Synthesis of Unsymmetrically Substituted 4*H*-1,2,4-Triazoles

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A general method was developed for the synthesis of unsymmetrically 3,5-disubstituted 4*H*-1,2,4-triazoles (Ph, H or Ph, CH_3) with allyl or benzyl groups in the 4-ring position. The reaction of the corresponding 3,5-disubstituted 1,3,4-oxadiazoles with allylamine or benzylamine gave the desired compounds. The oxadiazoles were prepared by heating at 100° *N,N'*-diacylhydrazines with phosphorus pentoxide.

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As a continuation of our interest in the thermal stability of 4-alkyl-4*H*-1,2,4-triazoles and their rearrangement reactions, we have undertaken an investigation of 4-allyl and 4-benzyl substituted 4*H*-1,2,4-triazoles. Previously, our group [1] and others [2] have shown that the 4-alkyl substituted 3,5-diaryl-4*H*-1,2,4-triazoles undergo thermal rearrangements to the corresponding 1-alkyltriazoles. The reactions were found most likely to proceed *via* nucleophilic type displacement reactions. Initial results dealing with the corresponding 4-allyl systems indicate a similar mechanism. However, we can not exclude, *e.g.*, [2,3]-allyl type shift reactions. The allyl group is expected to exhibit a larger migratory aptitude than phenyl groups. To establish possible sigmatropic rearrangements, we therefore decided to study the effect of substituents of different migratory aptitutes in the 3 and 5 ring positions. Thus, we decided to investigate the 4-allyl and 4-benzyl triazoles substituted with H or CH_3- groups in the 3-ring position.

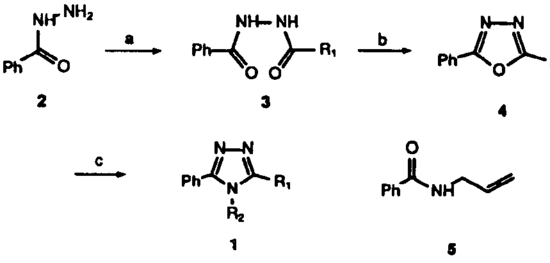
We found no general method described in the literature suitable for synthesis of the desired type of unsymmetrically 3,5-substituted triazoles, **1**. We therefore undertook an investigation of methods for the preparation of triazoles which were substituted with a 5-phenyl group and with H or CH_3 in the 3-ring positions, respectively.

Results and Discussion.

Initially we based our synthesis on a procedure analogous to the well established transformation of α,α'-dichloro-*N,N'*-benzylidenehydrazines with the appropriate amines [3]. However, in our hands all attempts failed to give the desired compounds, yielding very complex reaction mixtures or intractable materials. An alternative synthetic route involved the transformation of 1,3,4-oxadiazoles with amines to the corresponding triazoles, as reported earlier for symmetric triazoles [4]. Unsymmetric oxadiazoles have been synthesized before by a number of routes [5]. We found it convenient to prepare the oxadiazoles from the corresponding diacylhydrazines.

The appropriate diacylhydrazines, **3**, were prepared by acylation of benzoylhydrazine, **2**, with either the mixed formic acetic anhydride or acetyl chloride. Attempts to convert **3** into the 1,3,4-oxadiazoles, **4**, using the thionyl procedure described by Golfier *et al.* [6] failed to give the desired products, as did the method described by Rigo *et al.* [7]. In all cases reactions resulted in formation of intractable materials only. Some symmetric perfluoroalkyloxadiazoles have been prepared earlier by Brown *et al.* [8] by the dehydration of diacylhydrazines with phosphorus pentoxide. Similarly we found that the unsymmetric diacylhydrazines, **3**, readily cyclized by the reaction with phosphorus pentoxide. Thus, heating mixtures of **3** with an excess of neat phosphorus pentoxide at 100° for 24 hours without the use of solvents gave the desired products, **4**, in 83-55% isolated yields.

Scheme



a) CH_3COCl or $CH_3COOCHO$ b) P_2O_5 c) R_2-NH_2

R_1 : H or CH_3 R_2: Benzyl or Allyl

Heating of the 1,3,4-oxadiazoles **4** with allyl- or benzyl amine in sealed tubes at 150° for 2-12 days, resulted in formation of the desired triazoles in acceptable yields, 40-98%, after flash column chromatography or recrystallization. The reactions may be carried out in inert solvents such as benzene or toluene or without any solvent. In the reaction between 3-phenyl-1,3,4-oxadiazole and allylamine a major byproduct was isolated (30%), and identified as *N*-allylbenzamid, **5**. Formation of the product and byproduct may reflect attack by allylamine in the 5 and 3 ring positions, respectively. This byproduct was only detected for this specific reaction.

EXPERIMENTAL

General.

The ^{1}H and ^{13}C nmr spectra were recorded on a JEOL JNM-EX400 FT NMR system, using tetramethylsilane (TMS) as the internal standard. The ir spectra were obtained on a Nicolet 20-SXC FT-IR spectrometer. Mass spectra were recorded on a AEI MS-902 spectrometer at 70 eV (IP) and 150-200° inlet temperature. Measurements by glc were performed on a Perkin-Elmer Autosystem gas chromatograph equipped with a CP-Sil 5 CB capillary column (25 m). All melting points are uncorrected.

N-Acetyl-*N'*-benzoylhydrazine.

N-Benzoylhydrazine (50.04 g, 367.5 mmoles) dissolved in dry THF (1.5 l) was added triethylamine (58 g, 0.57 mole). Then acetyl chloride (34.54 g, 442.0 mmoles) dissolved in dry THF (100 ml) was slowly added to the reaction mixture over one hour at room temperature. The mixture was refluxed for 3 hours before the solvent was evaporated under reduced pressure. The crude product was recrystallized from water to yield 48.75 g (74%) of the pure product as white crystals with mp 175-176°; ^{1}H-nmr (400 MHz, DMF-d_6): δ 2.00 (s, 3H), 7.48-7.60 (m, 3H), 7.97-8.02 (m, 2H), 9.89 (s, NH), 10.27 (s, NH) ppm; ^{13}C-nmr (100 MHz, DMF-d_6) δ 20.7, 128.1, 129.1, 129.3, 132.3, 132.7, 133.8, 166.4, 169.3 ppm; ir (potassium bromide): 3202, 3015, 2869, 2832, 1702, 1644, 1578, 1548, 1489, 1446, 1378, 1337, 1282, 1157, 1009, 999, 971, 928, 891, 803, 729, 691, 645, 614, 591 cm^{-1}; ms: *m/z* (% relative intensity) 178 (9, M^+), 136 (8), 106 (8), 105 (100), 78 (2), 77 (35). Found: M^+ 178.0745. Calcd. for $C_9H_{10}N_2O_2$: M^+ 178.0742.

N-Benzoyl-*N'*-formylhydrazine.

A mixture of *N*-benzoylhydrazine (5.00 g, 36.7 mmoles, acetic acid formic anhydride (4.86 g, 55.2 mmoles) and formic acid (5.19 g, 113 mmoles) was stirred at room temperature for 19 hours. The resulting white slurry was then slowly added tetrachloromethane (50 ml). After stirring for another 15 minutes the product was filtered off and washed with tetrachloromethane. The product was recrystallized from a mixture of 20% ethanol in toluene to yield 4.03 g (67%) as white crystals with mp 161-162°; ^{1}H-nmr (400 MHz, DMF-d_6): δ 7.50-7.63 (m, 3H), 7.98-8.02 (m, 2H), 8.26 (s, 1H) ppm; ^{13}C-nmr (100 MHz, DMF-d_6): δ: 128.2, 129.1, 129.3, 132.5, 132.8, 133.5, 160.3, 166.1, 167.9 ppm; ir (potassium bromide): 3302, 3039, 3005, 2886, 1686, 1654, 1602, 1581, 1524, 1488, 1378, 1332, 1314, 1242, 1224, 1075, 1028, 802, 714, 691, 679, 613 cm^{-1}; ms: *m/z* (% relative intensity) 164 (5, M^+), 136 (3), 106 (7), 105 (100), 78 (4), 77 (50), 76 (2). Found: M^+ 164.0589. Calcd. for $C_8H_8N_2O_2$: M^+ 164.0586.

1,3,4-Oxadiazoles General Procedure.

The *N*-Acyl-*N'*-benzoylhydrazine (150 mmoles) was mixed with phosphorus pentoxide (60 g) and heated at 110° for 22 hours under a nitrogen atmosphere. The resulting solid was cooled to room temperature and then mixed with crushed ice (600 g). The solution was extracted with diethyl ether (600 ml), saturated with sodium chloride and again extracted with diethyl ether (3 x 300 ml). For 2-phenyl-1,3,4-oxadiazole the aqueous solution was neutralized with sodium hydroxide prior to extraction. The combined diethyl ether extracts were washed with saturated sodium chloride solution (100 ml) and dried over anhydrous magnesium sulfate. The crude products were isolated after evaporation of the solvent under reduced pressure.

2-Methyl-5-phenyl-1,3,4-oxadiazole was obtained as white crystals with mp 66.5-67° after recrystallization from pentane in 83% yield. The product exhibited the following spectroscopic properties: ^{1}H-nmr (400 MHz, deuteriochloroform): δ 2.61 (s, 3H), 7.47-7.52 (m, 3H), 8.01-8.04 (m, 2H) ppm; ^{13}C-nmr (100 MHz, deuteriochloroform): δ 11.1, 124.1, 126.8, 129.0, 131.5, 163.6, 164.9 ppm; ir (potassium bromide): 3066, 3055, 2934, 1581, 1554, 1496, 1484, 1450, 1351, 1292, 1250, 1092, 1074, 1045, 1020, 959, 928, 783, 708, 694, 662 cm^{-1}; ms: *m/z* (% relative intensity) 160 (100, M^+), 118 (5), 106 (2), 105 (32), 104 (18), 103 (9), 91 (3), 90 (19), 89 (4), 78 (5), 77 (12). Found: M^+ 160.0636. Calcd. for $C_9H_8N_2O$: M^+ 160.0637.

2-Phenyl-1,3,4-oxadiazole was obtained in 55% yield after sublimation (10 mbar, 80°) as a white crystalline product with mp 36°. The product exhibited the following spectroscopic properties: ^{1}H-nmr (400 MHz, deuteriochloroform): δ 7.50-7.58 (m, 3H), 8.08-8.10 (m, 2H), 8.48 (s, 1H) ppm; ^{13}C-nmr (100 MHz, deuteriochloroform): δ 123.5, 127.0, 127.1, 129.1, 132.0, 152.6, 164.8 ppm; ir (potassium bromide): 3126, 3092, 2987, 1606, 1555, 1512, 1492, 1480, 1453, 1339, 1290, 1241, 1110, 1067, 1025, 969, 955, 943, 923, 864, 779, 709, 691, 640 cm^{-1}; ms: *m/z* (% relative intensity) 147 (10), 146 (100, M^+), 118 (3), 106 (3), 105 (45), 104 (2), 103 (14), 91 (16), 90 (32), 89 (15), 78 (3), 77 (30), 76 (7). Found: M^+ 146.0482. Calcd. for $C_8H_6N_2O$: M^+ 146.0480.

4-Allyl-4*H*-1,2,4-triazole. General Procedure.

1,3,4-Oxadiazole (3.1 mmoles) was dissolved in allylamine (3.0 g), and heated in a sealed tube at 150° for 2-12 days. The crude product was then isolated by evaporation of the allylamine under reduced pressure.

4-Allyl-3-methyl-5-phenyl-4*H*-1,2,4-triazole was obtained from 2-methyl-5-phenyl-1,3,4-oxadizole (0.5 g, 3.1 mmoles) after 12 days in 99% crude yield (96% pure by glc). Crystallization from acetone gave 0.36 g (58%) of the pure product as colourless crystals with mp 86.5-87.5°. The product exhibited the following spectroscopic properties: ^{1}H-nmr (400 MHz, deuteriochloroform): δ 2.48 (s, 3H), 4.53 (dt, J = 4.4, 2.0 Hz, 2H), 4.98 (dt, J = 17.6, 2.0 Hz, 1H), 5.34 (dt, J = 10.7, 2.0 Hz, 1H), 5.90-5.99 (m, 1H), 7.45-7.49 (m, 3H), 7.59-7.62 (m, 2H) ppm; ^{13}C-nmr (100 MHz, deuteriochloroform): δ 10.9, 46.1, 117.7, 127.4, 128.6, 128.9, 130.0, 131.7, 152.4, 154.9 ppm; ir (potassium bromide): 3090, 2971, 2923, 1531, 1521, 1482, 1467, 1451, 1411, 1377, 1355, 1259, 1082, 997, 986, 932, 922, 785, 768, 719, 703, 674, 567, 517 cm^{-1}; ms: *m/z* (% relative intensity) 199 (100, M^+), 198 (41), 197 (2), 185 (2), 184 (18), 172 (2), 157 (2), 143 (2), 131 (2), 130 (3), 129 (3), 128 (2), 115 (2), 105 (3), 104 (16), 103 (4), 89 (3), 82 (3), 77 (7), 76 (2). Found M^+: 199.1112. Calcd. for $C_{12}H_{13}N_3$: M^+ 199.1110.

4-Allyl-3-phenyl-4*H*-1,2,4-triazole from 2-phenyl-1,3,4-oxadiazole (0.51 g, 3.5 mmoles) after 2 days gave the crude product which was purified by flash column chromatography (Merck Silica 60 (40-63 μm)) using acetone as the eluent. The yield was 0.28 g (43%) after recrystallization from acetone as colorless crystals with mp 74-75°; ^{1}H-nmr (400 MHz, deuteriochloroform): δ 4.64 (dt, J = 5.4, 1.7 Hz, 2H), 5.15 (dt, J = 17.1, 1.6 Hz, 1H), 5.36 (dt, J = 10.3, 1.2 Hz, 1H), 5.93-6.03 (m, 1H), 7.27-7.51 (m, 3H), 7.63-7.65 (m, 2H), 8.22 (s, 1H) ppm; ^{13}C-nmr

(100 MHz, deuteriochloroform): δ 47.3, 119.2, 126.6, 128.8, 128.9, 130.2, 131.8, 144.3, 154.1 ppm; ir (potassium bromide): 3089, 2992, 1645, 1509, 1473, 1459, 1445, 1430, 1408, 1380, 1350, 1262, 1202, 1172, 1082, 1056, 1026, 1000, 968, 905, 885, 774, 744, 729, 699, 669, 570, 549, cm^{-1}; ms: *m/z* (% relative intensity) 185 (100, M^+), 184 (50), 171 (4), 170 (34), 158 (4), 157 (3), 145 (3), 130 (4), 129 (3), 128 (3), 118 (3), 117 (2), 116 (6), 115 (4), 109 (12), 108 (8), 105 (3), 104 (26), 103 (11), 90 (6), 89 (24), 81 (4), 77 (12), 76 (7). Found M^+ 185.0951. Calcd. for $C_{11}H_{11}N_3$: M^+ 185.0953.

A byproduct was isolated (30%) and identified as *N*-allylbenzamide by comparison with an authentic sample and by its characteristic spectroscopic properties: ^{1}H-nmr (400 MHz, deuteriochloroform): δ 4.02 (d, J = 5.4 Hz, 2H), 5.11 (d, J = 10.3 Hz, 1H), 5.20 (d, J = 17.1 Hz, 1H), 5.87 (ddd, J = 5.7, 10.9, 22.3 Hz, 1H), 7.33-7.47 (m, 3H), 7.79-7.81 (m, 2H) ppm; ^{13}C-nmr (100 MHz, deuteriochloroform): δ 168.5, 133.7, 133.4, 131.8, 128.5, 127.3, 116.7, 42.7 ppm; ir (sodium chloride): 3296, 3066, 2921, 1640, 1538, 1489, 1421, 1310, 1256, 993, 922, 695 cm^{-1}; ms: *m/z* (% relative intensity) 162 (3), 161 (25, M^+), 106 (8), 105 (100), 78 (3), 77 (32).

4-Benzyl-4*H*-1,2,4-triazoles: General Procedure.

One g of oxadiazoles, **3**, was dissolved in benzylamine (10 ml) and heated at 150° for 8 to 12 days. The mixture was then dissolved in diethyl ether (100 ml), filtered through Silica gel (40 g) and washed with diethyl ether (300 ml). The triazole remained on the column and was recovered by washing with methanol (400 ml). Concentration under reduced pressure yielded the crude product as an oil of 94-98% purity (glc). The product crystallized upon standing. However, recrystallization failed to yield well defined crystals.

4-Benzyl-3-methyl-5-phenyl-4*H*-1,2,4-triazole.

Reacting 2-methyl-5-phenyl-1,3,4-oxadiazole (1.00 g, 6.25 mmoles) yielded 1.65 g (99%) of an oil, 94% pure by glc; ^{1}H-nmr (400 MHz, deuteriochloroform): δ 2.37 (s, 3H), 5.16 (s, 2H), 6.97-6.99 (m, 2H), 7.31-7.45 (m, 6H), 7.52-7.54 (m, 2H) ppm; ^{13}C-nmr (100 MHz, deuteriochloroform): δ 11.2, 47.4, 125.7, 127.3, 128.0, 128.2, 128.5, 128.7, 128.9, 129.3, 130.0, 135.1, 152.6, 155.2 ppm; ir (potassium bromide): 3083, 2992, 2977, 2953, 2934, 1645, 1509, 1473, 1459, 1445, 1430, 1380, 1350, 1286, 1262, 1202, 1172,1055, 1026, 1000, 968, 919, 905, 885, 775, 744, 729, 699, 669, 570, 549 cm^{-1}; ms: *m/z* (% relative intensity) 249 (56, M^+), 248 (14), 234 (4), 211 (3), 172 (2), 106 (2), 105 (5), 104 (7), 92 (8), 91 (100), 77 (2). Found: M^+ 249.1268. Calcd. for $C_{16}H_{15}N_3$: M^+ 249.1266.

4-Benzyl-3-phenyl-4*H*-1,2,4-triazole.

2-Phenyl-1,3,4-oxadiazole (1.00 g, 6.85 mmoles) yielded 0.64 g (40%) of an oil, 98% pure by glc; ^{1}H-nmr (400 MHz, deuteriochloroform): δ 5.21 (s, 2H), 7.05-7.10 (m, 2H), 7.31-7.59 (m, 8H), 8.19 (s, 1H) ppm; ^{13}C-nmr (100 MHz, deuteriochloroform): δ 48.8, 126.6, 126.9, 128.7, 128.9, 129.3, 130.3, 134.9 ppm; ir (potassium bromide): 3085, 3028, 2998, 1509, 1497, 1474, 1454, 1444, 1437, 1369, 1215, 1198, 1176, 1075, 1029, 968, 923, 875, 781, 762, 721, 698, 669, 536 cm^{-1}; ms: *m/z* (% relative intensity) 236 (6), 235 (34, M^+), 234 (7), 146 (5), 132 (6), 131 (2), 105 (4), 104 (4), 103 (4), 92 (8), 91 (100), 90 (3), 89 (6), 78 (2), 77 (7), 76 (2). Found: M^+ 235.1113. Calcd. for $C_{11}H_{11}N_3$: M^+ 235.1110.

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