Novel Synthesis of 5-Substituted Tetrazoles from Nitriles

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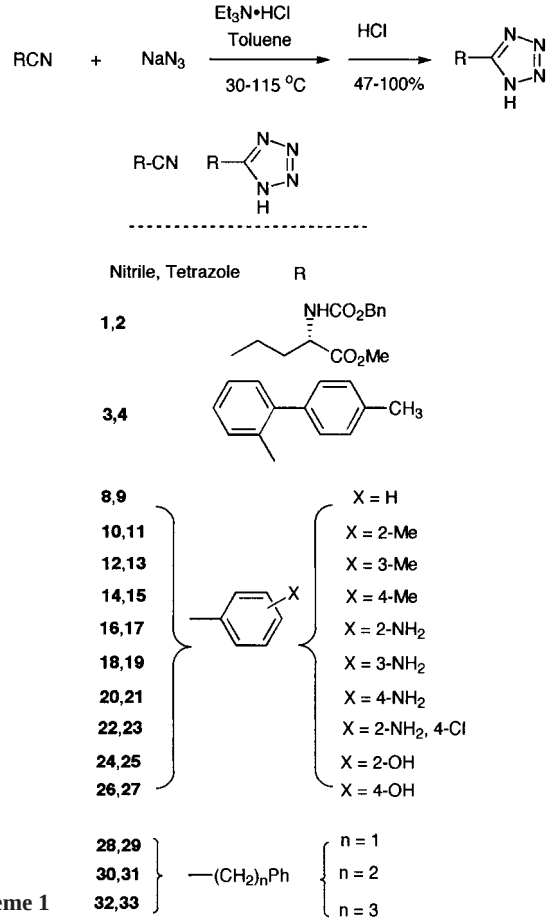
Abstract: A variety of 5-substituted tetrazoles were prepared through the respective reactions of sodium azide with corresponding nitriles in an aromatic solvent in the presence of an amine salt.

Key words: tetrazoles, aromatic hydrocarbons, azides, triethylamine, amine salts

Tetrazole derivatives have attracted much attention as raw materials for medicine, agricultural chemicals, foaming agents, and in the automobile inflator industry.[1, 2] Especially in recent years, remarkable related developments have been made in the medicinal field.[3, 4] Yet in order to use tetrazole compounds as starting materials in the fine chemicals field, compounds with high quality polyfunctional structures are required. However, a versatile method for synthesizing many kinds of tetrazoles through safe and simple manipulation had not been developed. We report here the novel synthesis of 5-substituted tetrazole derivatives of high purity, which can be applied to the synthesis of tetrazoles having polyfunctional groups (Scheme 1).

Until now, several methods for the synthesis of tetrazoles have been reported. However, these conventional methods for the synthesis of tetrazoles have several disadvantages. For example, the synthetic method that uses amine salts in dimethylformamide (DMF)[5–7] is laborious, due to the formation of byproducts, and the method is applicable only to the synthesis of tetrazoles starting from simple nitriles. The synthetic method using NH_4Cl in DMF[8, 9] also has disadvantages, in that the reaction is accompanied by the sublimation of explosive NH_4N_3, which is highly dangerous. The sublimation of explosive NH_4N_3 also occurs when aprotic polar solvents instead of DMF are used for the reaction. Although there is another conventional method that uses acid for the synthesis of tetrazole,[10] the reaction proceeds relatively slow at room temperature, while the reaction at high temperature produces many byproducts, resulting in low yields of the desired products. This method is also dangerous due to the production of poisonous and explosive HN_3. Aromatic solvents and organostannane catalysts are often used for the preparation of tetrazole compounds having polyfunctional groups from the respective nitriles.[3, 11–13] However, it is often difficult to completely separate the desired tetrazole from the stannane compounds, even though the stannane compounds used in these reactions are generally highly toxic.

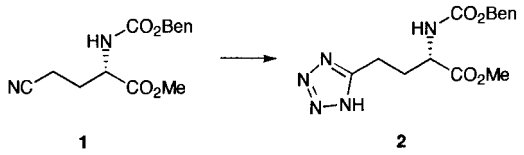
We have developed a novel synthetic method that is free from the above described problems. The method involves the reaction of a nitrile with an inorganic azide, using an amine salt in an aromatic solvent in a facile workup procedure, to produce tetrazoles with higher purity in greater yield. With the novel synthetic method we devised, nitriles with simple or complicated structures can be converted to 5-substituted tetrazoles by using the combination of readily available reagents. Our method has several advantages: the reaction produces no byproducts due to side reaction, the reaction takes place rapidly, and produces the products in excellent yield. Another characteristic is its simple workup procedures, through which products of excellent purity can be easily isolated. Moreover, the amines and solvents used in the method can be recycled without additional troublesome treatment.



Scheme 1

We attempted the synthesis of methyl (2*S*)-2-(benzyloxycarbonylamino)-4-(tetrazol-5-yl)butyrate (**2**). First, we attempted the reaction using triethylamine hydrochloride (Et_3N•HCl) in DMF. We confirmed, however, that the methyl (2*S*)-2-(benzyloxycarbonylamino)-4-cyanobutyrate (**1**) did not react with NaN_3 to produce **2**. Although this is a versatile method depending on the structure of the

nitrile, the troublesome formation of byproducts is often observed. Second, we employed the method of synthesizing the tetrazole using organostannane compounds in an organic solvent.[3,11] In this method, the production of tetrazole was facilitated by the increasing solubility of the azide through complex formation with the organostannane. As a result, **1** reacted with NaN_3 to produce **2**. Disappointingly, however, it was difficult to isolate **2** in a pure form from the remaining residue containing the organostannane compound. Generally, organostannane compounds have high toxicity, so they must be handled with caution. Since complete removal of the remaining organostannane compound is necessary, nonpolar organic solvents such as heptane[3] and hexane were used. Still, it was impossible to obtain pure **2**. Moreover, considering the problem of disposing of the organic waste containing the organostannane compounds, it was inevitable that this method would have to be abandoned.

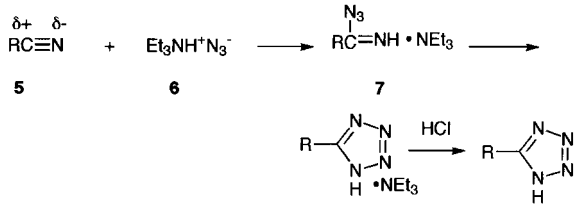


1 2

Scheme 2

We, thus, next examined the reaction without using organostannane compounds. As the result of our efforts, we discovered a new method to obtain **2** in high yield with excel]ent product purity. In this method, toluene is used as a solvent to cause **1** to react with NaN_3 in the presence of triethylamine hydrochloride, giving **2**. Since NaN_3 is barely soluble in aromatic solvents (ca. 1 ppm at 98 °C in toluene), previously aromatic solvents had not been used for this method. However, we found that a small amount of NaN_3 dissolved in toluene when the salt reacts with $Et_3N{\bullet}HCl$ to give $Et_3N{\bullet}HN_3$, which is soluble in toluene (ca. 4% at 98 °C). Furthermore, $Et_3N{\bullet}HN_3$ can actually react with **1** to give **2**. After the reaction was completed, water was added to bring the triethylamine salt of the product to the water layer, and the starting material **1** remained in the toluene layer. The addition of water simplifies the separation of the starting material and the product, and the addition of concentrated HCl, drop-by-drop, to the water layer salts out the desired product **2**. The product **2** could be obtained in high yield and purity through only these simple manipulations alone. It also should be noted that toluene could be recovered and recycled without any further treatment, or only by simple distillation, and that the aqueous waste could be disposed of easily.

Various features of this method were illuminated by synthesizing other tetrazoles from their corresponding nitriles (Table 1). For example, 4′-methyl-1,1′-biphenyl-2-carbonitrile (**3**) reacted even in DMF to give 4′-methyl-2-(tetrazol-5-yl)-1,1′-biphenyl (**4**); however, this reaction proceeded slower than when toluene was used as the solvent. The plausible reason for the facile reaction of the present method is that the intermediate complex [$Et_3N{\bullet}HN_3$ (**6**)] is first polarized as Et_3NH^+ and N_3^-, then, each of these react with the triple bond of the nitrile group to produce **7**, as shown in Scheme 3. However, when DMF is used as the solvent, the cationic moiety is solvated and stabilized, which decreases the reactivity toward the nitrile. In contrast to the reaction in DMF, when aromatic solvents such as toluene were used, both the cation and the anion are not solvated, and the reaction thus proceeds smoothly. Another reason for the facile reaction of the present method is that the equilibrium of the reaction shifts to produce the product because the product, amine salt of tetrazole, does not dissolve in the solvent, but escapes from the reaction system, that is, the solvent does not strongly solvate $Et_3N{\bullet}HN_3$, but it does dissolve nitrile, and a solvent that does not dissolve the product is assumed to be effective.



5 6 7

Scheme 3

As shown in the formula of **5**, the nitrile is polarized. When the R moiety is an electron-withdrawing substituent, the electron density of the nitrile moiety decreases, which results in polarization of a significant extent. On the other hand, when the R moiety is an electron-donating moiety, little polarization occurs. The larger the polarization of the nitrile moiety, the higher the reactivity becomes; although note also that the steric effect, the solubility of nitrile vis-a-vis the solvent, and the ease of isolation of the product also influence the reaction.

First, we examined the effect of amine salt on the reaction. A mixture of benzonitrile (**8**), NaN_3, amine salt, and toluene as the solvent was heated to 95–100 °C for 8 hours with stirring. After the reaction mixture was cooled, the product was extracted with water. The starting material **8** dissolved in the toluene layer, and the product dissolved in the water layer. When aqueous HCl was added dropwise, the product, 5-phenyl-1*H*-tetrazole (**9**), was salted out of the water. After filtration of the mixture, the solid was dried under reduced pressure. As shown in Table 2, ethylamine derivatives were better reagents than propylamine derivatives. As the side chain of aliphatic group becomes longer, the yield decreases. In the reaction with the series of propylamines, the yield decreased in the order of tertiary, secondary, and primary. The quaternary amine salt which had no proton could not generate the reaction. The aromatic primary amine could barely catalyze the reaction. The reactivity of the tertiary amine also differs depending on the structure of the amine. When an aliphatic amine and an aromatic amine were compared, the yield

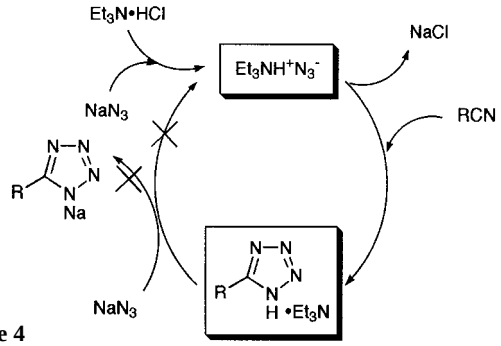
Table 1. Synthesis of 5-Substituted Tetrazoles from Nitriles[a]

Nitrile	NaN_3 (Equiv)	Temp (°C)/Time (h)	Product	Yield[b] (%)
1	1.5	83/25	**2**	76
3	1.3	99/30	**4**	67
8	1.3	95–99/8	**9**	96
10	1.3	95–99/24	**11**	63
12	1.3	95–99/7	**13**	93
14	1.3	95–99/7	**15**	96.5
16	1.3	95–99/23	**17**	9l
18	1.3	95–101/28	**19**	95
20	1.3	95–99/23	**21**	92
22	1.3	99–105/7	**23**	91
24	3.0	95–99/6	**25**	98
26	3.0	98–102/8	**27**	83
28	3.0	95–99/1	**29**	71
30	3.0	95–99/5	**31**	94
32	3.0	95–99/7	**33**	85

[a] The same equivalent mole of Et_3N•HCl to NaN_3 was used.
[b] Isolated yield.

for the aliphatic amine was relatively higher for the product tetrazole.

For the completion of the reaction, more than one equivalent of an amine salt to the nitrile was required. If the produced tetrazole•Et_3N salt acts as a catalyst instead of Et_3N•HCl, a reduction of the amount of Et_3N•HCl should be possible; however, amine salt only reacts with one equivalent of the substrate (Scheme 4) because amine is stable as tetrazole•Et_3N complex, and cannot be recycled in the system. For example, for the synthesis of **9**, when less than one mole equivalent of Et_3N•HCl to **8** is used, the yield proportionally decreases with the decrease in the amount of Et_3N•HCl used. The reason is that there are no exchanges of salt due to the small difference in the pKa of **9** (pKa 4.83) and of HN_3 (pKa 4.8).



Scheme 4

The effect of solvent was examined next. Various solvents were examined for the synthesis of **9**, using Et_3N•HCl as the amine salt. As shown in Table 3, the reaction proceeded with an aromatic hydrocarbon as the solvent, and **9** was obtained in high yields. When water was added to the system, reactivity decreased slightly. This is because Et_3N•HN_3 produced in the system is hydrophilic, is dissolved in the aqueous layer, and cannot move quickly to the toluene layer. However, production of **9** is not affected even with 5% of water to toluene, therefore, recycled toluene that is separated from the water layer without any treatment, or only by simple distillation, can be used for the reaction.

Synthesizing tetrazole **4** from nitrile **3** using an aliphatic solvent with very low polarity, such as heptane and cyclo-

Table 2. Effect of Amine Salt on Yield of 5-Substituted Tetrazoles from Benzonitrile[a]

Entry	Amine Salt or Ammonium Salt[b]	Yield[b] (%)
1	triethylamine hydrochloride	96
2	diethylamine hydrochloride	96
3	ethylamine hydrochloride	56
4	tripropylamine hydrosulfate	80
5	diisopropylamine hydrochloride	63
6	isopropylamine hydrochloride	59
7	tetramethylammonium chloride	0
8	tetrapropylammonium bromide	0
9	pyridine hydrochloride	9
10	aniline hydrochloride	0
11	dimethylaminopyridine sulfate	26

[a] Benzonitrile (50 mmol), NaN_3 (65 mmol) and amine salt (65 mmol) were used. Toluene (52 mL) was used and the mixture was heated at 100 °C for 8 h.
[b] Yield of **9**.

Table 3. Effect of Solvent on Yield of 5-Substituted Tetrazoles from Nitrile[a]

Entry	Nitrile	Solvent	Temp (°C)/ Time (h)	Tetrazole	Yield (%)
1	**8**	toluene	95–100/8	**9**	96
2	**8**	benzene	76–79/8	**9**	91
3	**8**	xylene	99–107/6	**9**	99
4	**8**	nitrobenzene	100–102/8	**9**	98
5	**8**	toluene[b]	93–96/8	**9**	98
6	**8**	ouluene[c]	97–89/8	**9**	84
7	**3**	toluene	98–99/30	**4**	67
8	**3**	butyl acetate	97–99/30	**4**	38[d]
9	**3**	butanol	95–97/30	**4**	21[d]
10	**3**	heptane	99–103/30	**4**	17
11	**3**	cyclohexane	83–85/30	**4**	0
12	**3**	DMF	97–l02/30	**4**	23

[a] Nitrile (50 mmol), NaN_3 (65 mmol), and Et_3N•HCl (65 mmol) in 52 mL for **1–6**, 96 mL for **7–12** of solvent were reacted. Yields shown here are isolated yield unless otherwise cited.
[b] Water (1% (volume) to toluene) was added.
[c] Water (5% (volume) to toluene) was added.
[d] Determined by HPLC.

Table 4. Effect of Acid on Yield of 5-Substituted Tetrazoles from Nitrile[a]

Entry	Acid	Temp (°C)/Time (h)	Yield (%)
1	HCl	95–100/8	96
2	HOAc	98–106/8	84
3	H_2SO_4[b]	98–100/6	97

[a] Benzonitrile (50 mmol), NaN_3 (65 mmol), Et_3N (65 mmol), and acid (65 mmol) in 52 mL of toluene were reacted. Yields are isolated yields.
[b] H_2SO_4 (32.5 mmol) was used.

Table 5. Summary of Analytical Data[a]

Product	mp (°C) Found	mp (°C) Reported	^{1}H NMR (DMSO-d_6) δ, J (Hz)	IR (KBr) ν (cm^{-1})
2	146–148	145–146[17]	1.95–2.35 (m, 2H), 2.96 (t, 2H, J = 7.7), 3.64 (s, 3H), 4.16 (m, 1H), 5.04 (s, 2H), 7.36 (s, 5H), 7.88 (d, 1H, J = 8.1)	3331, 2762, 1736, 1684, 1537, 1319, 1275, 1236, 1024, 756
4	151–153	146–149[3]	2.29 (s, 3H), 6.97 (d, 4H, J = 8.2), 7.12 (d, 2H, J = 8.1), 7.53–7.69 (m, 4H)	2980, 2831, 2608, 1603, 1485, 1448, 1398, 1159, 1009, 910, 826, 756
9	215.5–216	217–218[14]	7.61–8.06 (m, 5H)	2689, 2546, 1609, 1564, 1485, 1165, 1057, 993, 791, 725, 704, 689
11	153–154	157–158[14]	2.49 (s, 3H), 7.38–7.70 (m, 4H)	2716, 2550, 1607, 1560, 1489, 1161, 1060, 991, 783, 746
13	151–152	152–152.5[14]	2.41 (s, 3H), 7.40–7.88 (m, 4H)	2714, 2611, 1568, 1487, 1151, 1061, 1040, 804, 741, 689
15	245.5–246	250–250.5[14]	2.40 (s, 3H), 7.42–7.95 (m, 4H)	2768, 2543, 1614, 1570, 1504, 1165, 1055, 991, 824, 744, 505
17	144.5–145	143–144[15]	3.36 (br s, 2H), 6.67–7.73 (m, 4H)	3385, 2997, 2785, 1616, 1553, 1492, 1464, 997, 750, 698, 669
19	201.5–202	199–200[16]	6.74–7.26 (m, 4H)	3366, 3221, 2706, 1593, 1566, 1495, 1474, 1157, 1065, 1038, 744, 679
21	263–263.5	268–270[5]	5.79 (br s, 2H), 6.68–7.70 (m, 4H)	3485, 3387, 2735, 1622, 1607, 1512, 1408, 1317, 1196, 1058, 839
23	201–202		3.37 (br s, 3H), 6.75 (dd, 1H, J = 8.5, 2.0), 6.97 (d, 1H, J = 2.0), 7.73 (d, 1H, J = 8.8)	3481, 3348, 2781, 1626, 1566, 1491, 1454, 1263, 1254, 1059, 910, 750
25	225–226	221–222[18]	7.00–8.02 (m, 4H)	3274, 2964, 1616, 1546, 1489, 1466, 1361, 1298, 1070, 837, 812, 748
27	237–238	233–241[19]	6.95–7.88 (m, 4H)	3429, 2711, 1614, 1601, 1516, 1416, 1281, 1182, 1082, 845, 752, 523
31	99–100	100.5–101[14]	3.04 (t, 2H, J = 4.2), 3.19 (t, 2H, J = 4.2), 7.17–7.30 (m, 5H)	3010, 2604, 1570, 1454, 1109, 1051, 993, 758, 719, 698
33	90–91	92.5–93.5[14]	1.98–2.05 (m, 2H), 2.65 (t, 2H, J = 4.0), 2.89 (t, 2H, J = 4.0), 7.19–7.33 (m, 5H)	2866, 2623, 1570, 1497, 1454, 1421, 1256, 1107, 1049, 991, 746, 700

[a] Elemental analysis C ± 0.37, H ± 0.37, N ± 0.29 except **27** C ± 0.59 and **2** N ± 0.43.

hexane, the reaction barely proceeded, probably due to the extremely low solubilities of the nitrile and the amine salt to these solvents. The reaction in other aliphatic solvents proceeded, but the yields are lower than for an aromatic hydrocarbon.

Finally, we examined the effect of the acid on the reaction. Amine salt was prepared by addition of an acid (HCl, HOAc, and H_2SO_4) to a solution of triethylamine in toluene. To the resulting mixture, **8** and NaN_3 were added for the synthesis of **9**. As shown in Table 4, **9** was obtained in high yield, with only little decrease in yield during the reaction with acetic acid.

In conclusion, the novel method for the synthesis of tetrazole compounds we found is facile, inexpensive, safe, and applicable to a variety of 5-substituted tetrazoles.

Commercially available reagents and solvents were used. Compound **1** was synthesized according to the published method.[17] All HPLC analysis was performed with a UV detector (detection, 220 nm light), a flow rate of 1.0 mL/min and using a Nucleosil 5C-18 (4.5 × 150 mm) of column (eluent: MeCN/H_2O/H_3PO_4 2:8:0.001) except for **4** (with a UV detector (detection; 254 nm light), a flow rate of 1.0 mL/min and using a Inertsil ODS (6 × 150 mm) of column [eluent: MeCN/H_3PO_4 (1 mM) 65:35]. HPLC analysis were recorded by using a SHIMADZU SPD-10A UV-VIS detector, a SHIMADZU LC-10A LIQUID CHROMATOGRAPH, and a SHIMADZU C-R6A CHROMATOPAC. ^{1}H NMR spectra were obtained on a JEOL JNM-GX400 (400MHz) FT-NMR spectrometer, chemical shifts are reported relative to TMS. IR spectra were recorded on a Shimadzu 8200 PC spectrophotometer. Elemental analyses were performed with a Perkin–Elmer CHNS/O Analyzer 2400. Mps were obtained on a Mettler melting point apparatus FP61, and are uncorrected.

Preparation of Tetrazoles; General Procedure:
The mixture of a nitrile (50 mmol), NaN_3 (65–150 mmol) and an amine salt (65–150 mmol) in an aromatic solvent (50–150 mL) was heated to 30–100 °C for 1–30 h with stirring. After cooling, the product was extracted with water (50–150 mL). To the aqueous layer, 36% HCl was added dropwise to salt out the produced tetrazole. After filtration, the solid was dried under reduced pressure, yielding the tetrazole. The results are listed in Tables 1–5.

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