

Preparation of 1,5-Disubstituted Tetrazoles Under Phase-Transfer Conditions

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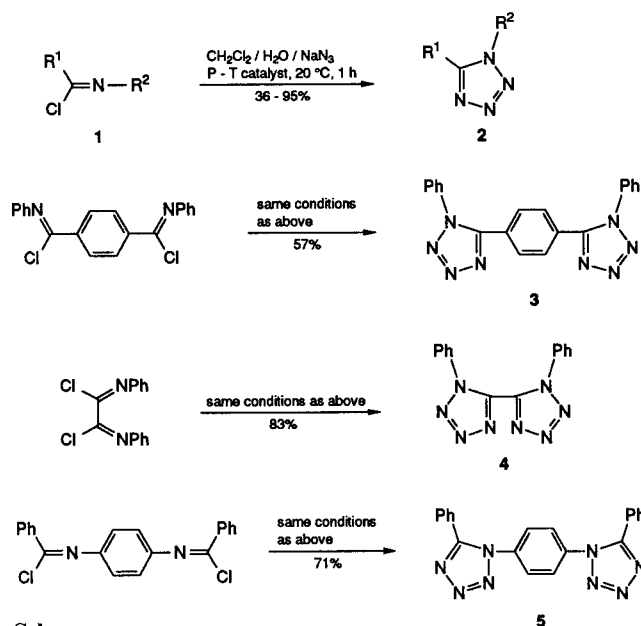
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Imidoyl chlorides, obtained by common methods from a wide range of aromatic mono- and diamides, are smoothly converted to the corresponding tetrazoles in high yields by treatment with NaN_3 under phase-transfer conditions.

1,5-Disubstituted tetrazoles can be synthesized by a number of methods, e.g. reaction of hydrazoic acid or its salts with imidoyl chlorides or imino ethers, addition of alkyl(aryl) azides to nitriles, diazo coupling of heterocyclic hydrazines, Schmidt synthesis from ketones and also by some other methods, which are of limited use in preparative organic chemistry.^{1–3} Among them, the reaction of imidoyl chlorides with hydrazoic acid^{4–6} or inorganic azides^{6–10} is the most widely employed method. However, the use of hydrazoic acid presents considerable experimental difficulties due to its toxicity and tendency to explode. Replacement of hydrazoic acid by inorganic azides, which are poorly soluble in organic solvents with low dielectric constants, causes an increase in reaction time and decrease in tetrazole yield. Attempts to overcome these difficulties were concentrated mainly on the search for solvents which could dissolve azide ion in high concentration and thus could provide sufficient efficiency of an overall process. Use of pentyl ether⁷ or acetone⁸ as solvent led to a significant increase in the reaction time. The best solvent turned out to be dimethylformamide, use of this solvent in the reaction of different imidoyl chlorides with sodium azide afforded 1,5-disubstituted tetrazoles in 70–94% yield.⁹ Replacement of organic solvents with aqueous buffer solutions did not lead to the desired results due to the formation of a mixture of tetrazoles and the corresponding amides, which was very difficult to separate.^{6,10} In this connection it was of interest to investigate the formation of 1,5-disubstituted tetrazoles from imidoyl chlorides and sodium azide under phase-transfer conditions.

Our first attempt¹¹ to obtain tetrazoles from imidoyl chlorides in a two-phase system was successful, which made it possible to apply this method to a wide range of different imidoyl chlorides. In order to further develop this method, the activity of different phase-transfer catalysts, tetrabutylammonium bromide, triethylbenzylammonium chloride, 5-butyl-2,3-diphenyltetrazolium bromide and 2,3,5-triphenyltetrazolium chloride, was investigated in the reaction of *N*-phenylbenzimidoyl chloride (**1a**) with sodium azide. The reaction was carried out in the two-phase system dichloromethane/water (1 : 1, v/v) at 20°C for 1 hour.

According to their activity the studied catalysts form the sequence, 5-butyl-2,3-diphenyltetrazolium bromide > 2,3,5-triphenyltetrazolium chloride > tetrabutylammonium bromide > triethylbenzylammonium chloride, and the desired 1,5-diphenyltetrazole was obtained in yields of 92, 91, 79 and 60%, respectively. Considering these data, two catalysts were chosen for the synthesis



Scheme

of other 1,5-disubstituted tetrazoles **2b–q** under phase-transfer conditions, tetrabutylammonium bromide as the most common catalyst and 5-butyl-2,3-diphenyltetrazolium bromide as the most efficient one. By employing this method some ditetrazoles **3–5** were also prepared (Table).

When highly reactive imidoyl chlorides are used as substrates, they are partly hydrolyzed during the course of the reaction to form the corresponding amides together with the desired tetrazoles. These difficulties could be overcome by reducing the volume of the aqueous phase ten-fold relative to the volume of the organic phase. Another way which enables the prevention of undesired hydrolysis and gives very good results is to carry out this reaction homogeneously in dichloromethane or chloroform, using 5-butyl-2,3-diphenyltetrazolium azide, which is readily soluble in these solvents.

All amides and diamides were prepared according to known methods.¹⁴ SOCl_2 , PCl_5 , NaN_3 as well as solvents were of reagent quality. IR spectra were recorded on a Specord M-40 spectrometer using KBr pellets. ^1H NMR spectra were measured in acetone- d_6 and in CDCl_3 , on a Varian 300 MHz NMR spectrometer. Melting points were detected on a Boëtius apparatus and are uncorrected.

1,5-Diphenyltetrazole (2c); Typical Procedure:

A mixture of benzanilide (1.20 g, 0.61 mmol) and SOCl_2 (3.30 g, 2.77 mmol) was heated at 75–80°C for 1 h. The excess of SOCl_2 was removed under reduced pressure and the obtained imidoyl chloride **1c** was dissolved in CH_2Cl_2 (10 mL). This solution was added to a mixture of NaN_3 (0.52 g, 0.80 mmol) and 2,3-diphenyl-5-butyltetrazolium bromide (0.10 g, 0.03 mmol) in a two-phase system of CH_2Cl_2 (10 mL) and water (20 mL) at 20–25°C. The mixture

Table. Compounds **2a–q** and **3–5** Prepared^a

Prod- uct ^b	R ¹	R ²	Yield (%)	mp (°C)		IR (KBr) ν (cm ⁻¹)
				found	reported	
2a	Ph	Me	87	102–103	102–103 ⁴	1610, 1545, 1470, 1410, 1290, 1220, 1120, 1090, 1060
2b	Ph	Et	90	68–69	70–71 ⁵	1610, 1540, 1475, 1410, 1290, 1180, 1120, 1085, 1060, 1000
2c	Ph	Ph	92	143–144	144–145 ⁵	1600, 1545, 1500, 1465, 1455, 1415, 1275, 1150, 1110, 1080, 1010
2d	Ph	4-MeC ₆ H ₄	93	128–130	130–132 ⁹	1520, 1470, 1415, 1270, 1145, 1110, 1080, 1060, 1010
2e	Ph	4-ClC ₆ H ₄	90	111–113	113–114 ⁹	1540, 1500, 1470, 1410, 1270, 1180, 1145, 1100, 1080, 1010
2f	Ph	4-BrC ₆ H ₄	92	108–109		1540, 1500, 1470, 1410, 1300, 1270, 1185, 1140, 1100, 1080, 1010
2g	4-BrC ₆ H ₄	Ph	99	166		1600, 1500, 1470, 1450, 1430, 1270, 1140, 1110, 1080, 1020, 1000
2h	Ph	4-MeOC ₆ H ₄	92	128–130	130–132 ⁹	1610, 1520, 1465, 1310, 1250, 1170, 1110, 1080, 1060, 1030, 1000
2i	Ph	3-NO ₂ C ₆ H ₄	91	129–130	133 ⁴	1540, 1490, 1470, 1460, 1410, 1355, 1275, 1150, 1110, 1080, 1010
2j	3-NO ₂ C ₆ H ₄	Ph	89	152	156 ⁴	3120, 1600, 1550, 1530, 1500, 1465, 1415, 1350, 1285, 1155, 1115, 1020
2k^c	Ph	2,4-Br ₂ C ₆ H ₃	94	137–138		1540, 1490, 1470, 1410, 1270, 1150, 1110, 1080, 1030, 1000
2l^d	Ph	2,4-(NO ₂) ₂ C ₆ H ₃	95	193	183 ¹²	3100, 1615, 1550, 1500, 1475, 1350, 1160, 1135, 1110, 1080, 1000
2m^d	4-NO ₂ C ₆ H ₄	4-NO ₂ C ₆ H ₄	91	268	262 ⁴	3100, 1600, 1530, 1470, 1450, 1350, 1145, 1120, 1010
2n	Ph	α-naphthyl	65	126	129–131 ⁹	1605, 1540, 1510, 1495, 1390, 1330, 1290, 1210, 1030
2o	Ph	2-pyridyl	36	101	100–101 ¹⁰	1600, 1580, 1540, 1475, 1440, 1410, 1275, 1150, 1095, 1080, 1050, 1010, 1000
2p	Ph	3-pyridyl	48	107–108		3070, 1590, 1540, 1495, 1460, 1435, 1290, 1185, 1145, 1110, 1080, 1030, 1000
2q	Ph	4-pyridyl	75	166	168 ⁹	1590, 1505, 1470, 1460, 1410, 1270, 1150, 1110, 1080, 1060, 1010, 1000
3			57	288–290		1600, 1560, 1505, 1470, 1450, 1300, 1280, 1270, 1180, 1150, 1110, 1080, 1010, 1000
4			83	212	212 ¹³	3085, 1600, 1500, 1470, 1410, 1380, 1300, 1270, 1195, 1115, 1080, 1000
5			71	271		1610, 1540, 1525, 1470, 1460, 1425, 1400, 1270, 1145, 1110, 1080, 1010, 1000

^a Compounds **2a–f** were prepared, using 5-butyl-2,3-diphenyltetrazolium bromide as phase-transfer catalyst and compounds **2g–j**, **l–q** and **3–5**, using tetrabutylammonium bromide as phase-transfer catalyst.

^b Satisfactory microanalyses were obtained for all new compounds: C ± 0.44, H ± 0.36, N ± 0.36 (Exception: **3**, C + 0.71)

^c Obtained by means of a homogeneous reaction with 5-butyl-2,3-diphenyltetrazolium azide in CH₂Cl₂.

^d Reaction was carried out in the two-phase system water/CH₂Cl₂ (1 : 5).

was stirred for 1 h, the layers were separated, the organic layer was washed with water (3 × 30 mL) and evaporated to dryness; yield: 1.25 g (92%); mp 143–144 °C (EtOH) (Lit.⁵ mp 144–145 °C).

Other imidoyl chlorides **1e**, **1f**, **1i–l**, **1o–q** and diphenylethanedi-imidoyl dichloride were obtained by reacting an equimolar quantity of PCl₅ with the corresponding amides. The corresponding imidoyl chlorides for the synthesis of tetrazoles **2g**, **2m**, **3** and **5** were prepared using SOCl₂ as solvent and PCl₅ as the reagent.

Tetrazoles **2a**, **2b**, **2d–j**, **2n–q** were obtained under the same conditions as **2c**. Tetrazoles **2l**, **2m**, and ditetrazoles **3**, **4** and **5** were obtained analogously, using a two-phase system, water/CH₂Cl₂ (1 : 5, v/v).

5-Butyl-2,3-diphenyltetrazolium Azide:

To a stirred solution of 5-butyl-2,3-diphenyltetrazolium bromide¹⁵ (1.00 g, 0.28 mmol) in water (17 mL) was added NaN₃ (1.50 g, 2.31 mmol) and the precipitate was filtered; yield: 0.58 g (65%); mp 163–165 °C (acetone).

C₁₇H₁₉N₇ calc. C 63.55 H 5.92 N 30.53
(321.4) found 63.15 5.92 30.54

IR (KBr): ν = 3050, 3030, 2970, 2950, 2880, 2015, 1500, 1470, 1300, 1165, 1030, 1005, 780, 690 cm⁻¹.

¹H NMR (CDCl₃): δ = 1.01 (t, J = 7.4 Hz, 3 H), 1.57 (m, 2 H), 2.03 (m, 2 H), 3.29 (t, J = 7.7 Hz, 2 H), 7.54 (m, 4 H, *m*-H_{arom}), 7.63 (m, 2 H, *p*-H_{arom}), 7.82 (m, 4 H, *o*-H_{arom}).

1-(2,4-Dibromophenyl)-5-phenyltetrazole (**2k**):

A mixture of *N*-(2,4-dibromophenyl)benzamide (1.07 g, 0.30 mmol) and PCl₅ (0.63 g, 0.30 mmol) was heated at 90–100 °C for 1 h, the POCl₃ formed was removed under reduced pressure and the imidoyl chloride **1k** formed was dissolved in anhyd CH₂Cl₂ (20 mL). To the mixture was added a solution of 5-butyl-2,3-diphenyltetrazolium azide (1.06 g, 0.33 mmol) in CH₂Cl₂ (30 mL). The mixture was stirred for 4 h, washed with water (4 × 30 mL) and evaporated to dryness; yield: 1.07 g (94%); mp 137–138 °C (EtOH).

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