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Supporting Information

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

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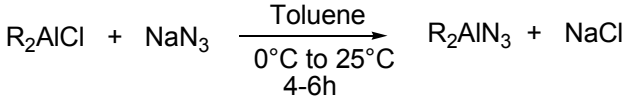
CONTENTS

A Materials

All reactions were carry out under a nitrogen atmosphere. The diethyl aluminum chloride was purchased from Aldrich or Chrompton. The starting nitriles were purchased from Lancaster, Aldrich, Across and Fluka. All melting points were taken on a Büchi 535 melting point apparatus and are uncorrected. Thin-layer chromatography was performed on precoated silica gel plates of type Kiesegel 60 F_{254} with a solvent system: toluene/ ethyl acetate/ acetic acid 20:20:1 and visualized by ultraviolet light. Optical rotation were measured on a Perkin Elmer polarimeter, Polarimeter 341, at the sodium D line (589 nm) at 20 °C. The solvent and concentrations (% m/m) are indicated. Infrared spectra were measured as a solid film on a Bruker Hyperion microscope coupled with a Bruker TENSOR 27 FTIR spectrometer over a wave number range of 4000-600 cm-1. NMR spectra were recorded on a Bruker 400 or 600 (^{1}H) and 125 MHz (^{13}C) in ppm with reference to TMS internal standard in d-DMSO. All mass spectral data were obtained using a Water ZQ2000 Quadripole, with an electrospray ion source operated in both positive and negative ion mode. The high resolution and high accuracy mass spectra were acquired on a 9.4 Tesla Bruker APEXIII Fourier Transform Ion Cyclotron Resonance Mass Spectrometer (FT/ICR-MS) equipped with an electrospray ion source operated in both positive and negative ion mode. 32 spectra were accumulated and internally calibrated using the signals from the Agilent ES tune mix solution. The products were satisfactorily characterized by melting point, IR, ^{1}H and ^{13}C-NMR, HR-MS and then possible, comparison of their analytical data has been made with available literature data.

B **Typical procedure for the preparation of diethylaluminum azide.**



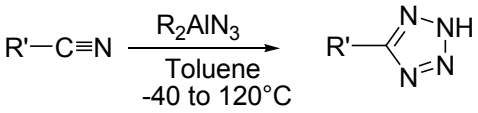
Scheme 1. Preparation of the dialkylaluminum azide

Notes: diethylaluminum chloride can be used in different solvents and molarities by following the same general procedure. For example solutions of diethylaluminum chloride were used 1.8 M in toluene, 2.5 M in toluene, 2.7 M in xylene.

A 100 ml, four-necked, oven dried round-bottomed flask equipped with an overhead mechanical stirrer, is charged, at 0 °C, under an atmosphere of argon, with of sodium azide (5.46 g, 84 mmol). Diethylaluminum chloride (46.7 mL, 84 mmol, 2.7 M in toluene) are added with a syringe. After 15 minutes, the white heterogeneous mixture is gradually warmed to room temperature, and stirred for four to six hours. During the formation of the reagent, a suspension of sodium chloride is formed.

C **Typical procedure for 1-3 dipolar cycloadditions between diethylaluminum azide and nitriles for the tetrazole ring formation.**

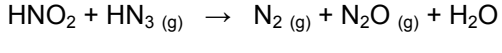
Cycloaddition:



Scheme 2. Synthesis of 5-substituted tetrazole

A 100 ml, four-necked, oven dried round-bottomed flask equipped with an overhead mechanical stirrer, containing a white suspension of diethylaluminum azide (84 mmol, 2.7 M in toluene) is charged, at room temperature, under atmosphere of argon, with phenylsulphonyl acetonitrile (10.87 g, 60 mmol) in two equal portions in intervals of five minutes. The mixture is gradually heated to 55 °C (external temperature) and stirred for two hours.

Work up:



Equation 1. Safe removal of hydrazoic acid

When the HPLC and the TLC analysis shows >98 % conversion the reaction mixture is cooled to 0 °C and, to destroy the excess of azide, added to a solution of NaOH (15 %, 67 mL, 252 mmol), containing sodium nitrite (17.38 g, 252 mmol) (pH 13.5) (Equation 1). The pH is adjusted to 1.5 with HCl (6 M). The biphasic mixture is transferred to a separatory funnel, and the product is extracted three times with ethyl

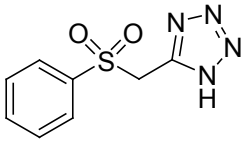
acetate (20 mL portion) ; the combined organic phase is washed once with water (20 mL), and then concentrated by rotary evaporation (45 °C, 210 to 50 mbar) to afford 13.0 g of crude product which is re-dissolved in ethyl acetate (30 mL), transferred to a separatory funnel, and extracted three times with potassium carbonate (10 % solution, 25 mL portion) to the aqueous phase as the potassium salt (pH 11). The combined basic aqueous phase is cooled to 0 °C under stirring and carefully treated with 6M HCl to adjust the pH to 2.5, monitored with pH-paper or electrode. The product is extracted three times with ethyl acetate (20 ml portion). The combined organic phase is washed once with water (30 ml). The solvent is removed to give the tetrazole **1** as a yellow crystalline material which is crystallized from ethyl acetate / toluene (10.23 g, 76 %).

Typical procedure for the protection of the hydroxyl group for the synthesis of the compounds 15, 16 and 20

A 25 mL, two necked, oven dried round bottomed flask equipped with a stirring bar, is charged, under atmosphere of argon, with triethylaluminum (5 mL, 9 mmol, 1.8 M in toluene). The solution is cooled to 0 °C and the mandelonitrile is carefully added over 15 minutes (0.88 mL, 7 mmol ; exothermic from 0 to 40 °C). The mixture is stirred two hours from 0 °C to room temperature.

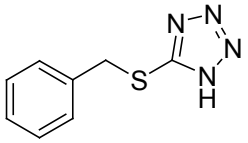
D Synthesis and characterization of compounds 1-32

(1) Preparation of 5-Phenylsulfonylmethyl)-1*H*-tetrazole [1]



1.4 equivalents of diethylaluminum azide (2.5 M in toluene) are used in a 60 mmol scale experiment. The reaction was heated for three hours at 55 °C to give 10.23 g of product (76 % yield) as a yellow crystalline with a mp of 172-174 °C; TLC: R_f= 0.44; IR: ν 3000 (m, ע(C-H)), 2930 (m, ע(C-H)), 2700-2500 (brm, ע(N-H)), 1590 (w, ע(C=C)), 1555 (w, tetrazole), 1447 (m, ע(C=C)), 1400 (m, δ_{sim} (CH_2)), 1297 (s, $ע_{asim}(SO_2)$), 1151 (s, $ע_{sim}(SO_2)$) cm^{-1}; ^{1}H-NMR (400 MHz, d_6-DMSO): δ = 5.22 (*s*, 2H), 7.64 (*dd*, *J*= 8.8, 7.0 Hz, 2H), 7.77 (*m*, 3H), 17.05 (*br*, NH); ^{13}C-NMR (125 MHz, d_6-DMSO): δ = 50.3 (CH_2), 128.0 (CH), 129.5 (CH), 134.5 (CH), 137.9 (Cq), 148.5 (Cq); EI-MS: *m/z* 223 $[M-H]^-$, 141$[M-CH_2CN_4H]^-$.

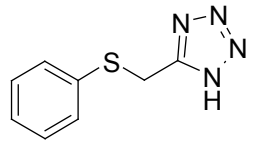
(2) Preparation of 5-(benzylthio)-*1H*-tetrazole [2]



1.5 equivalents of diethylaluminum azide (2.5 M in toluene) are used in a 20 mmol scale experiment. The reaction was heated for four hours and 30 min at 45 °C to give 1.77 g of product (46 % yield) as a yellow crystalline with a mp of 134-136 °C; TLC: R_f= 0.28; IR: ν 3050 (w, ע(C-H)), 2900 (w, ע(C-H)), 2700-2300 (brm, ע(N-H)), 1532 (m, tetrazole), 1493 (m, ע(C=C)), 1454 (m, ע(C=C)), 1433 (m, ע(C=C)) cm^{-1}; ^{1}H-NMR (500 MHz, DMSO): δ = 4.50 (*s*, 2H), 7.26 (*t*, *J*= 7.3 Hz, 1H,), 7.31 (*t*, *J*= 7.3 Hz, 2H, ArH), 7.39 (*d*, *J*= 7.3

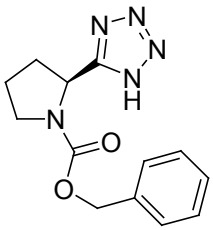
Hz, 2H, ArH), 16.59 (*br*, NH); ^{13}C-NMR (125 MHz, d_6-DMSO): δ = 36.4 (CH_2), 128.1 (CH), 129.0 (CH), 129.3 (CH), 137.1 (Cq), 153.7 (Cq); EI-MS: *m/z* 193 $[M+H]^+$, 191 $[M-H]^-$, 91 $[M-SCN_4H]^+$.

(3) Preparation of 5-Phenylsulfanylmethyl-1*H*-tetrazole (3) [3]



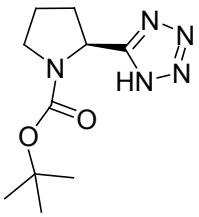
1.5 equivalents of diethylaluminum azide (2.5 M in toluene) are used in a 6 mmol scale experiment. The reaction was heated for thirty hours at 55°C to give 990 mg of product (86 % yield) as a yellow crystalline with a mp of 106-108 °C; TLC: R_f = 0.26; IR: ν 3100-2400 (brs, ע(N-H)), 3100 (s, ע(C-H)), 2980 (s, ע(C-H)), 1950-1750 (w, overtones γ(C-H, Ph)), 1571 (w, ע(C=C)), 750-694 (s, δ(C-H, Ph)) cm^{-1}; ^{1}H-NMR (500 MHz, d_6-DMSO): δ = 4.54 (*s*, 2H), 7.21 (*m*, 1H), 7.30 (*m*, 2H), 7.34 (*m*, 2H), 16.40 (*br*, NH); ^{13}C-NMR (125 MHz, d_6-DMSO): δ = 24.8 (CH_2), 127.6 (CH), 128.9 (CH), 129.2 (CH), 133.9 (Cq), 155.0 (Cq); EI-MS: *m/z* 191 $[M-H]^-$.

(4) Preparation of (*S*)-2-(1*H*-tetrazol-5-yl)-pyrrolidin-1-carboxylic acid benzyl ester 2 [4]



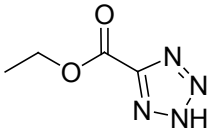
1.3 equivalents of diethylaluminum azide (2.7 M in xylene) are used in a 50 mmol scale experiment. The reaction was heated for nine hours at 50 °C to give 13.9 g of product (96 % yield) as a white crystalline material with a mp of 84-86 °C; TLC: R_f = 0.22 ; Optical rotation: *R*-enentiomer: $[\alpha]_D^{25}$ = + 50.1 ° (in MeOH, c = 1), + 49.7 ° (in EtOH, c = 1), + 85.3 ° (in $CHCl_3$, c = 1), + 41.8 ° (in DMSO, c = 1), + 65.4 ° (in DMF, c = 1); IR: ν 3000-2400 (brm, ע(N-H)), 3074 (vw, ע(C-H)), 3035 (w, ע(C-H)), 2973 (m, ע(C-H)), 2944 (m, ע(C-H)), 1900-1800 (w, overtones γ (C-H, Ph)), 1694 (s, ע(C=O)), 1523 (w, tetrazole), 1443 (s, ע (C=C)), 1404 (s, ע(C=C)), 1132 (s, ע(C-O)), 693 (w, γ(Ph)) cm^{-1}; ^{1}H-NMR (400 MHz, d_6-DMSO) rotamers (1:1): δ =1.94 (*m*, 3H), 2.35 (*m*, 1H), 3.53 (*m*, 2H), 5.00 (*m*, 1H), 5.24 (*dd*, 2H), 7.00 (*m*, 1H), 7.31 (*m*, 4H), 16.30 (*br*, NH); ^{13}C-NMR (125 MHz, d_6-DMSO) rotamers (1:1): δ = 32.0, 33.1 (CH_2), 46.7, 47.2 (CH_2), 66.3, 66.6 (CH_2), 127.3 (CH), 127.9 (CH), 128.8 (CH), 137.0 (Cq, Ar), 153.9 (Cq), 154.5 (Cq); EI-MS: *m/z* $[MH]^+$, 272 $[M-H]^-$, 230 $[M-HN_3]$.

(5) Preparation of (*S*)-2-(1*H*-Tetrazol-5-yl)pyrrolidine-1- carboxylic acid *tert*-buthyl ester [5]



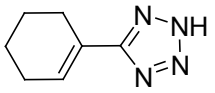
1.2 equivalents of diethylaluminum azide (2.5 M in toluene) are used in a 5 mmol scale experiment. The reaction was heated for thirty hours at 40 °C. The work up was done by using directly a solution of $KHSO_4$ (10 % solution) to pH 5 instead to HCl to avoid the cleavage of the Boc group to give 680 mg of product (57 % yield) as a white crystalline material with a mp of 122 °C; TLC: R_f = 0.22; Optical rotation: $[\alpha]^D$ = -75.68° (in MeOH, c = 0.63); IR: ν 3100-2500 (w, ע(N-H)), 2977 (m, ע(C-H)), 1669 (vs, ע(C=O)), 1553 (m, tetrazole), 1423 (vs, ע(C-N)), 1372 (m, δ(-CH_3)), 1160 (s, ע(C-O)) cm^{-1}; ^{1}H-NMR (500 MHz, d_6-DMSO, 300 K) rotamers (1:1): δ = 1.12 (*s*, 9H), 1.37 (*s*, 9H), 1.90 (*m*, 3H), 2.31 (*m*, 1H), 3.40 (*m*, 2H), 5.08 (*m*, 1H), 16.37 (*br*, NH), (500 MHz, d_6-DMSO, 397 K): 1.29 (*s*, 9H), 1.91 (*m*, 3H), 2.34 (*m*, 1H), 3.49 (*m*, 2H), 5.10 (*m*, 1H); ^{13}C-NMR: (150 MHz, d_6-DMSO, 300 K) rotamers (1:1): δ = 23.0, 23.1 (CH_2), 27.7, 28.1(CH_3), 31.67, 32.9 (CH_2), 46.2, 46.4 (Cq), 51.3, 51.6 (CH_2), 79.1, 78.8 (CH), 152.8, 153.5 (Cq), 158.6, 159.3 (Cq); EI-MS: *m/z* 240 $[MH]^+$, 238 $[M-H]^-$, 140 $[MH-Boc]^+$.

(6) Preparation of ethyl-1*H*-tetrazole-5-carboxylate [6]



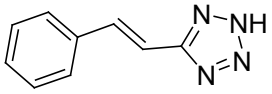
1.3 equivalents of diethylaluminum azide (2.5 M in toluene) are used in a 10 mmol scale experiment. The reaction was stirred one hours at room temperature to give 1.33 g of product (94 % yield) as a off white crystalline material with a mp of 92-94 °C; TLC: R_f = 0.19; IR: ν 3000-2400 (m, ע(N-H)), 2948 (m, ע(C-H)), 2916 (m, ע(C-H)), 2882 (m, ע(C-H)), 1750 (s, ע(C=O)), 1543 (vw, tetrazole), 1470 (w, tetrazole), 1455 (w, tetrazole), 1445 (w, tetrazole), 1223s ע(C-O) cm^{-1}; ^{1}H-NMR (500 MHz, d_6-DMSO): δ = 1.35 (*t*, ^3J= 7.1 Hz, 3H), 4.41 (*q*, ^3J= 7.1 Hz, 2H), 16.50 (*br*, NH); ^{13}C-NMR (125 MHz, d_6-DMSO): δ = 13.9 (CH_3), 62.3 (CH_2), 150.7 (Cq), 156.6 (Cq), EI-MS: *m/z* 142 $[M]^+$, 127 $[M-CH_3]^+$, 115 $[MH-N_2]^+$, 97 $[M-OC_2H_5]^+$; HR-MS: calc'd for $[M-H]^-$ = 141.0418, found 141.0418.

(7) Preparation of 5-(1-Cyclohexen-1-yl)-1*H*-tetrazole [7]



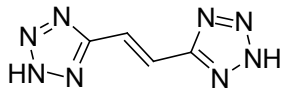
1.4 equivalents of diethylaluminum azide (2.5 M in toluene) are used in a 7 mmol scale experiment. The reaction was heated for twenty hours at 90 °C to give 680 mg of product (65 % yield) as a white crystalline obtained after direct crystallization of the crude from a mixture of ethyl acetate / toluene 1:1. mp of 151-153 °C; TLC: R_f = 0.32; IR: ν 3108 (m, ע(C-H)), 3000-2500 (brs, ע(N-H)), 2972 (s, ע(C-H)), 2931 (s, ע(C-H)), 1651 (s, ע(C=C)), 1556 (s, tetrazole), 1410 (s, tetrazole) cm^{-1}; ^{1}H-NMR (500 MHz, d_6-DMSO): δ = 1.61 (*m*, 2H), 1.70 (*m*, 2H), 2.21 (*m*, 2H), 2.45 (*m*, 2H), 6.77 (*m*, 1H), 16.20 (*br*, NH); ^{13}C-NMR (125 MHz, d_6-DMSO): δ =21.1 (CH_2), 21.5 (CH_2), 24.9 (CH_2), 25.0 (CH_2), 122.7 (Cq), 132.7 (CH), 155.6 (Cq); EI-MS: *m/z* 151 $[MH]^+$, 108 $[MH-HN_3]^+$, 149 $[M-H-N_2]^-$; HR-MS: calc'd for $[M-H]^-$= 149.0833, found 149.0833.

(8) Preparation of 5-Styryl-1*H*-tetrazole [8]



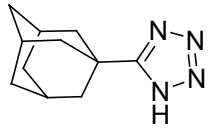
1.3 equivalents of diethylaluminum azide (2.7 M in xylene) are used in a 10 mmol scale experiment. The reaction was heated for 18 hours from 50 to 70 °C to give 1.667 g of product (97 % yield) as a off white crystalline with a mp of 158-160 °C; TLC: R_f = 0.36; IR: ν 3100-2400 (brs, ע(N-H)), 3032 (m, ע(C-H)), 1960-1800 (w, overtones γ(C-H, Ph)), 1650 (vs, ע(C=C)), 1559 (s, tetrazole), 1420 (s, ע(C=C)), 974 (s, δ(C-H, C=C trans), 776 (s, γ(C-H, Ph)), 688 (m, γ(Ph)) cm^{-1}; ^{1}H-NMR (400 MHz, d_6-DMSO): δ =7.35 (*d*, *J*= 16.6 Hz, 1H), 7.44 (*m*, 3H), 7.66 (*d*, *J*= 16.6 Hz, 1H), 7.74 (*m*, 2H), 16.50 (br, NH); ^{13}C-NMR (125 MHz, d_6-DMSO): δ = 110.4 (CH), 127.4 (CH, Ar), 129.1 (CH, Ar), 129.5 (CH, Ar), 134.7 (Cq), 137.8 (CH), 154.1 (Cq); EI-MS: 173 $[MH]^+$, 171 $[M-H]^-$, 130 $[MH-HN3]^+$, 186 $[MH-HN_3]^+$; HR-MS: calc'd for $[M-H]^-$ = 171.0676, found 171.0676.

(9) Preparation of fumaryl-2*H*-tetrazole [9]



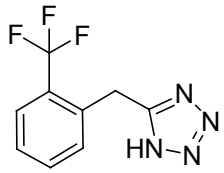
1.3 equivalents of diethylaluminum azide (2.7 M in xylene) are used in a 6 mmol scale experiment. The reaction was stirred for one hour thirty minutes at room temperature to give 480 mg of product (49 % yield) as a light brown crystalline material with a mp of 275 °C; TLC: R_f = 0.04; IR: ν 3200-2800 (brs, ע(N-H)), 3089 (s, ע(C-H)), 3043 (s, ע(C-H)), 1548 (s, tetrazole), 1427 (m, ע(C=C)) cm^{-1}; ^{1}H-NMR (500 MHz, d_6-DMSO): δ = 7.69 (*s*, 2H), 17.00 (*br*, NH); ^{13}C-NMR (125 MHz, d_6-DMSO): δ =119.2 (CH), 152.9 (Cq); EI-MS: *m/z* 165 $[MH]^+$; HR-MS: calc'd for $[M-H]^-$= 163.0486, found 163.0486.

(10) Preparation of 5-(1-Adamentyl)-1*H*-tetrazole [10]



2.23 equivalents of diethylaluminum azide (2.5 M in toluene) are used in a 3 mmol scale experiment. The reaction was heated for three days at 90-110 °C to give 500 mg of product (82 % yield) as a white crystalline with a mp of 250-253 °C; TLC: R_f = 0.38, (I_2); IR: ν 3100-2500 (brm, ע(N-H), 2989 (s, ע(C-H)), 2934 (s, ע(C-H)), 2909 (s, ע(C-H)), 1560 (w, tetrazole), 1409 (w, tetrazole) cm^{-1}; ^{1}H-NMR (500 MHz, d_6-DMSO): δ =1.75 (*m*, 6H), 1.98 (*m*, 6H), 2.05 (*m*, 3H), 16.10 (*br,* NH); ^{13}C-NMR (125 MHz, d_6-DMSO): δ = 27.3 (CH_2), 32.0 (Cq), 35.7 (CH_2), 40.4 (CH), 162.0 (Cq); EI-MS: *m/z* 205 $[MH]^+$, 203 $[M-H]^-$; HR-MS: calc'd for $[M+H]^+$ = 205.1448, found 205.1447.

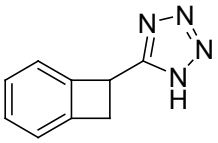
(11) Preparation of 5-(2-trifluoromethyl) benzyl-1*H*-tetrazole [11]



1.5 equivalents of diethylaluminum azide (in toluene 2.5 M) or dimethylaluminum azide (in hexane, 1M) are used in a 4 mmol scale experiment. The reaction was heated for seventy hours at 65 °C to give 730 mg of

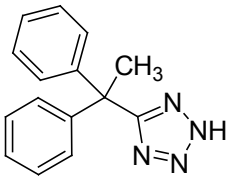
product (80 % yield) as a yellow crystalline material with a mp of 135-137 °C; TLC: R_f = 0.38; IR: ν 3000-2450 (brm, ע(C-H)), 3134 (w, ע(C-H)), 2983 (m, ע(C-H)), 2868 (m, ע(C-H)), 1586 (w, ע(C=C)), 1569 (w, ע (C=C)), 1547 (w, tetrazole), 1428 (w, ע(C=C)), 1109 (s, ע(CF_3)), 771 (s, δ(Ph)) cm^{-1}; ^{1}H-NMR (500 MHz, d_6-DMSO): δ = 4.45 (*s*, 2H), 7.51 (*m*, ^3J= 8.0, 7.6 Hz, 2H), 7.69 (*m*, ^3J=7.6 Hz, 1H), 7.77 (*d*, ^3J=8.0 Hz, 1H), 16.20 (*br*, NH); ^{13}C-NMR (125 MHz, d_6-DMSO): δ = 26.4 (CH_2), 124.4 (Cq), 126.1 (CH), 127.2 (Cq), 128.0 (CH), 132.3 (CH), 132.9 (CH), 133.6 (Cq), 154.5 (Cq); EI-MS: *m/z* 229 $[MH]^+$, 209 $[M\text{-}HF]^+$, 186 $[MH\text{-}HN_3]^+$; HR-MS: calc'd for $[M\text{-}H]^-$ = 227.0550, found 227.0550.

(12) Preparation of 5-(1,1-diphenylethyl)-1*H*-tetrazole [12]



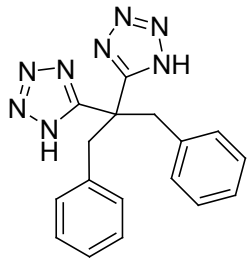
1.5 equivalents of diethylaluminum azide (1.8 M in toluene) are used in a 10 mmol scale experiment. The reaction was heated for forty nine hours at 70 °C to give 2.53 g of product (64 % yield) as a white crystalline material with a mp of 154-156 °C; TLC: R_f = 0.24; IR: ν 3117 (w, ע(C-H)), 3053 (m, ע(C-H)), 3000-2400 (brs, ע(N-H)), 2998 (s, ע(C-H)), 2716 (brs, ע(N-H)), 1575 (m, tetrazole), 1457 (s, ע(C=C)), 1435 (w, ע(C=C)), 751 (s, δ(C-H, Ph) cm^{-1}; ^{1}H-NMR (500 MHz, d_6-DMSO): δ =3.65 (*m*, 2H), 5.05 (*m*, 1H), 7.21 (*m*, 2H), 7.28 (*m*, 2H,), 16.30 (*br*, NH); ^{13}C-NMR (125 MHz, d_6-DMSO): δ = 35.7 (CH), 36.2 (CH_2), 122.7 (CH), 123.2 (CH), 127.5 (CH), 128.4 (CH), 143.4 (Cq), 143.6 (Cq), 156.4 (Cq); EI-MS: *m/z* 171 $[M\text{-}H]^-$.

(13) Preparation of 5-(1,1-diphenylethyl)-1*H*-tetrazole [13]



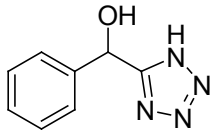
1.3 equivalents of diethylaluminum azide (2.7 M in xylene) are used in a 5 mmol scale experiment. The reaction was heated for eighty hours from 85 to 120 °C to give 550 mg of product (45 % yield) as a white crystalline material with a mp of 138-140 °C; TLC: R_f = 0.54; IR: ν 3091 (m, ע(C-H)), 3062 (w, ע(C-H)), 3025 (m, ע(C-H)), 2918 (m, ע(CH_3)), 2800-2350 (brm, ע(N-H)), 1900-1700 (w, overtones γ(C-H, Ph)), 1549 (m, tetrazole)), 1494 (s, ע(C=C)), 1447 (m, ע(C=C)), 1410 (m, ע(C=C)), 761 (s, γ(C-H, Ph)), 698 (s, γ(Ph)) cm^{-1}; ^{1}H-NMR (500 MHz, d_6-DMSO): δ = 2.18 (*s*, 3H), 7.07 (*m*, 4H), 7.30 (*m*, 6H), 16.20 (*br*, NH); ^{13}C-NMR (125 MHz, d_6-DMSO): δ =28.2 (CH_3), 45.9 (Cq), 126.6 (CH), 127.1 (CH), 127.9 (CH), 144.7 (Cq,); EI-MS: *m/z* 251 $[MH]^+$; HR-MS: calc'd for $[M\text{-}H]^-$= 173.0833, found 173.0833.

(14) Preparation of 1,3-diphenyl-2,2-bis (5-tetrazoyl) propane [14]



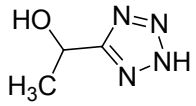
1.6 equivalents of diethylaluminum azide (2.7 M in xylene) are used in a 1.88 mmol scale experiment. The reaction was heated for eighty hours at 75 °C to give 488 mg of product (87 % yield) as a brown crystalline material with a mp of 217-219 °C; TLC: R_f = 0.6; IR: ν 3090 (s, ע(C-H)), 2889-2841 (s, ע(CH_2)), 1951-1700 (w, overtones γ(C-H, Ph)), 1563 (m, tetrazole), 1497 (m, ע(C=C)), 1459 (m, ע(C=C)), 747 (m, γ(C-H, Ph)), 700 (s, γ(Ph)); ^{1}H-NMR (500 MHz, d_6-DMSO): δ = 3.69 (*s*, 4H), 6.56 (*m*, 4H), 7.05 (*m*, 6H), 16.29 (*br*, NH); ^{13}C-NMR (125 MHz, d_6-DMSO): δ = 44.8 (Cq), 45.2 (CH_2), 126.6 (CH), 127.6 (CH), 129.2 (CH), 134.6 (Cq), 153.0(Cq); EI-MS: *m/z* 331 $[M-H]^-$, 333 $[M-H]^-$.

(15) Preparation of phenyl (2H-tetrazol-5-yl)-methanol or 5-(hydroxybenzyl)-tetrazole [15]



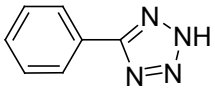
1.5 equivalents of diethylaluminum azide (2.7 M in xylene) are used in a 7 mmol scale experiment. The reaction was heated for one hour twenty minutes at 45 °C to give 1.04 g of product (82.4 % yield) as a white crystalline material with a mp of 157-159 °C; TLC: R_f = 0.23; IR: ν 3441 (brs, ν(O-H)), 3100 (m, ν(C-H)), 3000-2300 (brs, ν(N-H)), 2990 (m, ν(C-H)), 1569 (w, tetrazole), 1495 (w, ν(C=C)), 1456 (m, ν(C=C)), 1435 (s, ν(C=C)), 1059 (s, ν(C-OH)), 754 (s, γ(C-H, Ph)), 697 (s, γ(Ph)) cm^{-1}; ^{1}H-NMR (500 MHz, d_6-DMSO): δ = 6.11 (*d*, ^3J= 4.0 Hz, 1H), 6.75 (*s*, 1H, OH), 7.30 (*m*, 1H), 7.35 (*m*, 2H), 7.41 (*m*, 2H), 16.40 (*br*, NH); ^{13}C-NMR (125 MHz, d_6-DMSO): δ = 66.4 (CH), 126.4 (CH), 128.0 (CH), 128.4 (CH), 140.9 (Cq), 158.8 (Cq); EI-MS: *m/z* 177 $[MH]^+$, 175 $[M-H]^-$, 159 $[MH-H_2O]^+$, 131 $[MH-H_2O-N_2]^+$; HR-MS: calc'd for $[M-H]^-$ = 175.0625, found 175.0625.

(16) Preparation of 2*H*-tetrazole-5-methanol-α-methyl [16]



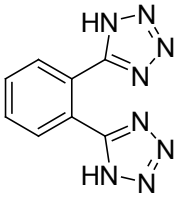
1.3 equivalents of diethylaluminum azide (2.7 M in xylene) are used in a 10 mmol scale experiment. The reaction was heated for twenty four hours from 0 °C to room temperature to give 780 mg of product (65 % yield) as a white crystalline material with a mp of 120-122 °C; TLC: R_f = 0.2 (CPS); IR**:** ν 3382 (brs, ע(O-H)), 3000-2400 (brm, ע(N-H)), 2990 (s, ע(C-H)), 1580 (m, tetrazole), 1256 (s, ע(C-O)) cm^{-1}; ^{1}H-NMR (500 MHz, d_6-DMSO): δ =1.48 (*d*, *J*= 6.5 Hz, 3H), 5.08 (*q*, ^3J=6.5 Hz, 1H), 6.01 (*br*, OH), 16.15 (*br*, NH); ^{3}C-NMR (125 MHz, d_6-DMSO): δ = 22.6 (CH_3), 60.6 (CH), 144.0 (Cq); MS: *m/z* 115 $[MH]^+$, 113 $[M-H]^-$; HR-MS: calc'd for $[M-H]^-$ = 113.0469, found 113.0469.

(17) Preparation of 5-Phenyl-1H-tetrazole [17]



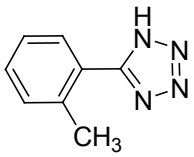
1.3 equivalents of diethylaluminum azide (2.7 M in xylene) are used in a 5 mmol scale experiment. The reaction was heated for twenty four hours at 80 °C to give 730 mg of product (99 % yield) as a white crystalline material with a mp of 214-216 °C; TLC: R_f = 0.6; IR: ν 3000-2400 (brs, ע(N-H)), 3078 (m, ע(C-H)), 3056 (m, ע(C-H)), 1609 (s, ע(C=C)), 1565 (s, tetrazole), 1487 (s, ע(C=C)), 1466 (s, ע(C=C)), 688 (s, γ(Ph)) cm^{-1}; ^{1}H-NMR (500 MHz, d_6-DMSO): δ =7.58 (*m*, 3H), 8.03 (*m*, 2H), 16.80 (*br*, NH); ^{13}C-NMR (125 MHz, d_6-DMSO): δ =123.8 (Cq), 126.6 (CH), 129.0 (CH), 130.8 (CH), 154.7 (Cq); EI-MS: *m/z* 147 $[MH]^+$, 104 $[MH\text{-}HN_3]^+$; HR-MS: calc'd for $[M\text{-}H]^-$ = 145.0520, found 145.0520.

(18) Preparation of 1,2-Bis(5-tetrazolyl)benzene [18]



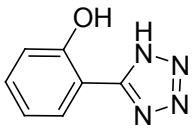
1.4 equivalents of diethylaluminum azide (2.7 M in xylene) are used in a 5 mmol scale experiment. The reaction was heated for three hours at 90 °C to give 800 mg of product (75 % yield) as a white off crystalline material with a mp of 226-227 °C; TLC: R_f = 0.07; IR: ν 3200-2400 (brs, ע(N-H)), 3114 (s, ע(C-H)), 3054 (s, ע(C-H)), 1957-1780 (w, overtones γ(C-H, Ph)), 1606 (m, ע(C=C)), 1592 (m, ע(C=C)), 1556 (s, tetrazole), 1481 (s, ע(C=C)), 1453 (s, ע(C=C)) cm^{-1}; ^{1}H-NMR: (500 MHz, d_6-DMSO): δ = 7.80 (*m*, 2H), 7.89 (*m*, 2H), 16.60 (*br*, NH); ^{13}C-NMR (125 MHz, d_6-DMSO): δ = 124.1 (Cq), 130.3 (CH), 130.9 (CH), 154.3 (Cq); EI-MS: *m/z* 215 $[MH]^+$; HR-MS: calc'd for $[M\text{-}H]^-$ = 213.0643, found 213.0643.

(19) Preparation of 5-(*o*-Methylphenyl)- 1*H* -tetrazole [19]



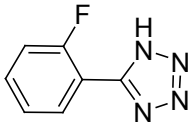
One equivalents of diethylaluminum azide (2.7 M in xylene) are used in a 7 mmol scale experiment. The reaction was heated for twenty five hours at 80 °C to give 670 mg of product (83 % yield) as a white crystalline material with a mp of 150-151 °C; TLC: R_f = 0.06; IR: ν 3062 (m, ע(C-H)), 3000-2300 (s, ע(C-H)), 2970 (s, ע(CH_3)), 1900-1700 (w, overtones γ(C-H, Ph)), 1608 (s, ע(C=C)), 1563 (s, tetrazole), 1490 (s, ע(C=C)), 746 (s, γ(C-H, Ph)) cm^{-1}; ^{1}H-NMR (500 MHz, d_6-DMSO): δ = 2.50 (*s*, 3H), 7.38 (*m*, 1H), 7.43 (*m*, 1H), 7.48 (*m*, 1H), 7.68 (*d*, 1H), 16.65 (*br*, NH); ^{13}C-NMR (125 MHz, d_6-DMSO): δ = 20.5 (CH_3), 123.8 (Cq), 126.3 (CH), 129.4 (CH), 130.7 (CH), 131.3 (CH), 137.1 (Cq), 155.0 (Cq); EI-MS: *m/z* 159 $[MH]^+$, 131 $[M\text{-}H\text{-}N_2]^-$; HR-MS: calc'd for $[M\text{-}H]^-$ = 159.0676, found 159.0676.

(20) Preparation of 5-(2-Hydroxy-phenyl)-1*H*-tetrazole [20]



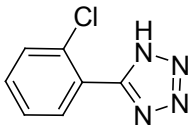
1.1 equivalents of diethylaluminum azide (2.7 M in xylene) are used in a 4 mmol scale experiment. The reaction was heated for two hours and thirty minutes at 80°C to give 628 mg of product (97 % yield) as a white crystalline with a mp of 220-222 °C; TLC: R_f = 0.46; IR: ν 3200-2500 (brs, ע(N-H), ע(O-H)), 3065 (s, ע(C-H)), 3050 (s, ע(C-H)), 1964-1600 (w, overtones γ(C-H, Ph)), 1615 (s, ע(C=C)), 1548 (s, tetrazole), 1487 (s, ע(C=C)), 1466 (s, ע(C=C)), 748 (s, γ(C-H, Ph) cm^{-1}; ^{1}H-NMR (500 MHz, d_6-DMSO): δ =7.01 (*t*, *J*= 8.0 Hz, 1H), 7.10 (*d*, *J*=8.2 Hz, 1H,), 7.41 (*dt*, *J*= 1.5, 8.0 Hz, 1H), 8.00 (*dd*, *J*= 1.5, 8.0 Hz, 1H), 11.00 (*br*, OH), 16.00 (*br*, NH); ^{13}C-NMR (125 MHz, d_6-DMSO): δ =110.5 (Cq), 116.3 (CH), 119.7 (CH), 129.0 (CH), 132.6 (CH), 151.6 (Cq), 155.3 (Cq); EI-MS: *m/z* 161.1 $[M-H]^+$, 163.1 $[M+H]^+$.

(21) Preparation of 5-(2-Fluoro-phenyl)-1*H*-tetrazole [21]



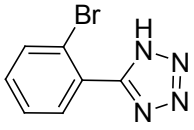
1.3 equivalents of diethylaluminum azide (1.8 M in toluene) are used in a 15 mmol scale experiment. The reaction was stirred seven hours at 90 °C to give 2.348 g of product (95 % yield). The same experiment was done with diethyl aluminum azide (in xylene, 2.5 M), and the reaction was stirred at 55 °C for 39 hours to give the same yield. The white crystalline product has a mp of 158-160 °C; TLC: R_f = 0.45; IR: ν 3100-2400 (brs, ע(N-H)), 3063 (s, ע(C-H)), 3023 (s, ע(C-H)), 1900-1750 (w, overtones γ(C-H, Ph)), 1622 (s, ע (C=C)), 1587 (m, tetrazole), 1494 (s, ע(C=C)), 1234 (s, ע(C-F)), 752 (s, γ(C-H, Ph) cm^{-1}; ^{1}H-NMR (500 MHz, d_6-DMSO): δ = 7.45 (*m*, 1H), 7.50 (*m*, 1H), 7.68 (*m*, 1H), 8.06 (*m*, 1H), 16.50 (*br*, NH); ^{13}C-NMR (125 MHz, d_6-DMSO): δ =112.5 (Cq), 116.6 (CH), 123.4 (CH), 130.2 (CH), 133.5 (CH), 158.1 (Cq), 159.8 (Cq); EI-MS: *m/z* 165 $[MH]^+$, 163 $[M-H]^-$, 135 $[MH-N_2]^-$, 122 $[MH-HN_3]^+$.

(22) Preparation of 5-(2-chloro-phenyl)-1*H*-tetrazole [22]



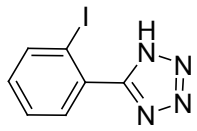
1.3 equivalents of diethylaluminum azide (2.7 M in xylene) are used in a 4 mmol scale experiment. The reaction was stirred for twenty seven hours at 50 °C to give 680 mg of product (95 % yield) as a white crystalline material with a mp of 173-175 °C; TLC: R_f = 0.48 ; IR: ν 3200-2400 (brs, ע(N-H)), 3108 (m, ע (C-H)), 3061 (m, ע(C-H)), 3034 (s, ע(C-H)), 1900-1600 (w, overtones γ(C-H, Ph)), 1603 (s, ע(C=C)), 1564 (s, tetrazole), 1472 (m, ע(C=C)), 748 (s, γ(CH, Ph) cm^{-1}; ^{1}H-NMR (400 MHz, d_6-DMSO): δ = 7.55 (*m*, 1H), 7.63 (*m*, 1H), 7.71 (*m*, 1H), 7.80 (*m*, 1H), 16.90 (*br*, NH); ^{13}C-NMR (125 MHz, d_6-DMSO): δ =124.1 (Cq), 127.8 (CH), 130.4 (CH), 131.7 (CH), 132.0 (CH), 132.6 (Cq), 153.4 (Cq); EI-MS: *m/z* 181 $[MH]^+$, 179 $[M-H]^-$, 151 $[M-H-N_2]^-$.

(23) Preparation of 5-(2-bromo-phenyl)-1*H*-tetrazole [23]



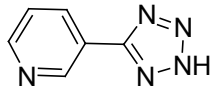
1.5 equivalents of diethylaluminum azide (2.7 M in xylene), or 1.5 equivalents of dimethylaluminum azide (1M in hexane) are used in a 3 mmol scale experiment. The reaction was stirred for thirty hours at 50 °C to give 480 mg of product (71 % yield) as a white crystalline material with a mp of 174-176 °C; TLC: R_f = 0.4; IR: ν 3100-2400 (sbr, ע(N-H)), 3068 (m, ע(C-H)), 3035 (m, ע(C-H)), 1988-1700 (w, overtones γ(C-H, Ph)), 1605 (s, ע(C=C)), 1476 (s, ע(C=C)) cm^{-1}; ^{1}H-NMR (500 MHz, d_6-DMSO): δ = 7.55 (*m*, *J* = 8.0 Hz, 2H), 7.68 (*dd*, *J* = 8.0, 4.0 Hz, 1H), 7.85 (*dd*, *J* = 8.0, 4.0 Hz, 1H), 16.70 (*br*, NH); ^{13}C-NMR (125 MHz, d_6-DMSO): δ = 121.4 (Cq), 126.1 (Cq), 127.7 (CH), 131.6 (CH), 132.2 (CH), 133.1 (CH), 154.2 (Cq); EI-MS: *m/z* 225 $[MH]^+$, 197 $[M\text{-}H\text{-}N_2]^-$, 182 $[MH\text{-}HN_3]^+$.

(24) Preparation of 5-(2-iodo-phenyl)-1*H*-tetrazole [24]



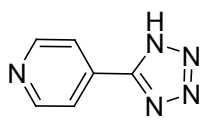
1.3 equivalents of diethylaluminum azide (2.7 M in xylene) are used in a 3 mmol scale experiment. The reaction was stirred for three days at 50 °C to give 690 mg of product (85 % yield) as a white crystalline material with a mp of 214-216 °C; TLC: R_f = 0.42; IR: ν 3100-2300 (brs, ע(N-H)), 3027 (m, ע(C-H)), 1900-1700 (w, overtones γ(C-H, Ph)), 1601 (s, ע(C=C)), 1569 (s, tetrazole), 1473 s, ע(C=C)), 1441 (s, ע(C=C)), 747 (s, γ(C-H, Ph)) cm^{-1}; ^{1}H-NMR (500 MHz, d_6-DMSO): δ = 7.34 (*m*, ^3J = 8.0 Hz, 1H), 7.59 (*m*, 2H), 8.09 (*d*, ^3J = 8.0 Hz, 1H), 17.00 (*br*, NH); ^{13}C-NMR (125 MHz, d_6-DMSO): δ = 97.6 (Cq), 128.5 (CH), 130.5 (Cq), 131.2 (CH), 132.4 (CH), 139.7 (CH), 155.8 (Cq); EI-MS: *m/z* 271 $[M\text{-}H]^-$, 243 $[M\text{-}H\text{-}N_2]^-$, 127 $[I]^-$; HR-MS: calc'd for $[M+H]^+$ = 272.9632, found 272.9630, calc'd for $[M+Na]^+$ = 294.9451, found 294.9450.

(25) Preparation of 5-(3-pyridyl)-2*H*-tetrazole [25]



1.3 equivalents of diethylaluminum azide (2.7 M in xylene) are used in a 5 mmol scale experiment. The reaction is stirred for three hours from 0 °C to room temperature. The mixture is quenched with HCl (2 M) and the pH adjusted with potassium carbonate to pH 6, the aqueous phase is saturated with solid NaCl and extracted to give 570 mg of product (78 % yield) as a white crystalline material with a mp of 226-228 °C; TLC: R_f = 0.04; IR: ν 3200-2400 (brs, ע(N-H)), 3086 (s, ע(C-H)), 3063 (s, ע(C-H)), 3036 (s, ע(C-H)), 1610 (s, ע(C=C)), 1583 (m, ע(C=C)), 1528 (m, tetrazole), 1485 (m, ע(C=C)) cm^{-1}; ^{1}H-NMR (500 MHz, d_6-DMSO): δ = 7.69 (*ddd*, ^3J = 4.9, 7.9 Hz, 1H), 8.51 (*m*, ^3J = 7.9, ^4J = 1.7 Hz), 8.77 (*dd*, ^3J = 4.9, ^4J = 1.7 Hz, 1H), 9.28 (*m*, 1H), 16.70 (*br*, NH); ^{13}C-NMR (125 MHz, d_6-DMSO): δ = 121.2 (Cq), 124.6 (CH), 135.3 (CH), 147.1 (CH), 151.1 (CH), 153.6 (Cq, C_7); EI-MS: *m/z* 148 $[MH]^+$, 146 $[M\text{-}H]^-$, 105 $[MH\text{-}HN_3]^+$; HR-MS: calc'd for $[M\text{-}H]^-$ = 146.0472, found 146.0472.

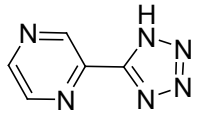
(26) Preparation of 5-(4-pyridyl)-1*H*-tetrazole [26]



1.3 equivalents of diethylaluminum azide (2.7 M in xylene) are used in a 5 mmol scale experiment. The reaction is stirred for three hours from 0 °C to room temperature. The mixture is quenched with HCl (2 M),

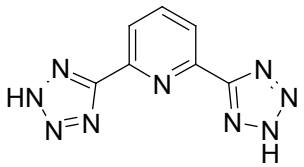
and the pH adjusted with potassium carbonate to pH 6, the aqueous phase is saturated with solid NaCl and extracted to give 700 mg of product (95 % yield) as a white crystalline material with a mp of 255-258 °C; TLC: R_f = 0.04; IR: ν 3200-3000 (brs, ע(N-H)), 3040 (m, ע(C-H)), 1619 (s, ע(C=C)), 1580 (s, tetrazole), 1448 (s, ע(C=C)); ^{1}H-NMR (500 MHz, d_6-DMSO): δ =7.78 (*d*, *J*= 6.0 Hz, 2H), 8.51 (*d*, *J*= 6.0 Hz, 2H,), 16.30 (*br*, NH); ^{13}C-NMR (125 MHz, d_6-DMSO): δ =120.9 (CH), 139.4 (Cq), 149.8 (CH), 158.9 (Cq); EI-MS: *m/z* 146 $[M-H]^-$, 118 $[M-H-N_2]^+$.

(27) Preparation of 2-(1*H*-tetrazol-5-yl)-pyrazine [27]



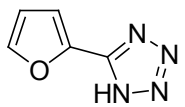
One equivalent of diisobutylaluminum azide (1.8 M in toluene) are used in a 4 mmol scale experiment. The reaction was stirred for three hours from -40 to 0 °C. The mixture reaction is quenched with HCl (2 M) and the pH adjusted with potassium carbonate to pH 6, the aqueous phase is saturated with solid NaCl and extracted to give 380 mg of product (64 % yield) as a off white crystalline material with a mp of 178-180 °C; TLC: R_f = 0.06; IR: ν 3139 (w, ע(C-H)), 3197 (w, ע(C-H)), 3175 (w, ע(C-H)), 3000-2300 (brm, ע(N-H)), 1603 (w, ע(C=C)), 1572 (w, tetrazole) cm^{-1}; ^{1}H-NMR (500 MHz, d_6-DMSO): δ = 8.87 (*m*, *J*= 4.0 Hz, 1H), 9.39 (*d*, *J*= 4.0 Hz, 2H), 17.50 (*br*, NH); ^{13}C-NMR (125 MHz, d_6-DMSO): δ = 139.7 (Cq), 142.9 (CH), 144.4 (CH), 146.3 (CH), 153.2 (Cq); EI-MS: *m/z* 147 $[M-H]^-$; HR-MS: calc'd for $[M-H]^-$ = 147.04247, found 147.04247.

(28) 2,6-Bis-(2*H*-tetrazol-5-yl)-pyridine [28]



3 equivalents of diethylaluminum azide (2.7 M in xylene) are used in a 2 mmol scale experiment. The mixture reaction is quenched with HCl (2 M) and the pH adjusted with potassium carbonate to pH 6, the aqueous phase is saturated with solid NaCl and extracted to give 360 mg of product (84 % yield) as an off white crystalline material with a mp up to 260 °C; TLC: R_f = 0.03**;** IR: *v* 3119 (s, ע(C-H)), 3092 (s, ע(C-H)), 3080 (s, ע(C-H)), 3043 (s, ע(C-H)), 3015 (s, ע(C-H)), 1557 (s, tetazole), 1455 (s, (C=C)) cm^{-1}; ^{1}H-NMR (500 MHz, d_6-DMSO): δ = 8.33 (*m*, 3H), 16.80 (*br*, NH); ^{13}C-NMR (125 MHz, d_6-DMSO): δ = 132.6 (CH), 133.8 (Cq), 140.3 (CH), 162.0 (Cq); MS: *m/z* 214 $[M-H]^-$.

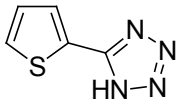
(29) Preparation of 5-furan-2-yl-1*H*-tetrazole [29]



1.2 equivalents of diethylaluminum azide (2.7 M in xylene) are used in a 5 mmol scale experiment. The reaction was stirred for twelve hours at 55 °C to give 591 mg of product (87 % yield) as a yellow crystalline material with a mp of 198-200 °C; TLC: R_f = 0.31; IR: ν 3108 (s, ע(C-H)), 3073 (w, ע(C-H)),

3022 (m, ע(C-H)), 3000-2300 (brs, ע(N-H)), 1642 (s, ע(C=C)), 1541 (s, tetrazole)), 1488 (w, ע(C=C)) cm^{-1}; ^{1}H-NMR (500 MHz, d_6-DMSO): δ = 6.77 (*dd*, *J*= 3.5 Hz, 1H), 7.26 (*d*, *J*= 3.5, 1.7 Hz, 1H), 8.02 (*d*, *J*= 1.7 Hz, 1H), 17.10 (*br*, NH); ^{13}C-NMR (125 MHz, d_6-DMSO): δ = 112.5 (CH), 112.9 (CH), 139.9 (Cq), 146.0 (CH), 148.2 (Cq); EI-MS: *m/z* 137 $[MH]^+$, 135 $[M-H]^-$; HR-MS: calc'd for $[M-H]^-$ = 135.0312, found 135.0312.

(30) Preparation of 5-thiophen-2-yl-1*H*-tetrazole [30]



1.2 equivalents of diethylaluminum azide (2.7 M in xylene) are used in a 5 mmol scale experiment. The reaction was stirred for twelve hours at 55 °C to give 616 mg of product (81 % yield) as a yellow crystalline material with a mp of 206-207 °C; TLC: R_f = 0.4; IR: ν 3110 (m, ע(C-H)), 3076 (s, ע(C-H)), 3030 (m, ע(C-H)), 3000-2300 (brs, ע(N-H)), 1594 (s, ע(C=C)), 1507 (m, tetrazole), 1410 (s, ע(C=C)) cm^{-1}; ^{1}H-NMR (500 MHz, d_6-DMSO): δ = 7.28 (*dd*, *J*=3.7, 5.0 Hz, 1H), 7.79 (*dd*, *J*= 3.7, 1.2 Hz,1H), 7.86 (*dd*, *J*= 5.0, 1.2 Hz, 1H), 16.90 (*br*, NH); ^{13}C-NMR (125 MHz, d_6-DMSO): δ =125.4 (CH), 128.6 (CH), 129.1 (CH), 130.4 (Cq), 151.4 (Cq); EI-MS: *m/z* 153 $[MH]^+$, 151 $[M-H]^-$, 110 $[MH-HN_3]^+$.

E References

[1] J. Polanski, K. Jarzembeck, *Pure Appl. Chem*. **2002**, *74*, 1227.

[2] a) B. W. LeBlanc, B. S. Banko, *Synth. Commun.* **1998**, *28*, 3591; b) E. Lieber, T. Enkoji, *J. Org. Chem.* **1961**, *26*, 4472; c) Z. P. Demko, K. B. Sharpless, *J. Org. Chem*. **2001**, *66*, 7945.

[3] a) R. L. Buchman, V. Spancmanis, R. A. Portyka, *J. Med. Chem.* **1969**, *12*, 1001; b) G. Sedelmeier, Novartis Pharma AG, **2005**, WO2005/14602 A1.

[4] a) V. Franckevicius, K. R. Knudsen, M. Ladlow, D. A. Longbottom, S. V. Ley, *Synlett* **2006**, *6*, 889; b) A. J. A. Cobb, D. M. Shaw, D. A. Longbottom, J. B. Gold, S. V. Ley, *Org. Biomol. Chem*. **2005**, *3*, 84; c) N. Momiyama, H. Torii, S. Saito, H. Yamamoto, *Proc. Nat. Acad. Sci. U. S. A.* **2004**, *101*, 5374; d) Z. P. Demko, K. B. Sharpless, *Org. Lett.* **2002**, *4*, 2525; e) A. Hartikka, P. I. Arvidsson, *Eur. J. Org. Chem.* **2005**, *20*, 4287; f) V. Aureggi, G. Sedelmeier, Novartis Pharma AG, **2007**, WO 2007/009716

[5] a) T. Nowak, A. P. Thomas, Astrazeneca, **2005**, WO 2005040159 A1; b) M. G. Palermo, S. K. Sharma, C. Straub, R.-M. Wang, L. Zawel, Y. Zhang, Z. Chen, Y. Wang, F. Yang W. Wrona, G. Liu, M. G. Charest, F. He, Novartis AG, **2005**, WO 2005097791 A1; c) V. Aureggi, G. Sedelmeier, Novartis Pharma AG, **2007**, WO 2007/009716

[6] a) N. Nazaré, V. Laux, A. Bauer, M. Wagner, Aventis Pharma, **2004**, EP1479679 A1; b) E. Olivieri-Mandala, *Gazz. Chim. Ital*. **1911**, 41, 59; c) M. S. Poonian, E. F. Nowoswiat, J. F. Blount, T. H. Williams, R. G. Pitcher, M. J. Kramer, *J. Med. Chem*. **1976**, *19*, 286; d) P. M. O'Brien, D. R. Slislovich, J. A. Picard, H. T. Lee, C. F. Purchase, B. D. Roth, A. D. White, M. Anderson, S. B. Muller, *J. Med. Chem*. **1996**, *39*, 2354; e) J. Diago-Meseguer, A. L. Palomo-Coll, J. R. Fernandez-Lizarbe, A. Zugaza-Bilbao, *Synthesis* **1980**, *7*, 547.

[7] O. Kazuyuki, T. Makoto, M. Tohru, O. Hiroyuki. Ono Pharmaceutical Co., Ltd., Japan, **1997**, EP 761680 A2.

[8] a) Z. P. Demko, K. B. Sharpless, *J. Org. Chem*. **2001**, *66*, 7945; b) H. Detert, D. Schollmeier, *Synthesis* **1999**, *6*, 999; c) H. Detert, D. Schollmeier, *Synthesis* **1999**, *6*, 999; d) M. Alterman, A. Hallberg, *J. Org. Chem*. **2000**, *65*, 7984.

[9] Z. P. Demko, K. B. Sharpless, *J. Org. Chem*. **2001**, *66*, 7945.

[10] a) T. J. Bleisch, S. A. Filla, P. L. Ornstein, Eli Lilly and Company, USA, **2002**, WO 2002053556 A2; b) C. P. Hegarty, H. C. Pietryk, American Home Products Corp., USA, **1977**, US 4032659.

[11] T. Utsunomiya et all, Nissan Chem. Industries, **1999**, Patent written in Japanese, WO9906380 A1.

[12] O. Kazuyuki, T. Makoto, M. Tohru, O. Hiroyuki, Ono Pharmaceutical Co., Ltd., Japan, **1997**, EP 761680 A2.
[13] J. V. Duncia, M. E. Pierce, J. B. Santella, III, *J. Org. Chem*. **1991**, *56(7)*, 2395.
[14] H. Illy, Ciba-Geigy AG., Switz., Ger. Offen. **1978**, DE 2731323 (A1).
[15] a) Z. P. Demko, K. B. Sharpless, *J. Org. Chem*. **2001**, *66*, 7945.
[16] B. E. Fisher, A. J. Tomson, J. P. Horwitz, *J. Org. Chem*. **1959**, *24*, 1650.
[17] a) Z. P. Demko, K. B. Sharpless, *J. Org. Chem*. **2001**, *66*, 7945; b) K. Sisido, K. Nabika, I. Tyuzo, S. Kozima, *J. Organomet. Chem*. **1971**, *33*, 337; c) B. S. Jursic, B. W. Leblanc, *J. Heterocycl. Chem*. **1998**, *35(2)*, 405; d) J.-J. Shie, J.-M. Fang, *J. Org. Chem*. **2003**, *68*, 1158; e) D. Amantini, R. Beleggia, F. Fringuelli, F. Pizzo, L. Vaccaro, *J. Org. Chem*. **2004**, *69*, 2896; f) M. Alterman, A. Hallberg, *J. Org. Chem*. **2000**, *65*, 7984; g) J. S. Mihina, R. M. Herbst, *J. Org. Chem*. **1950**, *15*, 1082; h) J. Kaczmarek, Z. Grzonka, *Pol. J. Chem*. **1980**, *54*, 1297.
[18] a) Z. P. Demko, K. B. Sharpless, *J. Org. Chem*. **2001**, *66*, 7945; b) A. Fleming, F. Kelleher, M. F. Mahon, J. McGinley, V. Prajapati, *Tetrahedron* **2005**, *61*, 7002; c) W. Ried, S. Aboul-Fetouh, *Tetrahedron* **1988**, *44*, 3399; d) J. Kaczmarek, Z. Grzonka, *Pol. J. Chem*. **1980**, *54*, 1297.
[19] a) J. S. Mihina, R. M. Herbst, *J. Org. Chem*. **1950**, *15*, 1082; b) J. Kaczmarek, Z. Grzonka, *Pol. J. Chem*. **1980**, *54*, 1297.
[20] a) K. Koguro, T. Oga, S. Mitsui, R. Orita, *Synthesis* **1998**, *6*, 910; b) J. Kaczmarek, Z. Grzonka, *Pol. J. Chem*. **1980**, *54*, 1297; c) G. Sedelmeier, Novartis Pharma AG, **2005**, WO2005/014602 A1; d) A. Kumar, R. Narayanan, H. Shechter, *J. Org. Chem*. **1996**, *61*, 4462.
[21] a) R. K. Russell, W. V. Murray, *J. Org. Chem*. **1993**, *58*, 5023; b) G. Sedelmeier, Novartis Pharma AG, **2005**, WO2005/14602 A1; b) K. Koguro, T. Oga, S. Mitsui, R. Orita, *Synthesis* **1998**, *6*, 910; c) E. F. George, W. R. Riddell, Imperial Chemical Industries Ltd., UK, **1975**, US 3865570; d) K. Srinivas, C. K. S. Nair, S. Ramesh, M. Pardhasaradh, *Org. Prep. Proc. Int*. **2004**, *36*, 69.
[22] a) E. F. George, W. R. Riddell, Imperial Chemical Industries Ltd., UK, **1975** US 3865570; b) K. Srinivas, C. K. S. Nair, S. Ramesh, M. Pardhasaradhi, *Org. Prep. Proc. Int*. **2004**, *36*, 69; c) G. Sedelmeier, Novartis Pharma AG, **2005**, WO2005/14602 A1; d) R.N. Butler, V. C. Garvin, *J. Chem. Soc*., Perkin Trans. 1, **1981**, *2,* 390.
[23] a) S. J. Wittember, B. G. Donner, *J. Org. Chem*. **1993**, *58*, 4139; b) J. Kaczmarek, Z. Grzonka, *Polish J. Chem*. **1980**, *54*, 1297.
[24] a) J. Kaczmarek, Z. Grzonka, *Pol. J. Chem*. **1980**, *54*, 1297; b) J. Boivin, S. Husinec, S. Z. Zard, *Tetrahedron* **1995**, *51)*, 11737.
[25] a) J. M. McManus, R. M. Herbst, *J. Org. Chem*. **1959**, *24*, 1462; b) D. Amantini, R. Beleggia, F. Fringuelli, F. Pizzo, L. Vaccaro, *J. Org. Chem*. **2004**, *69*, 2896; c) T. T. Denton, X. Zhang, J. R. Cashman, *J. Med. Chem.* **2005**, *48*, 224; d) M. Alterman, A. Hallberg, *J. Org. Chem*. **2000**, *65*, 7984.
[26] a) H. Detert, D. Schollmeier, *Synthesis* **1999**, *6*, 999; b) J. M. McManus, R. M. Herbst, *J. Org. Chem*. **1959**, *24*, 1462; c) M. Alterman, A. Hallberg, *J. Org. Chem*. **2000**, *65*, 7984.
[27] a) Z. P. Demko, K. B. Sharpless, *J. Org. Chem*. **2001**, *66*, 7945; b) G. F. Holland, J. N. Pereira, *J. Med. Chem*. **1967**, *10*, 149; c) G. A. Wächter, M. C. Davis, A. R. Martin, S. G. Franzblau, *J. Med. Chem*. **1998**, *41(13)*, 2436.
[28] a) J. M. McManus, R. M. Herbst, *J. Org. Chem.* **1959**, *24*, 1462; b) M. Duati, S. Tasca, F. C. Lynch, H. Bohlen, J. G. Vos, S. Stagni, M. D. Ward, *Inorg. Chem*. **2003**, *42*, 8377
[29] a) F. Lenda, F. Guenoun, B. Tazi, N. Ben Iarbi, H. Allouchi, J. Martinez, F. Lamaty, *Eur. J. Org. Chem*. **2005**, *2*, 326; b) A. Antonowa, S. Hauptmann, *Zeitschrift fuer Chemie* **1976**, *16*, 17; c) J.-J. Shie, J.-M. Fang, *J. Org. Chem*. **2003**, *68*, 1158; d) D. Amantini, R. Beleggia, F. Fringuelli, F. Pizzo, L. Vaccaro, *J. Org. Chem*. **2004**, *69*, 2896.
[30] a) F. Lenda, F. Guenoun, B. Tazi, N. Ben Iarbi, H. Allouchi, J. Martinez, F. Lamaty, *Eu. J. Org. Chem*. **2005**, *2*, 326; b) A. Antonowa, S. Hauptmann, *Zeitschrift fuer Chemie* **1976**, *16*, 17; c) J.-J. Shie, J.-M. Fang, *J. Org. Chem*. **2003**, *68*, 1158.