture at temperatures over 65 °C (Scheme 4).[25b] Although the purity of **3** is high according to NMR spectroscopy, broad peaks detected by IR spectroscopy suggest the presence of water-soluble inorganic materials that are difficult to remove.

Aromatic nitriles are also suitable substrates for this methodology. At a given temperature, heteroaromatic and heteroatom-substituted aromatic nitriles require shorter reaction times than benzonitrile (Table 2 entry 1). For example, 2-hydroxybenzonitrile (Table 2, entry 4) is converted to the corresponding tetrazole in 2 h instead of 24 h. In this case, again, it is necessary to protect the hydroxy group. The reaction proceeds well in the case of *ortho*-substituted aryl nitriles for which steric hindrance might be anticipated to reduce yield (Table 2, entries 3–8). Reactions of *ortho*-halogen-substituted aromatic nitriles (Table 2, entries 5–8) reach completion within thirty hours at 50 °C. The *ortho*-fluoro, -chloro and -bromo benzonitriles have comparable reactivities, whereas the more sterically hindered *ortho*-iodo benzonitrile predictably takes longer (3 days) to undergo complete conversion. Our method is complementary to that proposed by Sharpless and co-workers,[22] as we have been able to achieve good yields (83 %) of aromatic nitriles bearing an sp^3-hybridized substituent in the challenging *ortho* position (Table 2, entry 3). Further electron-poor heteroaromatic nitriles such as pyridinecarbonitriles and cyanopyrazine give the corresponding tetrazoles in a few hours at low temperature with good yields (Table 2, entries 9–12). Excellent results were also obtained with the heteroaromatic nitriles 2-furancarbonitrile and 2-thiophene carbonitrile (Table 2, entries 13, 14), which have similar reactivities and give the corresponding tetrazoles in 12 h at 55 °C in very good yields.

In conclusion, this new, efficient process offers several advantages over many of the previously published procedures, including reduced environmental impact resulting from the elimination of toxic waste. The use of dialkyl aluminum azides as an azide source greatly reduces the hazard posed by in situ generation of hydrazoic acid and avoids ammonium and alkyl ammonium azide formation. The reaction is suitable for use on a large scale, as special care is not required when recycling wastewater, because aluminum is far less toxic than organometallic tin compounds. As dialkyl aluminum chlorides are available in large quantities and are relatively inexpensive, the reaction is also economically attractive. Dialkyl aluminum azides are prepared in a short time (4–8 h, RT),[24,26] are soluble in organic solvents, are cheap, and are nontoxic. The cycloaddition occurs under mild conditions, and it is possible to synthesize a broad variety of tetrazoles in the presence of different functional groups. Because of the low

Table 2: Synthesis of aromatic tetrazoles.

Entry	*T* [°C]	*t* [h]	Product	Yield [%]
1[a]	80	24		99
2[a]	90	3		75
3[a]	80	25		83
4[a,b]	80	2.5		97
5	90[a] 55[a]	7 30		95
6[a]	50	27		95
7[a,c]	50	30		71
8[a]	50	72		85
9[a]	0 to RT	3		78
10[a]	0 to RT	3		95
11[d]	−40 to 0	3		64
12[a]	0	1		84
13[a]	55	12		87
14[a]	55	12		81

[a] Et_2AlN_3 in xylene (2.7 M). [b] i) Et_3Al in toluene (1.8 M), 0 °C to RT, 2 h; ii) Et_2AlN_3 in toluene (2.5 M). [c] Me_2AlN_3 in hexane (1 M). [d] iBu_2AlN_3 in toluene (1.8 M).

pK_a value of tetrazoles (approximately 3–5) and their highly crystalline nature, a simple workup procedure is usually sufficient to provide the pure tetrazoles. The high reactivity, low cost, and ecocompatibility of aluminum make this novel process particularly attractive for large-scale preparation. Therefore, the discovery and the development of this new methodology for the preparation of tetrazoles is significant with respect to safety, economy, ecology, and diversity of substrates.

Experimental Section

An oven-dried flask was charged with sodium azide (5.46 g, 84 mmol) and diethylaluminum chloride (46.7 mL, 84 mmol, 2.7 M in toluene) at 0 °C under argon or nitrogen and stirred for 15 min. The white,

heterogeneous mixture was then warmed to room temperature and stirred for 4–6 hours. During the formation of the reagent, a suspension of sodium chloride was formed. Phenylsulphonyl acetonitrile (10.87 g, 60 mmol) was added at room temperature in two portions. The mixture was gradually heated to 55 °C (external temperature) and stirred for two hours. When HPLC and TLC analysis showed greater than 98 % conversion, the reaction mixture was cooled to 0 °C and added to a solution of NaOH (15 %, 67 mL, 252 mmol) containing sodium nitrite (17.38 g, 252 mmol; solution pH 13.5). The pH value was adjusted to 1.5 with HCl (6 M). The solution was extracted with ethyl acetate (3 × 20 mL) to afford the crude product (13.0 g), which was redissolved in ethyl acetate (30 mL) and extracted with aqueous potassium carbonate (10 %, 3 × 25 mL) to the aqueous phase as the potassium salt (pH 11). The combined basic aqueous phase was cooled to 0 °C and carefully treated with HCl (6 M) to adjust the pH value to 2.5. The product was extracted with ethyl acetate (3 × 20 mL) and crystallized from ethyl acetate/toluene to give 5-phenylsulfonylmethyl)-1*H*-tetrazole (10.23 g, 76 %; Table 1, entry 1). More details and analytical data are provided in the Supporting Information. The yields given in Tables 1 and 2 are not optimized.

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