SYNTHESIS OF 1,5-SUBSTITUTED TETRAZOLES FROM SECONDARY THIOAMIDES

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Dedicated to Prof. R. Huisgen

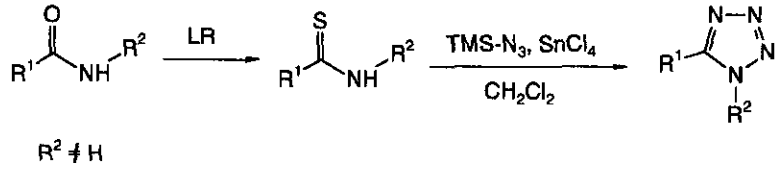
Abstract - A new, rather simple method for the conversion of thioamides and similar structures into 1,5-substituted tetrazoles is described. The procedure employs TMS-N_3 and a mild Lewis acid, like $SnCl_4$, in an inert solvent at room temperature and leads to high yields. Such compounds are of increasing interest for their pharmaceutical properties.

Since the use of 6,7,8,9-tetrahydro-5*H*-tetrazoloazepine (**4c**) ("cardiazole, metrazole") as a cardic stimulant[1] several new medical applications of tetrazoles have been developed. The traditional methods of preparing tetrazoles often require drastic conditions,[2] barely suitable for all, but the most simple tetrazoles

Aromatic 1*H*-tetrazoles play an important role as acidic catalysts in nucleotide chemistry.[3] These reagents are usually prepared by conversion of nitriles with sodium azide at high temperatures.[4] Many tetrazoles have been made from amides via imidioyl chloride intermediates using phosphorous pentachloride.[5] More recently, a tetrazole synthesis from secondary amides was introduced by activation of the carbonyl moiety *via* PPh_3/DEAD in order to form tetrazoles with TMS-N_3 [6] Another very effective method is the activation of the secondary amide using triflic anhydride.[7] In many cases however, there is still a need for alternative methods. Already in 1954, Wiberg found that thioamides form tetrazoles when treated with aluminum azide under reflux conditions.

[8] To our knowledge, no further attempt to use thioamides was made. These can be derived from many starting materials. The conversion of amides into thioamides, for example, is inexpensive, simple and provides very good yields in most cases.

We used phosphorous pentasulfide in xylene (method A[9]) or Lawesson's reagent (LR, method B[10]). The latter can be easily prepared by condensation of phosphorous pentasulfide with readily available anisole.[11] The yields are generally high, often exceeding 95%

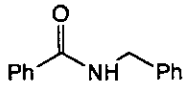
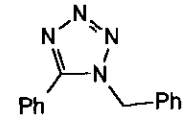
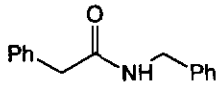
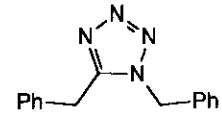
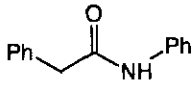
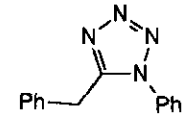
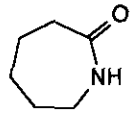
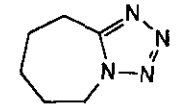
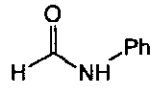
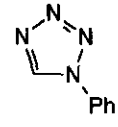
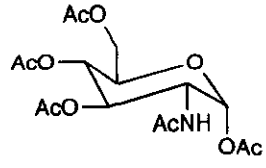
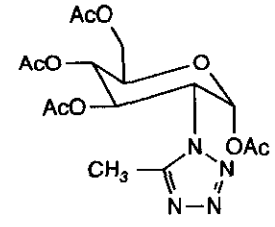
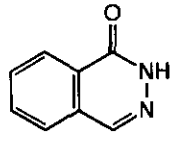
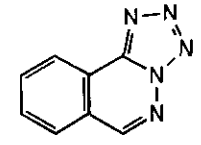
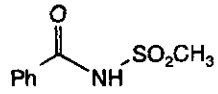
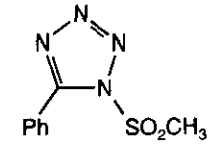


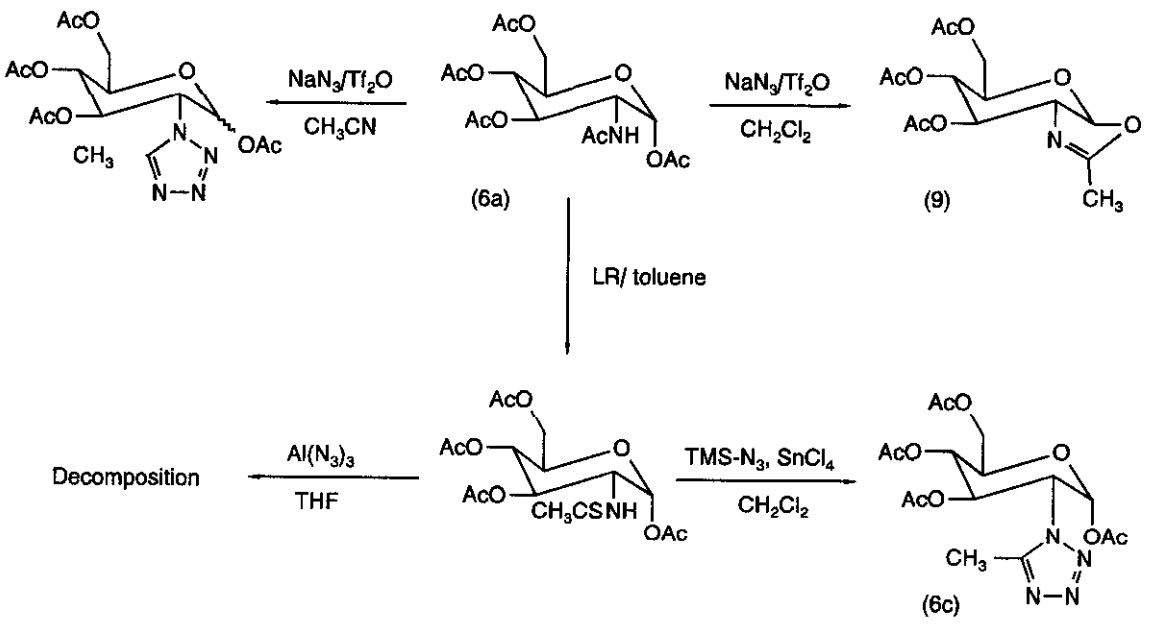
Scheme1: Conversion of amides into tetrazoles via thioamides

All amides were commercially available or synthesized by standard procedures. 1*H*-substituted tetrazoles can not be made directly. They must be prepared by using a cleavable substituent, e g. the ß-cyanoethyl group. However, 5*H*-phenyltetrazole (**5c**) was prepared straight-forward.

Thioureas have not been used successfully yet, while thiosulfonamides gave totally insoluble and noncrystalline materials in most cases Nevertheless, **8b** gave the corresponding tetrazole (**8c**) in moderate yields. This was probably due to unoptimized reaction conditions.

However, thiophthalazone (**7b**) led to tetrazole (**7c**) in excellent yields, proving this methods scope beyond standard 1,5-dialkyl/aryl-tetrazoles. We also tested the Tf_2O/NaN_3 method on amide (**6a**) as well as the $Al(N_3)_3$ method to compare its virtues. While latter procedure led to total destruction of the glycoside structure, the Tf_2O/NaN_3 method using acetonitrile as solvent gave a 5:2 (α:ß) mixture of both possible anomeric tetrazoles They could not be separated. The use of the solvent CH_2Cl_2 gave oxazole (**9**).

#	Amide (**a**)	Method of preparation of thioamide (**b**)	Tetrazole (**c**)	Yield (%)
1		B		57
2		B		91
3		B		93
4		A		72
5		A		71
6		B		78
7		B		95
8		A		40



Scheme2. Comparison of different tetrazole forming methods on glycoside amide

It should be noted that the use of sodium azide in CH_2Cl_2 may be hazardous [12] All results have been achieved by using $SnCl_4$ as a Lewis acid Also $FeCl_3$ gave the same results.However, it is rather insoluble and therefore required somewhat longer reaction times. The use of two equivalents of TMS-N_3 is not due to reaction stoichiometrics, but in order to obtain significantly greater yields. However, the use of only one equivalent gave more than 50% of tetrazole.

Carrying out the experiments, we found a great variety in the ^{13}C-nmr-shift values of the tetrazole-C-atom beyond its usual range of 150-160 ppm. For example, in the case of tetrazolo[5,1-*a*]phthalazine (**7c**), we performed ROESY, HMBC and gated decoupling experiments in order to obtain a complete set of exactly determined shift values. In this case we found a ^{13}C-nmr shift value of the tetrazole C at only 142.0 ppm.

EXPERIMENTAL

All solvents were dried after standard procedures. Melting points are uncorrected. Ir-spectra were taken in KBr-pellets on Perkin-Elmer model 177 and 255 instruments. ^{1}H-nmr-spectra were recorded at 360 MHz and 200MHz respectively. ^{13}C-nmr-spectra were recorded at 90 MHz. TMS was used as an internal standard. Ms were recorded using impact at 70 eV (EI) or by using isobutane (CI).

1-Methyl-5-[1,3,4,6-tetra-O-acetyl-2-desoxy-α-D-glucopyranosyl]-1*H*-tetrazole (**6c**): Typical procedure

2 07 g (5.0 mmol) of the thioamide (**6b**) and 1.15 g (10 mmol) TMS-N_3 in 20 ml of CH_2Cl_2 were stirred under argon atmosphere until a clear solution resulted. Then 6 0 ml of 1 M $SnCl_4$-solution in CH_2Cl_2 was added dropwise over a period of 30 min at room temperature. The mixture showed a reddish colour and after 10- 40 min light preticipation took place. Stirring is continued for 22 h, whereafter the reaction is quenched with 15 ml of sat aq $NaHCO_3$. Phases were separated and the aqueous portion was washed twice with 30 ml of CH_2Cl_2. The combined organic phases were dried over Na_2SO_4, filtered, and evaporated. The resulting material was recrystallized from CH_2Cl_2/Et_2O to give 78 % **6c** as a white powder, mp 180°C.

^{1}H-Nmr ($CDCl_3$) δ· 1.83 (s, 3H, C*H*$_3$-CN); 2.07, 2 10, 2.12 (3s, 9H, C*H*$_3$-CO); 2.63 (s, 3H, C*H*$_3$CO-C1); 4.13 (*dd*, 1*H*, ^{2}J= 12.4 Hz, ^{3}J= 1.8 Hz, H6), 4.35 (ddd, 1H, ^{3}J= 8.0 Hz, ^{3}J= 3.8 Hz, ^{3}J= 1.8 Hz, H5), 4 44 (dd, 1H, ^{2}J= 12.4 Hz, ^{3}J= 3 8 Hz, H6'); 4.77 (dd, 1H, ^{3}J= 11.0 Hz, ^{3}J= 3 4 Hz, H2); 5 27 (dd, 1H, ^{3}J= 8.0 Hz, ^{3}J= 9 6 Hz, H4), 6.21 (dd, 1H, ^{3}J= 9 6 Hz, ^{3}J= 11.0 Hz, H3), 6 39 (d, 1H, ^{3}J= 3 4 Hz, H1) ^{13}C-Nmr ($CDCl_3$) δ. 9 0 (*C*H$_3$-CN); 20.3, 20 5, 20.6, 20.7 (4x *C*H$_3$-CO); 58 4 (C2); 61 5 (C6); 68.3, 69.1, 70.3 (C3, C4, C5), 88 5 (C1); 152.5 (C-tet); 168.3, 69.0, 169.7, 170 4 (4x CO). Ir (ν_{max})· 1225, 1750 cm^{-1} Ms ($^m/_z$, %): 471 ((M+ isobutane-H)$^+$, 32.2), 415 ((M+ H)$^+$, 100), 355 ((M+ H- AcOH)$^+$, 295 ((M+ H- 2x AcOH)$^+$, 7 5).

$[\alpha]_{20}^{D} = +90.8°$ (c=6, $CHCl_3$).

5-Benzyl-1-phenyl-1*H*-tetrazole (**1c**)

After quenching, the reaction mixture was evaporated to dryness and then extracted with hot ethanol (3x 15 ml). After cooling to 4°C **1c** was obtained as white crystals in 57 % yield, mp 93°C.

^{1}H-Nmr (MeOD-d_4) δ: 4 94 (s, 2H, CH_2); 7.30- 7 83 (m, 10H, 2x Ph). ^{13}C-Nmr (MeOD-d_4) δ 47.9 (CH_2); 128 5 (2C), 129.1, 129.6 (2C), 129 7, 130 3, 130 7, 135.0 (ipso-C), 136.0 (ipso-C); 166.1 (tet-C). Ms ($^m/_z$, %)· 208 ((M- N_2)$^+$, 13.1), 91 ($PhCH_2^+$, 100), 65 ($C_5H_5^+$, 27 1).

1,5-Dibenzyl-1*H*-tetrazole (**2c**)

After quenching, the reaction mixture was evaporated to dryness and then extracted with acetone (3x 15 ml). The extract was poured into cold ethanol (60 ml) and the precipitates were filtered off. After removal of the solvent 91 % of **2c** resulted as a white, waxy oil

^{1}H-Nmr (DMSO-d_6) δ: 3.79 (s, 2H, CH_2N); 4 46 (s, 1H, CH_2CN); 4.49 (s, 1H, CH_2CN); 7.25- 7 43 (m, 10H, 2x Ph). ^{13}C-Nmr (DMSO-d_6) δ: 38.44 (CH_2N); 45.43 (CH_2CN), 127 9 (3C), 128.1, 128.8 (2C), 128.9 (2C), 129.0 (2C), 134.4 (ipso-C), 135.3 (ipso-C), 165.9 (tet-C) *Anal.* Calcd for $C_{15}H_{14}N_4$. C, 71.98, H, 5.64; N, 22.38. Found· C, 72.18, H, 5.60, N, 22 64.

1-Benzyl-5-phenyl-1*H*-tetrazole (**3c**)

Usual procedure gave 93 % of **3c** as a light yellow oil.

^{1}H-Nmr ($CDCl_3$) δ. 2,19 (s, 2H, CH_2); 7.18- 7.37 (m, 10H, 2x Ph). ^{13}C-Nmr ($CDCl_3$) δ: 31.3 (CH_2), 125.6, 126.2, 127.5, 127.7, 128.9, 129 0, 129.1, 129.2, 130.4, 130 8 (10C, 2xPh); 132 4 (ipso-C); 133.2 (ipso-C); 154.5 (tet-C). *Anal.* Calcd for $C_{14}H_{12}N_4$: C, 71 17; H, 5.12; N, 23 71. Found. C, 71.00; H, 5.09; N, 23 99

6,7,8,9-Tetrahydro-5*H*-tetrazoloazepine (**4c**)

Product obtained after standard procedure was recrystallized from toluene to yield 72 % of **4c**, mp 60°C.

^{1}H-Nmr ($CDCl_3$) δ: 1.66- 1 95 (m, 6H, 3x CH_2); 3 03 (m, 2H, CH_2-N); 4 42 (m, 2H, CH_2-CN). ^{13}C-Nmr ($CDCl_3$) δ· 24 2, 24.6, 27 2, 29.9 (4x CH_2); 49.3 (CH_2-N); 165 6 (tet-C). *Anal.* Calcd for $C_6H_{10}N_4$: C, 52 16; H, 7 30; N, 40 55. Found· C, 52.40; H, 7.11, N, 40.55.

1-Phenyl-5*H*-tetrazole (**5c**)

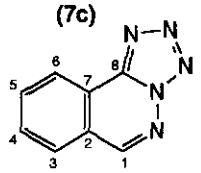
After evaporation of the organic solvent pure **5c** was obtained (71 %), mp 65°C.

^{1}H-Nmr ($CDCl_3$) δ· 7 57- 7 76 (m, 5H, Ph); 9.06 (s, 1H, CH) ^{13}C-Nmr ($CDCl_3$) δ· 121.1 (2C), 130.0, 130.1 (2C); 133.7 (tet-C); 140.5 (ipso-C). *Anal.* Calcd for $C_7H_6N_4$· C, 57.54; H, 4.13; N, 38 33. Found C, 57 90; H, 4.19, N, 38 50

Tetrazolo-[5,1-*a*]phthalazine (7c)

After evaporation of the organic solvent rather pure **7c**, mp 206°C, was obtained. Further purification by flash chromatography (hexane/ethylacetate 3:1, v·v) gave 95 % pure **7c**, mp 208°C

(7c)



^{1}H-Nmr ($CDCl_3$) δ 8 04 (dtr, 1H, $^3J_{4,3,4,5}$= 7.6 Hz, $^4J_{4,6}$= 1 2 Hz, H4), 8 14 (dtr, 1H, $^3J_{4.5,5\,6}$= 7 6 Hz, $^4J_{3,5}$= 1.2 Hz, H5), 8.18 (d, 1H, $^3J_{3,4}$= 8 0 Hz, H3); 8 77 (d, 1H, $^3J_{5,6}$= 8 0 Hz, H6); 8.97 (s,1H, H1). ^{13}C-Nmr ($CDCl_3$) δ. 122.2 (C-2), 124.5 (C-6); 124 8 (C-7), 128.5 (C-3); 132.6 (C-4), 134 8 (C-5); 142.0 (C-8); 149 1 (C-1) ^{1}H- ^{13}C-coupling ($CDCl_3$): C-1: $^1J_{C\text{-}1,H\text{-}1}$= 186.2 Hz, $^4J_{C\text{-}1,H\text{-}3}$= 4 9 Hz; C-3 $^1J_{C\text{-}3,H\text{-}3}$= 165 0 Hz, $^4J_{C\text{-}3,H\text{-}5}$= 9.2 Hz; C-4: $^1J_{C\text{-}4,H\text{-}4}$= 165.4 Hz, $^4J_{C\text{-}4,H\text{-}6}$= 7.9 Hz, C-5. $^1J_{C\text{-}5,H\text{-}5}$= 164 9 Hz, $^4J_{C\text{-}5,H\text{-}3}$= 7.8 Hz, C-6 $^1J_{C\text{-}6,H\text{-}6}$= 168.2 Hz, $^4J_{C\text{-}6,H\text{-}4}$= 6.9 Hz. Ms ($^m/_z$, %)· 210 ((M+ H+ isobutane)$^+$, 2.2), 172 ((M+ H)$^+$, *100*).

5-Methylsulfonyl-1-phenyl-1*H*-tetrazole (**8c**)

After quenching with $NaHCO_3$ the mixture was evaporated to dryness and extracted with 50 ml of hot ethanol After cooling to room temperature precipitates were filtered off and the residue was again treated with 10 ml of ice-cold ethanol **8c** did not go into solution again to give white crystals, mp 165°C (yield 40 %)

^{1}H-Nmr (DMSO-d_6) δ: 3 25 (s, CH_3); 7.46- 7.60 (m, Ph). ^{13}C-Nmr (DMSO-d_6) δ: 127.7, 128 5, 129.2 (5C, Ph); 131 6 (ipso-C), 163.1 (tet-C). *Anal.* Calcd for $C_8H_8N_4O_2S$. C, 42 85; H, 3.60, N, 25.00 Found· C, 42 80; H, 3 44, N, 25.20.

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