Synthesis and Chemical Transformation of Fused Tetrazoles Derived from 2-Bromomethyl- and 2-Iodomethyl-3,5,6,7-tetrahydro-4(2*H*)-benzofuranones

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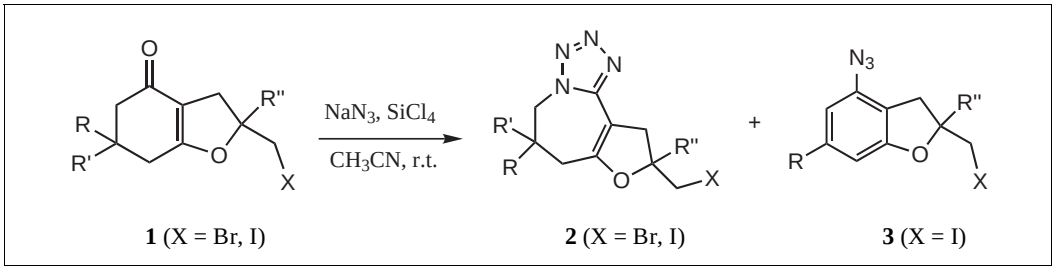

1 (X = Br, I) **2** (X = Br, I) **3** (X = I)

The 2-bromomethyl-3,5,6,7-tetrahydrobenzofuranones **1a-d** were subjected to triazidochlorosilane-sodium azide–mediated Schmidt rearrangement to afford the corresponding tetrazolofuroazepine derivatives **2a-d** *via* methylene shift. Under similar reaction conditions, the 2-iodomethyl-3,5,6,7-tetrahydrobenzofuranones **1e-h** afford mixtures of the corresponding tetrazolofuroazepines **2e-h** and the 4-azido-2-iodomethyl-2,3-dihydrobenzofuran derivatives **3a-c**. A mechanism is proposed to account for the divergence in the reactivity of these 2-halogenomethyltetrahydrobenzofuranones (X = Br *versus* I). In turn, the 2-halogenomethyltetrazolofuroazepines **2a**,**b**,**d-h** and the 4-azido-2-iodomethyl-2,3-dihydrobenzofurans **3a**,**b** underwent nucleophilic substitution with triethyl phosphite and dehydrohalogenation using DBU in refluxing toluene to give the corresponding tetrazolofuroazepines **4a-d** and **5a-c** and benzofurans **6a,b**.

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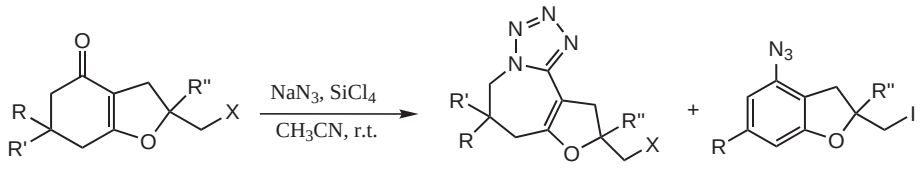
Introduction.

The 2-halogenomethyl-3,5,6,7-tetrahydrobenzofuranones contain several reaction centers for further studies of chemical transformation; they have been found to undergo dehydrohalogenation and subsequent isomerization to afford the 2-methyldihydrobenzofuranones [1,2]. Their cyclohexenone moiety undergoes iodine-methanol promoted oxidative aromatization to afford the corresponding 2-halogenomethyl-4-methoxy-2,3-dihydrobenzofuran derivatives [1]. The oxime derived from 2,6,6-trimethyl-6,7-dihydro-5*H*-benzofuranone was previously shown to undergo polyphosphoric acid–mediated Beckmann rearrangement to afford furazepinone [3,4]. Thionation and subsequent reaction of the latter with ammonia derivatives afford products that can be further transformed to furo[3,2-*c*]azepines [3] or benzazeto-azepines [4] with potential antibacterial or *in vitro* antitumour activity, respectively. Our interest in the synthesis of molecules bearing tetrazole group [5] and the application of tetrazoles as raw material for medicine, agrochemicals, foaming agents and in the automobile inflator industry [6], prompted us to incorporate the tetrazole moiety into the 2-halogenomethyltetrahydro-benzofuranones. The latter have been chosen as substrates because of the good leaving potential of the halogen atoms (X = Br, I) to enable further transformation of the resulting tetrazole derivatives.

Results and Discussion.

Herein we subjected the 2-halogenomethyltetrahydro-benzofuranones **1a-h** (X = Br, I) to silicon tetrachloride and sodium azide in acetonitrile (Scheme 1). This reagent mixture was chosen because it affords tetrazoles in quantitative yields as sole products [5]. The 2-bromo-methyl derivatives **1a-d** afforded the corresponding hitherto unknown tetrazolofuroazepine derivatives **2a-d** *via* methylene carbon (C-5) shift as sole products. In the case of the 2-iodomethyl derivatives **1e-f** we isolated the 2-iodomethyltetrahydrotetrazolofuroazepine **2e-h** and the second product characterized using a combination of spectroscopic techniques as the corresponding previously undescribed 4-azido-2-iodomethyl-2,3-dihydrobenzofuran **3a-c**. The ^{1}H nmr spectra of products **3a-c** are characterized by the presence of groups of signals in the aliphatic region and resonances corresponding to the aromatic protons. The presence of the azido group, on the other hand, is confirmed by the strong ir absorption bands in the regions υ_{max} 2105.3 – 2109.1 cm^{-1} (asymmetric) and υ_{max} 1236.4 – 1258.3 cm^{-1} (symmetric) in agreement with the literature values for organic azides [7].

Scheme 1

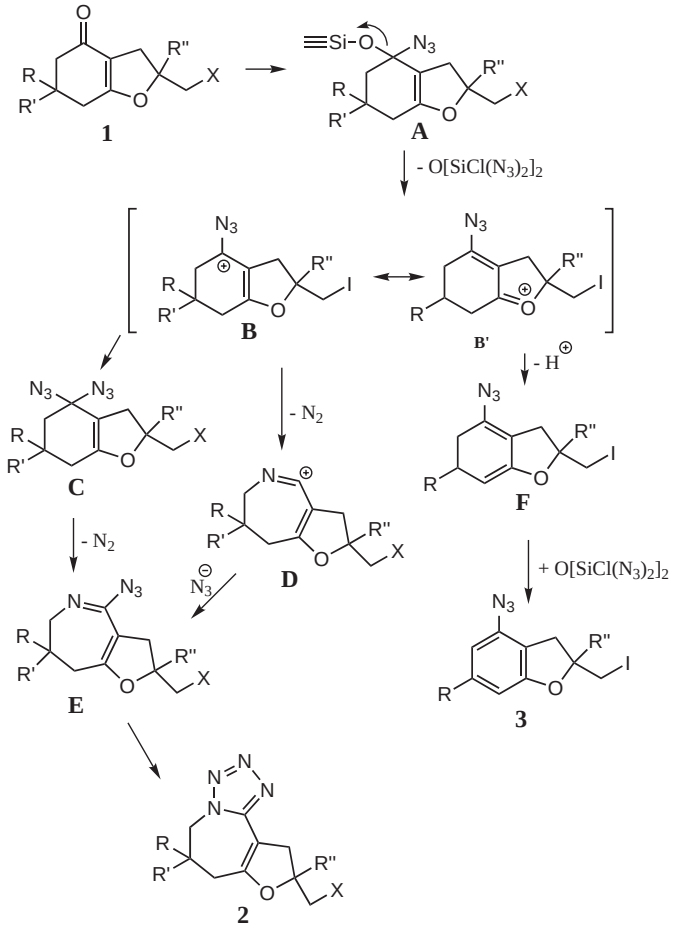


1 **2** **3**

Substrate	R	R'	R"	X	Yield of **2** (%)	Yield of **3** (%)
1a	H	H	H	Br	**2a** (68)	-
1b	H	CH_3	H	Br	**2b** (56)	-
1c	H	H	CH_3	Br	**2c** (89)	-
1d	CH_3	CH_3	H	Br	**2d** (65)	-
1e	H	H	H	I	**2e** (42)	**3a** (18)
1f	H	CH_3	H	I	**2f** (44)	**3b** (14)
1g	H	H	CH_3	I	**2g** (42)	**3c** (19)
1h	CH_3	CH_3	H	I	**2h** (50)	-

The divergence in the reactions of the 2-bromomethyl- and the 2-iodomethyl derivatives **1** is presumably the consequence of the influence of remote factors such as inductive effect of the halogen atom on the nucleophilicity of the ethereal oxygen. We propose a mechanism outlined in Scheme 2, which involves the initial collapse

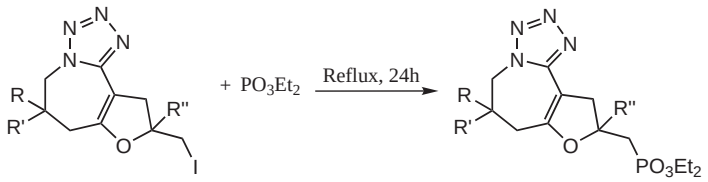
Scheme 2



of the siloxy azide **A** to the resonance stabilized azidocarbenium ion **B**. The latter presumably undergoes Schmidt type rearrangement to yield the iminocarbenium ion **D**, which is attacked by excess azide ion to yield **E**. Subsequent cyclization of **E** into the thermodynamically more stable [8] tetrazole derivative **2** then occurs in analogy with the mechanisms proposed in literature [9,10,11]. Although we cannot completely rule out the possibility of formation of **E** from the gem-diazide **C**, the latter if formed will probably be the result of attack of **B** by azide ion. Until recently, the gem-diazide was believed to be formed directly from the siloxy azide through nucleophilic substitutions of the siloxy group by azide ion [9,11]. Our observation provides experimental evidence for the competing route that involves the participation of the azidocarbenium ion that was previously suggested by Salama and coworkers [10]. We strongly believe the formation of products **3** to be the consequence of initial deprotonation of the azidocarbenium intermediate **B'** to **F** and subsequent dehydrogenation by an oxidant presumably siloxane $O[SiCl(N_3)_2]_2$ or some species derived from it. Siloxanes are used as oxidizing agents in shampoos or conditioners [12]. This step is presumably favoured by the combined electron delocalization of the ethereal oxygen and electron donating inductive effect of the adjacent methylene group attached to the less electronegative iodine atom. Recourse to literature revealed only one method describing the one-pot synthesis of 4-azidoquinolines from the reaction of quinolin-4(1*H*)-ones with diphenylphosphoryl azide-triethylamine mixture in dimethyl formamide under reflux [13]. These products are the result of addition of the azide ion to the phosphoric ester intermediate and subsequent displacement of the phosphate mediated by lone pair electron delocalization by nitrogen at the β-position. The azido group is conventionally incorporated into the aromatic ring by indirect methods such as diazotization of aniline derivatives and subsequent reaction of the intermediate diazonium salts with sodium azide [14]. We can now also add these high-value intermediates to the synthetic chemist's toolbox.

Since our ambition was to access compounds that might interact with biological systems, further studies of chemical transformation of the above products were undertaken. The applications of aminophosphonic acids as antibacterial, antiviral, pesticidal, insecticidal and herbicidal agents in pharmacological and agrochemical industries has prompted us to introduce the phosphonate moiety into systems **2**. The iodotetrazolo derivatives **2e-h** were subjected to triethyl phosphite under reflux for 24 h to afford the corresponding 2-(diethoxy phosphonomethyl)hexahydrotetrazolofuroazepines **4a-d** albeit in relatively low yields (Scheme 3). The structures of these products were confirmed using a combination of nmr, ir and mass spectroscopic techniques.

Scheme 3



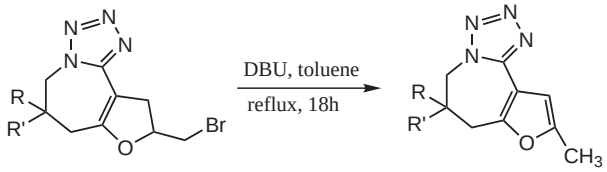
2 **4**

Substrate	R	R’	R”	Yield of **4** (%)
2e	H	H	H	**4a** (52)
2f	H	CH_3	H	**4b** (40)
2g	H	H	CH_3	**4c** (31)
2h	CH_3	CH_3	H	**4d** (47)

The 2-bromomethyl derivatives **2a**,**b**,**d** were reacted with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in dry toluene under reflux to afford the corresponding C_9-C_{10} unsaturated derivatives **5a-c** in reasonable yields (Scheme 4). Dehydrohalogenation and subsequent isomerization are confirmed by the presence of methyl and olefinic protons signals at δ *ca*. 2.30 and 6.53 ppm in the ^{1}H nmr spectra of **5**. The latter are structural analogues of azetopyrroloazepinones derived from furazepinones, and the former are known to exhibit *in vitro* antitumour activity [4].

The 4-azido-2-iodomethyldihydrobenzofuran derivatives **3a,b** were also subjected to DBU in refluxing toluene to afford the corresponding hitherto unknown 4-azido-2-methylbenzofuran derivatives **6a,b** (Scheme 5). Products **6** are easily distinguished from the corresponding precursors by the presence of methyl (δ *ca*. 3.30 ppm) and sets of signals in the aromatic region of their ^{1}H nmr spectra.

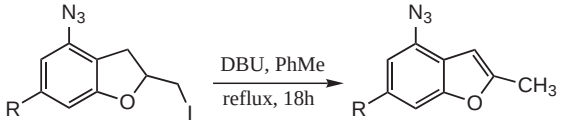
Scheme 4



2 **4**

Substrate	R, R'	Yield of **5** (%)
2a	H, H	**5a** (65)
2b	H, CH_3	**5b** (63)
2d	CH_3,CH_3	**5c** (60)

Scheme 5



3 **6**

Substrate	R	Yield of **6** (%)
3a	H	**6a** (64)
3b	CH_3	**6b** (62)

The above results extend the usefulness of triazidochlorosilane as a reagent to promote the Schmidt rearrangement of cycloalkenone derivatives to afford differently functionalized 2-halogenomethyltetrazolofuroazepines and 4-azido-2-iodomethyldihydrobenzofurans in yields ranging from moderate to very good. Moreover, the synthesized products were transformed to derivatives that can be subjected to further studies of chemical transformation, conformational effects and biological activity.

EXPERIMENTAL

Solvents and commercially available reagents were purified by conventional methods before use. Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. For column chromatography, Merck kieselgel 60 (0.063 – 0.200 mm) was used as stationary phase. The nmr spectra were obtained as deuteriochloroform solutions using Varian Mercury 300 MHz nmr spectrometer and the chemical shifts are quoted relative to the solvent peaks (δ_H 7.25 and δ_C 77.0 ppm). The ir spectra were recorded neat (powder or oil) using FTS 7000 Series Digilab Win-IR Pro spectrometer. Low- and high-resolution mass spectra were recorded at an ionization potential of 70 eV using Micromass Autospec-TOF (double focusing high resolution) instrument. Elemental (C, H, N) analysis were performed at the ARC Institute for Soil, Climate and Water (Pretoria). The syntheses and characterization of substrates **1** have been described before [1].

Schmidt Rearrangement of **1**. General Procedure for the preparation of **2a-h** and **3a-c**.

Silicon tetrachloride (0.14 g, 085 mmol) was added dropwise to a stirred mixture of **1a-d** (0.20 g, 0.77 mmol)) and NaN_3 (0.16 g, 2.47 mmol) in acetonitrile (5 mL) under nitrogen atmosphere. The mixture was stirred at room temperature for 24 hours and then quenched with ice-cold saturated sodium carbonate solution. The mixture was extracted with chloroform and the organic phase was sequentially washed with water, dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure. The residue was purified by column chromatography with ethyl acetate as the eluent to afford **2a-d**. The above procedure was employed on **1e-h**. Work-up and column chromatography eluting sequentially with hexane and then with ethyl acetate-hexane (3:2, v/v, in the case of **3a** and **2e**) or toluene-ethyl acetate (4:2 v/v, in the case of **3b,c** and **2f-h**) afforded **3a-c** and **2e-h**, respectively.

9-Bromomethyl-6,7,9,10-tetrahydro-5*H*-furo[3,2-*c*]tetrazolo-[1,5-*a*]azepine (**2a**).

This compound was obtained as solid (0.6 g, 68%), mp 135 - 137˚C; ^{1}H nmr (300 MHz, $CDCl_3$): δ 2.14 - 2.23 (2H, m), 2.67 - 2.71 (2H, m), 3.11 (1H, tttt, J = 2.3, 7.1, 15.0 Hz), 3.39 (1H, tttt, J = 2.3, 10.5, 15.2 Hz), 3.55 (2H, d, J = 5.4 Hz), 4.56 (2H, t, J = 5.1 Hz), 5.80 (1H, doublet of quint., J = 3.3, 5.4, 6.0 Hz); ^{13}C

nmr (75 MHz, $CDCl_3$): δ 21.3, 28.2, 34.4, 35.5, 48.4, 80.6, 95.8, 149.2, 161.9; ir (neat): 960.5, 1182.4, 1539.2, 1670.4 cm^{-1}; HRMS (EI) calculated for $C_9H_{11}N_4OBr$: 270.0116. Found: 270.0113.

Anal. Calcd. for $C_9H_{11}N_4OBr$: C, 39.87; H, 4.09; N, 20.67. Found: C, 40.08; H, 4.39; N, 20.66.

9-Bromomethyl-6,7,9,10-tetrahydro-6-methyl-5*H*-furo[3,2-*c*]-tetrazolo[1,5-*a*]azepine (**2b**).

This compound was obtained as solid (0.13 g, 56%), mp 87 - 89˚C; ^{1}H nmr (300 MHz, $CDCl_3$): δ 1.11 (3H, d, J = 0.9 Hz), 2.30 - 2.43 (1H, m), 2.45 (1H, tttt, J = 2.4, 11.8, 15.2 Hz), 2.65 - 2.73 (1H, 2 x m), 2.98 - 3.14 (1H, m), 3.25 - 3.42 (1H, m), 4.58 (2H, dd, J = 1.3, 14.3 Hz), 4.91 - 5.02 (1H, m); ^{13}C NMR (75MHz, $CDCl_3$) δ 18.4, 18.5, 26.8, 26.9, 34.4, 34.5, 35.2, 35.3, 35.7, 53.7, 80.3, 80.4, 149.1, 160.6; ir (neat): 975.9, 1182.4, 1678.1 cm^{-1}; HRMS (EI) calculated for $C_{10}H_{13}N_4OBr$: 284.0273. Found: 284.0273.

Anal. Calcd. for $C_{10}H_{13}N_4OBr$: C, 42.12; H, 4.60; N, 19.65. Found: C, 42.01; H, 4.73; N, 19.17.

9-Bromomethyl-6,7,9,10-tetrahydro-9-methyl-5*H*-furo[3,2-*c*]-tetrazolo[1,5-*a*]azepine (**2c**).

This compound was obtained as solid (0.52 g, 89%), mp 164 - 167˚C; ^{1}H nmr (300 MHz, $CDCl_3$): δ 1.58 (3H, s), 2.13 - 2.22 (2H, m), 2.63 - 2.70 (1H, m), 3.02 (1H, dt, J = 2.1, 15.3 Hz), 3.30 (1H, dt, J = 2.7, 15.1 Hz), 3.48 (1H, d, J = 10.8 Hz), 3.53 (1H, d, J = 10.8 Hz), 4.53 - 4.57 (2H, m); ^{13}C nmr (75 MHz, $CDCl_3$): δ 21.2, 25.4, 28.4, 39.5, 41.0, 48.4, 86.5, 95.3, 149.3, 161.1; ir (neat): 991.4, 1190.7, 1375.5, 1670.5 cm^{-1}. HRMS (EI) calculated for $C_{10}H_{13}N_4O^{79}Br$: 284.0273. Found: 284.0273.

Anal. Calcd. for $C_{10}H_{13}N_4OBr$: C 42.12; H 4.60; N, 19.65. Found: C, 42.50; H, 4.71; N, 19.57.

9-Bromomethyl-6,7,9,10-tetrahydro-6,6-dimethyl-5*H*-furo[3,2-*c*]-tetrazolo[1,5-*a*]azepine (**2d**).

This compound was obtained as solid (0.15 g, 65%), mp 126 - 129˚C; ^{1}H nmr (300 MHz, $CDCl_3$): δ 1.06 (6H, s), 2.51 (2H, d, J = 1.8 Hz), 3.12 (1H, tttt, J = 2.3, 6.9, 15.0 Hz), 3.40 (1H, tttt, J = 2.3, 10.5, 15.2 Hz), 3.54 (2H, dd, J = 1.5, 5.4 Hz), 4.30 (2H, s), 4.93 - 5.03 (1H, m); ^{13}C nmr (75 MHz, $CDCl_3$): δ 26.1, 26.2, 29.8, 34.6, 35.3, 41.6, 57.9, 80.3, 95.2, 149.1, 160.1; ir (neat) 982.6, 1090.7, 1154.2, 1205.5, 1670.6 cm^{-1}; HRMS (EI) calculated for $C_{11}H_{15}N_4OBr$: 298.0429. Found: 298.0428.

Anal. Calcd. for $C_{11}H_{15}N_4OBr$: C, 44.16; H, 5.05; N, 18.73. Found: C, 44.27; H, 4.95; N, 17.97.

4-Azido-2,3-dihydro-2-iodomethylbenzofuran (**3a**).

This compound was obtained as oil (0.57 g, 18%); ^{1}H nmr (300 MHz, $CDCl_3$): δ 2.95 (1H, dd, J = 6.6, 16.4 Hz), 3.30 (1H, dd, J = 9.6, 16.6 Hz), 3.32 (1H, dd, J = 7.5, 10.3 Hz), 3.42 (1H, dd, J = 4.8, 10.2 Hz), 4.84 - 4.93 (1H, m), 6.56 (1H, d, J = 7.8 Hz), 6.65 (1H, d, J = 8.1 Hz), 7.14 (1H, t, J = 8.4 Hz); ^{13}C nmr (75 MHz, $CDCl_3$): δ 8.9, 33.9, 82.0, 106.0, 110.6 (2 x C), 129.6, 136.8, 160.5; ir (neat)762.9, 961.5, 1236.4, 1456.7, 1602.7, 2109.1 cm^{-1}; ms (EI) m/z 301 (M^+, 82), 273 (96), 146 (73), 118 (93), 117 (84), 91 (80), 65 (63), 51 (75), 39 (100); HRMS (EI) calculated for $C_9H_8N_3OI$: 300.9712. Found: 300.9712.

Anal. Calcd for $C_9H_8N_3OI$: C, 35.90; H, 2.68; N, 13.95. Found: C, 35.94; H, 2.58; N, 13.80.

6,7,9,10-Tetrahydro-9-iodomethyl-5*H*-furo[3,2-*c*]tetrazolo[1,5-*a*]azepine (**2e**).

This compound was obtained as solid (1.56 g, 42%), mp 169 - 173˚C; ^{1}H nmr (300 MHz, $CDCl_3$): δ 2.14 - 2.22 (2H, m), 2.66 - 2.71 (2H, m), 2.99 (1H, tttt, J = 2.1, 7.2, 15.0 Hz), 3.37 (1H, tttt, J = 2.1, 10.5, 15.2 Hz), 3.38 (2H, d, J = 5.7 Hz), 4.55 (2H, t, J = 5.1 Hz), 4.81 (1H, doublet of quint., J = 3.3, 5.4, 6.0 Hz); ^{13}C nmr (75 MHz, $CDCl_3$): δ 8.6, 21.2, 28.3, 37.1, 48.4, 80.8, 95.7, 149.1, 161.9; ir (neat): 950.9, 1178.78, 1669.1 cm^{-1}; HRMS (EI) calculated for $C_9H_{11}N_4OI$: 317.9977. Found: 317.9979.

Anal. Calcd. for $C_9H_{11}N_4OI$: C, 33.98; H, 3.49; N, 17.61. Found: C, 34.29; H, 3.32; N, 17.56.

4-Azido-2,3-dihydro-2-iodomethyl-6-methylbenzofuran (**3b**).

This compound was obtained as oil (0.28 g, 14%); ^{1}H nmr (300 MHz, $CDCl_3$): δ 2.29 (3H, s, 3H), 2.90 (1H, dd, J = 6.3, 16.4 Hz), 3.26 (1H, dd, J = 9.3, 16.1 Hz), 3.31 (1H, dd, J = 7.5, 10.3 Hz), 3.40 (1H, dddd, J = 0.6, 5.0, 10.5 Hz), 4.81 - 4.91 (1H, m), 6.39 (1H, s), 6.45 (1H, s); ^{13}C nmr (75 MHz, $CDCl_3$): δ 8.8, 21.6, 33.7, 82.2, 106.9, 111.2, 114.2, 136.2, 140.3, 160.6; ir (neat): 817.2, 978.8, 1238.3, 1596.6, 2105.3 cm^{-1}; ms (EI) m/z 315 (M^+, 86), 287 (100), 160 (84), 132 (83), 117 (87), 53 (92); HRMS (EI) calculated for $C_{10}H_{10}N_3OI$: 314.9869. Found: 314.9868.

Anal. Calcd. for $C_{10}H_{10}N_3OI$: C, 38.12; H, 3.20; N, 13.34. Found: C, 38.17; H, 3.18; N, 13.30.

2-Iodomethyl-7-methyl-2,3,4,6,7,8-hexahydro-5*H*-tetrazolo[1,5-*c*]furoazepine **(2f)**.

This compound was obtained as solid (0.95 g, 44%), mp 126 - 129˚C; ^{1}H nmr (300 MHz, $CDCl_3$): δ 1.12 (3H, d, J = 6.6 Hz), 2.65 - 2.74 (1H, m), 2.91 - 2.99 (1H, m), 3.35 - 3.40 (2H, m), 4.16 - 4.26 (1H, m), 4.60 (2H, dd, J = 14.4 Hz), 4.75 - 4.83 (1H, m); ^{13}C nmr (75 MHz, $CDCl_3$): δ 8.6, 8.8, 18.5, 18.5, 26.9, 27.0, 35.8, 37.0, 37.1, 53.7, 80.5, 80.7, 95.3, 149.1, 160.5; ir (neat): 970.3, 1180.9, 1678.8 cm^{-1}; HRMS (EI) calculated for $C_{10}H_{13}N_4OI$: 332.0134. Found: 332.0135.

Anal. Calcd. for $C_{10}H_{13}N_4OI$: C, 36.16; H, 3.94; N, 16.87. Found: C, 36.56; H, 3.97; N, 17.30.

4-Azido-2,3-dihydro-2-iodomethyl-2-methylbenzofuran (**3c**).

This compound was obtained as oil (0.66 g, 15%); ^{1}H nmr (300 MHz, $CDCl_3$): δ 1.66 (3H, s), 2.98 (1H, d, J = 16.5 Hz), 3.24 (1H, d, J = 16.2 Hz), 3.42 (2H, s), 6.55 (1H, dd, J = 0.6, 7.8 Hz), 6.66 (1H, dd, J = 0.9, 8.1 Hz), 7.15 (1H, tt, J = 0.6, 0.9, 8.2 Hz); ^{13}C nmr (75 MHz, $CDCl_3$): δ 15.1, 26.1, 39.0, 87.2, 106.2, 110.3, 129.3, 129.6, 136.9, 159.9; ir (neat): 763.1, 976.0, 1257.9, 1454.3, 1602.6, 2112.4 cm^{-1}; ms (EI) m/z 315 (M^+, 93), 287 (97), 160 (93), 132 (86), 117 (92), 55 (84), 39 (100); HRMS (EI) calculated for $C_{10}H_{10}N_3OI$: 314.9868. Found: 314.9868.

Anal. Calcd. for $C_{10}H_{10}N_3OI$: C, 38.12; H, 3.20; N, 13.34. Found: C, 38.06; H, 3.22; N, 13.23.

6,7,9,10-Tetrahydro-9-iodomethyl-9-methyl-5*H*-furo[3,2-*c*]tetrazolo[1,5-*a*]azepine (**2g**).

This compound was obtained as solid (1.57 g, 50%), mp 118 - 121˚C; ^{1}H nmr (300 MHz, $CDCl_3$): δ 1.62 (3H, s), 2.13 - 2.20 (2H, m), 2.62 - 2.68 (2H, m), 3.02 (1H, ttt, J = 2.1, 15.4 Hz), (1H, tt, J = 2.4, 15.3 Hz), 3.36 (1H, d, J = 10.8 Hz), 3.41 (1H, d, J = 10.8 Hz), 4.54 (2H, t, J = 5.4 Hz); ^{13}C nmr (75 MHz, $CDCl_3$): δ 14.9, 21.2, 26.1, 28.3, 42.2, 48.3, 86.1, 95.2, 149.3,

161.0; ir (neat): 989.5, 1205.3, 1667.8 cm^{-1}; HRMS (EI) calculated for $C_{10}H_{13}N_4OI$: 332.0134. Found: 332.0134.

Anal. Calcd. for $C_{10}H_{13}N_4OI$: C, 36.16; H, 3.94; N, 16.89. Found: C, 36.54; H, 3.97; N, 16.47.

6,7,9,10-Tetrahydro-9-iodomethy-6,6-dimethyl-5*H*-furo[3,2-*c*]-tetrazolo[1,5-*a*]azepine (**2h**).

This compound was obtained as solid (2.75 g, 52%), mp 80 - 83˚C; ^{1}H nmr (300 MHz, $CDCl_3$): δ 1.07 (3H, s), 1.07 (3H, s), 2.51 (2H, d, J = 2.4 Hz), 3.02 (1H, tttt, J = 2.1, 6.9, 15.3 Hz), 3.37 (2H, dd, J = 1.2, 5.4 Hz), 3.40 (1H, tttt, J = 2.3, 10.5, 15.2 Hz), 4.30 (2H, d, J = 0.9 Hz), 4.74 - 4.84 (1H, m); ^{13}C nmr (75 MHz, $CDCl_3$): δ 8.9, 26.1, 26.2, 29.9, 37.0, 41.7, 57.9, 80.4, 95.1, 149.1, 160.0; ir (neat): 985.5, 1087.8, 1194.7, 1668.4 cm^{-1}; HRMS (EI) calculated for $C_{11}H_{15}N_4OI$: 346.0291. Found: 346.0290.

Anal. Calcd. for $C_{11}H_{15}N_4OI$: C, 38.16; H, 4.37; N, 16.18. Found: C, 40.69; H, 4.64; N, 15.79.

The Preparation of **4a-d** from **2e-h** with Triethyl Phosphite.

A stirred mixture of the **2e-h** (0.30 g, 0.94 mmol) and triethyl phosphite (0.63 g, 3.77 mmol) was heated under reflux for 24 hours. The residue was subjected to silica gel column chromatography (9:1 ethyl acetate-methanol, v/v) and the by-product diethyl ethylphosphonate was distilled off *in vacuo* at *ca*. 100˚C/0.5 mmHg on a Buchii bulb-to-bulb to afford pure **4a-d**.

Diethyl [(6,7,9,10-tetrahydro-5*H*-furo[3,2-*c*]tetrazolo[1,5-*a*]azepin-9-yl)methyl]phosphonate **(4a**).

This compound was obtained as oil (0.16 g, 52%); ^{1}H nmr (300 MHz, $CDCl_3$): δ.30 (6H, tt, J = 2.1, 7.2 Hz), 2.08 - 2.38 (5H, m), 2.61 - 2.66 (2H, m), 2.99 (1H, tttt, J = 2.1, 7.8, 15.0 Hz), 3.39 (1H, tttt, J = 2.1, 10.2, 14.9 Hz), 4.03 - 4.15 (4H, m), 4.50 - 4.54 (2H, m), 4.98 - 5.12 (1H, m); ^{13}C nmr (75 MHz, $CDCl_3$): δ 16.3 (d, J = 2.6 Hz), 16.4 (d, J = 2.6 Hz), 21.2, 28.3, 32.9 (d, J = 139.1 Hz), 37.3 (d, J = 8.0 Hz), 48.3, 61.8 (d, J = 6.5 Hz), 62.0 (d, J = 6.3 Hz), 77.7, 95.5, 149.3, 161.7; δ_p 26.68; ir (neat): 960.4, 1023.3, 1246.0, 1672.7 cm^{-1}; HRMS (EI) calculated for $C_{13}H_{21}N_4O_4P$: 328.1300. Found: 328.1301.

Anal. Calcd. for $C_{13}H_{21}N_4O_4P$: C, 47.56; H, 6.45; N, 17.07. Found: C, 47.46; H, 6.42; N, 17.01.

Diethyl [(6,7,9,10-tetrahydro-6-methyl-5*H*-furo[3,2-*c*]tetrazolo-[1,5-*a*]azepin-9-yl)methyl]phosphonate **(4b**).

This compound was obtained as oil (0.16 g, 40%); ^{1}H nmr (300 MHz, $CDCl_3$): δ 1.08 (3H, d, J = 6.9 Hz), 1.26 - 1.32 (6H, m), 2.06 - 2.46 (5H, m), 2.65 (1H, d, J = 18.0 Hz), 2.91 - 3.04 (1H, m), 3.29 - 3.45 (1H, m), 3.99 - 4.21 (5H, m), 4.57 (1H, d, J = 13.2 Hz), 4.96 - 5.09 (1H, m); ^{13}C nmr (75 MHz, $CDCl_3$): δ 16.3 (d, J = 2.6 Hz), 16.4 (d, J = 4.1 Hz), 18.4, 32.9 (dd, J = 4.3, 139.1 Hz), 35.8, 37.1 (t, J = 8.3 Hz), 61.7 (d, J = 6.8 Hz), 61.9 (d, J = 6.6 Hz), 77.5 (d, J = 8.3 Hz), 95.2 (d, J = 11.6 Hz), 149.2, 160.4 (d, J = 3.5 Hz); δ_p 26.69; ir (neat): 965.3, 1024.2, 1189.1, 1251.3, 1672.6 cm^{-1}; HRMS (EI) calculated for $C_{14}H_{23}N_4O_4P$: 342.1457. Found: 342.1457.

Anal. Calcd. for $C_{14}H_{23}N_4O_4P$: C, 49.12; H, 6.77; N, 16.37. Found: C, 49.18; H, 6.72; N, 16.40.

Diethyl [(6,7,9,10-tetrahydro-5-methyl-5*H*-furo[3,2-*c*]tetrazolo-[1,5-*a*]azepin-9-yl)methyl]phosphonate **(4c**).

This compound was obtained as oil (0.16 g, 31%); ^{1}H nmr (300 MHz, $CDCl_3$): δ 1.25 - 1.34 (6H, m), 1.61 (3H, s), 2.17 (2H, quint., J = 6.6, 7.5 Hz), 2.28 (2H, J = 19.2 Hz), 2.62 - 2.68 (2H, m), 3.04 91H, tt, J = 2.1, 15.0 Hz), 3.36 (1H, tt, J = 2.1, 15.0 Hz), 4.01 - 4.16 (4H, m), 4.53 - 4.57 (2H, m); ^{13}C nmr (75 MHz, $CDCl_3$): δ 16.4 (d, J = 2.6 Hz), 21.4, 27.8 (d, J = 5.4 Hz), 28.6, 37.6 (d, J = 138.8 Hz), 43.0 (d, J = 4.9 Hz), 48.4, 61.6 (d, J = 2.6 Hz), 61.7 (d, J = 2.8 Hz), 85.9, 95.3, 149.6, 160.8; δ_p 26.09; ir (neat): 960.1, 1022.1, 1244.3, 1670.4 cm^{-1}; HRMS (EI) calculated for $C_{14}H_{23}O_4N_4P$: 342.1457. Found: 342.1457.

Anal. Calcd. for $C_{14}H_{23}N_4O_4P$: C, 49.12; H, 6.77; N, 16.37. Found: C, 49.18; H, 6.78; N, 16.29.

Diethyl [(6,7,9,10-tetrahydro-6,6-dimethyl-5*H*-furo[3,2-*c*]tetrazolo[1,5-*a*]azepin-9-yl)methyl]phosphonate **(4d**).

This compound was obtained as oil (0.19 g, 47%); ^{1}H nmr (300 MHz, $CDCl_3$): δ 1.04 (6H, s), 1.33 (6H, J = 1.8, 7.1 Hz), 2.10 - 2.40 (2H, m), 2.48 (2H, s), 3.04, (1H, tttt, J = 1.8, 7.8, 15.0 Hz), 3.44 (1H, tttt, J = 1.8, 9.9, 15.0), 4.12 (4H, quint., J = 7.2, 11.2 Hz), 4.29 (2H, s), 4.99 - 5.20 (1H, m); ^{13}C nmr (75 MHz, $CDCl_3$): δ 16.4 (d, J = 6.2 Hz), 26.1, 26.2, 29.9, 33.0 (d, J = 139.5 Hz), 37.1 (d, J = 8.0 Hz), 41.8, 57.9, 61.8 (d, J = 6.5 Hz), 62.0 (d, J = 6.8 Hz), 77.6, 95.1, 149.3, 159.9; δ_p 26.64; ir (neat): 960.9, 1021.6, 1206.3, 1670.6 cm^{-1}. HRMS (EI) calculated for $C_{15}H_{25}N_4O_4P$: 356.1613. Found: 356.1614.

Anal. Calcd. for $C_{15}H_{25}N_4O_4P$: C, 50.56; H, 7.07; N, 15.72. Found: C, 50.60; H, 7.10; N, 15.64.

General Procedure for the Dehydrohalogenation of **2a,b,d** and **3a,b**.

A stirred solution of **2a,b,d** or **3a,b** (0.50 g, 1.8 mmol) in dry toluene (5 mL) was treated with DBU (0.84 g, 5.5 mmol). The mixture was refluxed for 18 hours, cooled and then quenched with water. The solution was extracted with chloroform and the combined organic extracts were washed with saturated ammonium chloride solution, dried over sodium sulfate, filtered and then evaporated under reduced pressure. The residue was purified by column chromatography on silica gel with ethyl acetate (in the case of **5a-c**) or toluene-hexane (1:1 in the case of **6a,b**) as the eluent to afford **5a-c** or **6a,b**.

6,7-Dihydro-9-methyl-5*H*-furo[3,2-*c*]tetrazolo[1,5-*a*]azepine (**5a**).

This compound was obtained as solid (0.26 g, 74%), mp 151 - 153˚C; ^{1}H nmr (300 MHz, $CDCl_3$): δ 2.24 (3H, quint., J = 6.3, 7.3 Hz), 2.30 (3H, s), 4.62 (2H, t, J = 6.0 Hz), 4.63 (2H, t, J = 4.5 Hz), 6.53 (1H, s); ^{13}C nmr (75 MHz, $CDCl_3$): δ 13.3, 21.6, 28.1, 48.8, 105.3, 107.2, 148.5, 152.6, 153.5; ir (neat) 817.1, 926.2, 1102.0, 1198.6, 1602.5, 1649.1, 3130.2 cm^{-1}; ms (EI) m/z 190 (M^+, 100), 134 (83.0), 43 (50.0), 28 (98.5); HRMS (EI) calculated for $C_9H_{10}N_4O$: 190.0855. Found: 190.0854.

Anal. Calcd. for $C_9H_{10}N_4O$: C, 56.83; H, 5.30; N, 29.46. Found: C, 57.06; H, 5.41; N, 29.46.

6,7-Dihydro-6,9-dimethyl-5*H*-furo[3,2-*c*]tetrazolo[1,5-*a*]azepine (**5b**).

This compound was obtained as solid (0.05 g, 63%), mp 138 - 140˚C; ^{1}H nmr (300 MHz, $CDCl_3$): δ 1.16 (3H, d, J = 6.9 Hz), 2.29 (3H, s), 2.39 - 2.50 (1H, m), 2.89 (1H, dd, J = 8.7, 18.0 Hz), 3.16 (1H, dd, J = 3.9, 18.0 Hz), 4.30 (1H, td, J = 1.3, 14.1 Hz), 6.51 (1H, d, J = 0.9 Hz); ^{13}C nmr (75 MHz, $CDCl_3$): δ 13.2, 18.4, 27.3, 35.7, 54.2, 105.1, 107.0, 148.4, 152.3, 152.6; ir (neat) 69.6, 854.7, 1199.7, 1452.4, 1600.7, 1647.5, 3101.2 cm^{-1}; ms (EI) m/z

204 (M^+, 100), 148 (38.0), 134 (61.0), 120 (46.0), 43 (77.5); HRMS (EI) calculated for $C_{10}H_{12}ON_4$: 204.1011. Found: 204.1011.

Anal. Calcd. for $C_{10}H_{12}N_4O$: C, 55.81; H, 5.92; N, 27.43. Found: C, 56.19; H, 5.67; N, 27.46.

6,7-Dihydro-6,6,9-trimethyl-5*H*-furo[3,2-*c*]tetrazolo[1,5-*a*]-azepine (**5c**).

This compound was obtained as solid (0.13 g, 60%), mp 176 - 179˚C; ^{1}H nmr (300 MHz, $CDCl_3$): δ 1.10 (6H, s), 2.31 (3H, s), 2.95 (2H, s), 4.37 (1H, d, J = 5.4 Hz), 6.54 (1H, d, J = 1.2 Hz); ^{13}C nmr (75 MHz, $CDCl_3$): δ 13.3, 26.1, 30.12, 41.7, 58.3, 105.0, 106.8, 148.9, 152.0, 152.7; ir (neat): 775.4, 846.4, 1103.3, 1218.7, 1605.0, 1642.5, 3108.8 cm^{-1}; ms (EI) m/z 218 (M^+, 93.0), 135 (52.0), 120 (50.0), 70 (100), 43 (74.0); HRMS (EI) calculated for $C_{11}H_{14}N_4O$: 218.1168. Found: 218.1167.

Anal. Calcd. for $C_{11}H_{14}N_4O$: C, 60.53; H, 6.47; N, 25.67. Found: C, 60.15; H, 6.56; N, 25.23.

4-Azido-2-methylbenzofuran (**6a**).

This compound was obtained as oil (0.064 g 74%); ^{1}H nmr (300 MHz, $CDCl_3$): δ 2.44 (3H, d, J = 2.4 Hz), 6.44 (1H, s), 6.89 (1H, dd, J = 3.3 and 5.1 Hz), 7.17 (1H, d, J = 5.7 Hz), 7.18 (1H, d, J = 3.3 Hz); ^{13}C nmr (75 MHz, $CDCl_3$): δ 14.1, 99.8, 99.9, 107.4, 111.8, 123.8, 131.6, 155.6, 155.7; ir (neat): 770.9, 1254.0, 1431.2, 1595.7, 2111.8 cm^{-1}; HRMS (EI) calculated for $C_9H_7N_3O$: 173.0589. Found: 173.0589.

Anal. Calcd. for $C_9H_9N_3O$: C, 62.42; H, 4.07; N, 24.26. Found: C, 62.03; H, 4.00; N, 24.10.

4-Azido-2,5-dimethylbenzofuran (**6b**).

This compound was obtained as solid (0.056 g, 62%); ^{1}H nmr (300 MHz, $CDCl_3$): δ 2.41 (3H, d, J = 0.9 Hz), 2.42 (3H, s), 6.38 (1H, d, J = 0.9 Hz), 6.71 (1H, t, J = 0.6 Hz), 6.99 (1H, s); ^{13}C nmr (75 MHz, $CDCl_3$): δ 14.0, 21.6, 99.5, 107.9, 113.0, 119.6, 131.0, 134.3, 154.8, 156.1; ir (neat): 812.0, 1246.0, 1325.2, 1587.4, 2109.7 cm^{-1}; ms (EI) m/z. HRMS (EI) calculated for $C_{10}H_9N_3O$: 187.0746. Found: 187.0750.

Anal. Calcd. for $C_{10}H_9N_3O$: C, 64.16; H, 4.85; N, 22.45. Found: C, 64.03; H, 4.81; N, 22.43.

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