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An Efficient Approach to the [1,2,4]-Triazolo[3,2-d][1,5]Benzoxazepine Skeleton-A Novel Tricyclic Ring System

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AN EFFICIENT APPROACH TO THE [1,2,4]-TRIAZOLO[3,2-d][1,5]BENZOXAZEPINE SKELETON-A NOVEL TRICYCLIC RING SYSTEM

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ABSTRACT: Unprecedented [1,2,4]-Triazolo[3,2-d][1,5]benzoxazepine skeleton was easily achieved by cycloaddition of the allene-like cations **3**, derived from 4-chromanone arylhydrazones, to the triple bond of nitriles and ensuing ring enlargement. The structural assignment of one product (**5d**) has been ultimately accomplished by X-ray diffraction analysis.

Since the first synthesis of 1,4-benzodiazepines in the early 1960's[1], various benzoanellated seven-membered heterocycles containing O, N, or S atoms have been the object of extensive investigation due to their wide spectrum of *in vivo* activities. For example, 1,5-benzothiazepines, as diltiazem, nictiazem, and

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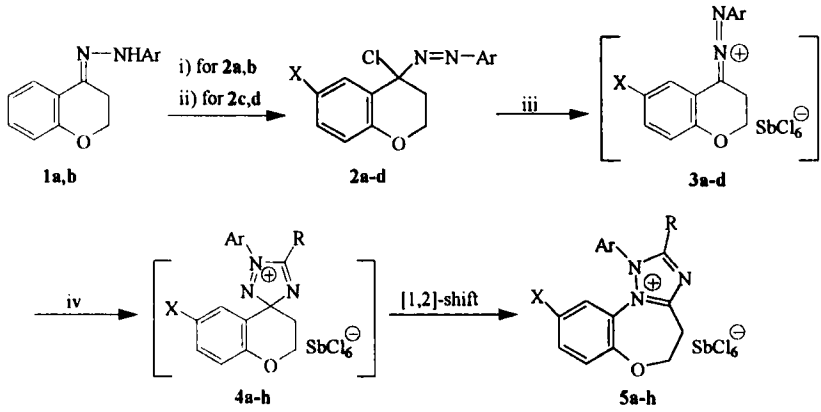
tiazesim exhibit coronary vessel dilatating and antidepressive activity, respectively[2]. 1,4-Benzodiazepines act as candidates for use as therapeutic agents with anxiolytic, anticonvulsant, muscle relaxant, and sedative/hypnotic activities[3].

Further investigations have revealed that attachment of a triazolo ring to the heptatomic ring can enhance the pharmacological activity and/or offer more interesting properties[2,4-8]. Thus, the well known triazolo derivatives estazolam, triazolam, and alprazolam are successfully applied for clinical practice as tranquilizers, hyponotics and antidepressants[2]. Moreover, various 1*H*-1,2,4-triazolo[3,4-a][2]benzazepines have been prepared, and the preliminary data show that they possess selective and potent blocking effects on D_4 receptor and can be useful as antipsychotic agents for diseases such as schizophrenia[9]. Among the newly developed 6-7-5-membered tricyclic heterocyles, derivatives of triazolooxazepine ring system have received special attention because of their unique pharmaceutical values[9-12]. This new kind of compounds exhibit a range of novel physiological activities and can be used as drugs in inhibiting phospholipase A_2[12], as antipsychotic agents[9], as carrageenin-induced edema inhibitors[12], and for treatment of osteoporosis[13]. However, there are very limited ways in the literature for the synthesis of such fused heterocycles[14].

In 1992, Wang and Jochims first described the *in situ* generation of a number of 1-aza-2-azoniaallenen salts ($R^1R^2C=N^+=NR^3$) and their cycloadditions to the triple bond of nitriles, leading to 1,2,4-triazolium salts[15]. In continuation of our investigations on these polar cycloadditions, we were able to synthesize new tricyclic compounds in which a s-triazolo ring fused at 4- and 5-positions of 1,5-benzoxazepine moiety. Being closely related to the reported benzoxazepines, novel pharmacological interest for these new heterocycles should be expected. We report herein our preliminary results on their preparations.

Scheme A



i: 1.0 equiv. *t*-BuOCl/CH_2Cl_2, 0°C, 2h; ii: 3.3 equiv. *t*-BuOCl/CH_2Cl_2, 25°C, 2h; iii: 1.2 equiv. $SbCl_5/CH_2Cl_2$, -30°C, 1h; iv: 1.6 equiv. RCN/CH_2Cl_2, -30°C~30°C, ~3h

1a: Ar=2,4,6-$Cl_3C_6H_2$; **1b:** Ar=p-NO_2-C_6H_4;
2a,3a: X=H, Ar=2,4,6-$Cl_3C_6H_2$; **2b,3b:** X=H, Ar=p-NO_2-C_6H_4;
2c,3c: X=Cl, Ar=2,4,6-$Cl_3C_6H_2$; **2d,3d:** X=Cl, Ar=p-NO_2-C_6H_4;
4a,5a: X=H, R=Me, Ar=2,4,6-$Cl_3C_6H_2$; **4b,5b:** X=H, R=Et, Ar=2,4,6-$Cl_3C_6H_2$;
4c,5c: X=Cl, R=Me, Ar=2,4,6-$Cl_3C_6H_2$; **4d,5d:** X=Cl, R=Et, Ar=2,4,6-$Cl_3C_6H_2$;
4e,5e: X=H, R=Et, Ar=p-NO_2-C_6H_4; **4f,5f:** X=H, R=CH_2Ph, Ar=p-NO_2-C_6H_4;
4g,5g: X=Cl, R=Et, Ar=p-NO_2-C_6H_4; **4h,5h:** X=Cl, R=CH_2Ph, Ar=p-NO_2-C_6H_4

Under comparable conditions[15], the arylhydrazones of 4-chromanone (**1**) were treated with one equivalent of hypochlorous acid 1,1-dimethylethyl ester at 0°C to give very cleanly, in high yields, the corresponding α-chloroazo compounds **2a** and **2b**. On the other hand, if three folds of the chlorinating agent were applied and the reaction was carried out at 25°C, the hydrogen on the phenyl ring at the para position to the oxygen was spontaneously displaced by chlorine giving the 6-chlorinated α-chloroazo compounds **2c** and **2d**. Few reports seem to be known concerning the aromatic chlorination with hypochlorous acid 1,1-dimethylethyl ester in the literature[16]. Compounds **2** turn out to be stable under usual conditions and can be kept at low temperatures (~0 °C) for months. On treatment with a Lewis acid ($SbCl_5$) at low temperature (-30 °C), compounds **2**

were readily converted to allene-like cations **3** as reactive intermediates by departure of the chloride ion. The allene-like salts **3** can be reasonably viewed as positively charged 1,3-dipoles. In the presence of a nitrile, the extremely moisture-sensitive salts **3** underwent cycloadditions providing the 3-spiro substituted 3*H*-1,2,4-triazolium salts **4**. Within the context of Sustmann's classification, the reaction ranks among the 1,3-dipolar cycloadditions with reverse electron demand[17]. The primarily formed salts **4** were rather unstable, thus precluding their isolation. Elevating the temperature to about 30 °C, the salts **4** rearranged to the tricyclic products **5** by [1,2]-shift with simultaneous ring enlargement and insertion of the nitrogen atom into the carbon skeleton. The rearrangement was found to proceed with exclusive migration of the aromatic side of the ring. No isomeric compounds resulted from migration of the aliphatic side of the ring could be detected from the ^{1}H NMR spectra of the crude products. The results are depicted in Scheme A. The structures of compounds **5** were affirmatively substantiated by spectroscopic methods along with microanalyses. For compound **5d** the structural assignment was unambiguously achieved by X-ray diffraction analysis. A perspective drawing of **5d** is supplied in Figure **1**.

To our knowledge, compounds **5** are a hitherto unknown class of heterocycles. By starting from the corresponding ethoxycarbonylhydrazones, the N(1) unsubstituted neutral s-triazolo[3,2-d][1,5]benzoxazepines have also been synthesized. The results of these studies will be presented at a later date.

In summary, the procedure reported here represents an efficient synthetic entry to the so far unknown [1,2,4]-triazolo[3,2-d][1,5]benzoxazepine ring system. The ready availability of the starting materials and the simplicity of the performance render this procedure especially attractive.

EXPERIMENTAL

Melting points were uncorrected. All solvents were pretreated in the usual way. All experiments were carried out with exclusion of moisture. The elemental

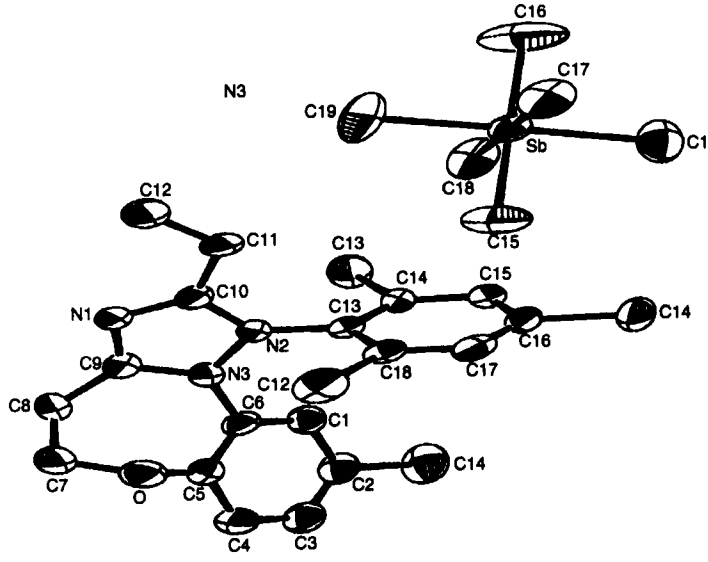


Figure 1. X-ray Structure of **5d**

analyses for C, H, N were performed by a Carlo Erba 1106 elemental analyser. IR spectra were recorded on a Mattson Alpha-centauri FT-IR spectrometer. ^{1}H NMR and ^{13}C NMR were acquired on a Bruker 300 spectrometer in CD_3CN or $CDCl_3$ with TMS as internal reference. X-Ray diffraction analysis of **5d**: Reflections were measured with a Rigaku AFC7R diffratometer. 4-Chromanone was prepared according to the method described in the literature[18].

Preparation of the Hydrazones 1:

A mixture of 4-chromanone (50 mmol) and the corresponding arylhydrazine (50 mmol) in ethanol (80 mL)/acetic acid (1 mL) was refluxed for 3h. Removal of the solvent and crystallization of the residue from hot ethanol/water afforded the pure hydrazone.

4-Chromanone (2,4,6-trichlorophenyl)hydrazone (**1a**): From 4-chromanone (7.41 g, 50 mmol) and (2,4,6-trichlorophenyl)hydrazine (10.57 g, 50 mmol). Yield:

15.37 g (90%) of colorless crystals; mp 94-95°C. IR (KBr): 3300, 1610, 1540, 1300; ^{1}H NMR ($CDCl_3$) δ: 2.60 (t, J = 6.78 Hz, 2H, CH_2), 4.21 (t, 2H, J = 6.78 Hz, OCH_2), 6.54 (NH), 6.90~7.82 (m, 6H, Ar-H). Anal. calcd. for $C_{15}H_{11}Cl_3N_2O$ (%): C, 52.74; H, 3.25; N, 8.20. Found: C, 52.70; H, 3.19; N, 8.16.

4-Chromanone (4-nitrophenyl)hydrazone (**1b**): From 4-chromanone (7.41 g, 50 mmol) and (4-nitrophenyl)hydrazine (7.67 g, 50 mmol). Yield: 12.32 g (87%) of red crystals; mp 232-233°C. IR (KBr): 3320, 1650, 1534, 1320; ^{1}H NMR ($CDCl_3$) δ: 2.62 (t, J = 6.78 Hz, 2H, CH_2), 4.20 (t, J = 6.78 Hz, 2H,OCH_2), 6.70 (NH), 6.95~8.02 (m, 8H, Ar-H). Anal. calcd. for $C_{15}H_{13}N_3O_3$ (%): C, 63.60; H, 4.63; N, 14.83. Found: C, 63.58; H, 4.59; N, 14.79.

Preparation of the α-Chloroazo Compounds 2 :

Method A: The reaction was carried out in the dark. To a solution of the hydrazone (20 mmol) in CH_2Cl_2 (20 mL) was added dropwise over 15 min *t*-BuOCl (20 mmol) under cooling with an ice-bath. After the mixture was stirred at 0°C for 2h and then dried with $CaCl_2$, volatiles were thoroughly removed by rotary evaporation. The NMR spectrum of the residue was relatively clean. Following this method, the α-chloroazo compounds **2a** as well as **2b** have been prepared in about quantitative yields, which were used without further purification.

2a: From **1a** (6.83 g, 20 mmol) and *t*-BuOCl (2.20 g, 20 mmol). Yield: 6.69 g (89%) of an orange oil. IR (neat): 1700, 1576, 1300, 1230; ^{1}H NMR ($CDCl_3$) δ: 2.62 (t, J= 6.78 Hz, 2H, CH_2), 4.21 (t, J = 6.78 Hz, 2H, OCH_2), 6.90~7.82 (m, 4H, Ar-H), 7.90 (s, 2H, $Cl_3C_6H_2$).

2b: From **1b** (5.66 g, 20 mmol) and *t*-BuOCl (2.20 g, 20 mmol). Yield: 5.08 g (80 %) of an orange oil. IR (neat): 1710, 1566, 1315, 1230; ^{1}H NMR ($CDCl_3$) δ: 2.62 (t, J = 6.78 Hz, 2H, CH_2), 4.21 (t, J = 6.78 Hz, 2H, OCH_2), 6.94~8.00 (m, 8H, Ar-H).

Method B: The reaction was carried out in the dark. To a solution of the hydrazone (20 mmol) in CH_2Cl_2 (20 mL) was added dropwise *t*-BuOCl (65 mmol) in CH_2Cl_2 (20 mL) at 25 °C. After being stirred for 2h and dried with $CaCl_2$, the solvent was removed under reduced pressure. The orange-yellow residue was relatively clean as shown by NMR analysis. According to this procedure, 6-chlorinated azo compound **2c** as well as **2d** have been prepared and used as obtained.

2c: From **1a** (6.83 g, 20 mmol) and *t*-BuOCl (7.06 g, 65 mmol). Yield: 7.64 g (93%) of an orange oil. IR (neat): 1705, 1576, 1300, 1230; ^{1}H NMR ($CDCl_3$) δ: 2.70 (t, J = 6.78, 2H, CH_2), 4.32 (t, J = 6.78, 2H, OCH_2), 7.02~7.80 (m, 3H, Ar-H), 7.93 (s, 2H, $Cl_3C_6H_2$).

2d: From **1b** (5.66 g, 20 mmol) and *t*-BuOCl (7.06 g, 65mmol). Yield: 6.41 g (91 %) of an orange oil. IR (neat): 1720, 1562, 1315, 1230; ^{1}H NMR ($CDCl_3$) δ: 2.68 (t, J = 6.78 Hz, 2H, CH_2), 4.29 (t, J = 6.78 Hz, 2H, OCH_2), 6.94~8.00 (m, 7H, Ar-H).

Reaction of the α-Chloroazo Compounds 2 with Nitriles to Prepare Heterocycles 5:

To a solution of **2** (10 mmol) and the appropriate nitrile (16 mmol) in absolute CH_2Cl_2 (20 mL) was added dropwise $SbCl_5$ (3.60 g, 12 mmol) in CH_2Cl_2 (10 mL) at –30 °C. The mixture was allowed to react under stirring at the same temperature for an additional 1h. Subsequently, the reactants were warmed up gradually to 30°C (oil bath temperature) and kept at this temperature for 10-15 minutes. Ether (120 mL) was then added to the resulting deep colored mixture and the precipitate collected to furnish the heterocycles **5**. Recrystallization from MeOH provided the analytically pure **5**.

4,5-Dihydro-2-methyl-1-(2,4,6-trichlorophenyl)-1*H*-1,2,4-triazolo[3,2-d][1,5]-benzoxazepinium Hexachloroantimonate (**5a**): From **2a** (3.76 g, 10 mmol) and acetonitrile (0.66 g, 16 mmol). Yield: 6.23 g (87 %) of white crystals; mp 200-202°C (dec). IR (KBr): 2916, 1556, 1260, 1219; ^{1}H NMR (CD_3CN) δ: 2.76 (s, 3H, CH_3), 3.53 (t, J= 6.79 Hz, 2H, CH_2), 4.95 (t, J = 6.78 Hz, 2H, OCH_2), 7.05~7.79 (m, 4H, Ar-H), 7.93 (s, 2H, $Cl_3C_6H_2$); ^{13}C NMR (CD_3CN) δ: 12.71 (CH_3), 25.87 (CH_2), 77.19 (OCH_2), 123.35, 123.78, 124.58, 126.70, 130.57, 130.64, 134.30, 135.67, 141.65, 149.48, 162.28, 163.15 (Ar, C=N). Anal. calcd. for $C_{17}H_{13}Cl_9N_3OSb$ (%): C, 28.51; H, 1.83; N, 5.87. Found: C, 28.48; H, 1.80; N, 5,85.

4,5-Dihydro-2-ethyl-1-(2,4,6-trichlorophenyl)-1*H*-1,2,4-triazolo[3,2-d][1,5]-benzoxazepinium Hexachloroantimonate (**5b**): From **2a** (3.76 g, 10 mmol) and propionitrile (0.88 g, 16 mmol). Yield: 6.43 g (88 %) of white crystals; mp 198-200°C (dec). IR (KBr): 2900, 1550,1265, 1200; ^{1}H NMR (CD_3CN) δ: 1.36 (t, J = 7.41 Hz, 3H, CH_3), 3.02 (q, J = 7.41 Hz, 2H, CH_2), 3.57 (t, J = 6.69 Hz, 2H, CH_2), 4.86 (t, J = 6.69 Hz, 2H, OCH_2), 6.97~7.81 (m, 4H, aryl), 8.24 (s, 2H, $Cl_3C_6H_2$); ^{13}C NMR (CD_3CN) δ: 9.65 (CH_3), 20.11 (CH_2), 28.04 (CH_2), 76.96 (OCH_2), 123.56, 123.73, 124.15, 128.36, 130.60 , 134.15, 135.70, 141.32, 149.51, 150.51, 162.37, 166.21 (Ar, C=N). Anal. calcd. for $C_{18}H_{15}Cl_9N_3OSb$ (%): C, 29.61; H, 2.07; N, 5.76. Found: C, 29.57; H, 1.99; N, 5.71.

9-Chloro-4,5-dihydro-2-methyl-1-(2,4,6-trichlorophenyl)-1*H*-1,2,4-triazolo[3, 2-d][1,5]benzoxazepinium Hexachloroantimonate (**5c**): From **2c** (4.11 g, 10 mmol) and acetonitrile (0.66 g, 16 mmol). Yield: 6.83 g (91 %) of white crystals; mp 188-190°C (dec). IR (KBr): 2920, 1550, 1253, 1210; ^{1}H NMR (CD_3CN) δ: 2.77 (s, 3H, CH_3), 3.55 (t, J = 6.90 Hz, 2H, CH_2), 4.96 (t, J = 6.90 Hz, 2H, OCH_2), 7.02~7.79 (m, 3H, Ar-H), 7.96 (s, 2H, $Cl_3C_6H_2$); ^{13}C NMR (CD_3CN) δ: 12.65

(CH_3), 25.89 (CH_2), 77.20 (OCH_2), 123.35, 123.76, 124.62, 126.73, 130.77, 131.25, 134.23, 135.34, 141.71, 149.40, 162.25, 163.17 (Ar, C=N). Anal. calcd. for $C_{17}H_{12}Cl_{10}N_3OSb$ (%): C, 27.20; H, 1.61; N, 5.60. Found: C, 27.20; H, 1.59; N, 5.52.

9-Chloro-4,5-dihydro-2-ethyl-1-(2,4,6-trichlorophenyl)-1*H*-1,2,4-triazolo[3,2-d][1,5]benzoxazepinium Hexachloroantimonate (**5d**): From **2c** (4.11 g, 10 mmol) and propionitrile (0.88 g, 16 mmol). Yield: 6.90 g (90 %) of white crystals; mp 210-212°C (dec). IR (KBr): 2987, 1569,1256, 1220; ^{1}H NMR (CD_3CN) δ: 1.48 (t, J = 7.52 Hz, 3H, CH_3), 3.00 (q, J = 7.47 Hz, 2H, CH_2), 3.56 (t, J = 6.74 Hz, 2H, CH_2), 4.96 (t, J = 6.74 Hz, 2H, OCH_2), 7.03~7.79 (m, 3H, aryl), 7.97 (s, 2H, $Cl_3C_6H_2$); ^{13}C NMR (CD_3CN) δ: 9.63 (CH_3), 20.10 (CH_2), 28.10 (CH_2), 76.96 (OCH_2), 123.62, 124.10, 124.32, 128.40, 131.60, 134.12, 135.75, 142.33, 149.59, 151.51, 162.42, 166.23 (Ar, C=N). Anal. calcd. for $C_{18}H_{14}Cl_{10}N_3OSb$ (%): C, 28.28; H, 1.85; N, 5.50. Found: C, 28.19; H, 1.81; N, 5.49.

Crystal data for **5d**: $C_{18}H_{14}Cl_{10}ON_3Sb$; FW = 764.61; monoclinic, space group $P2_1/c$(#14), a = 13.457(4), b = 11.583(2), c = 18.992(3) Å; β = 110.11(1)°; V = 2780(1) Å^3; Z = 4; D_{calc} = 1.827 g/cm^3, ω-2θ scan, scan width (1.63 + 0.30 tan θ)°; 18.35 < 2θ < 21.10°; F (000) = 1488.00; $\mu_{Mo\text{-}K\alpha}$ = 19.69 cm^{-1}; T = 293 K. A total of 4846 reflections were measured on a Rigaku AFC7R diffractometer with graphite monochromated Mo-Kα radiation (λ = 0.71069 Å); 4614 independent reflections, 3094 observed reflections (I > 3.00σ (I)). The structure was solved by direct methods and expanded using Fourier techniques. The refinement converged at R = 0.036 and Rw = 0.046 for all data.

4,5-Dihydro-2-ethyl-1-(4-nitrophenyl)-1*H*-1,2,4-triazolo[3,2-d][1,5]benzoxazepinium Hexachloroantimonate (**5e**): From **2b** (3.18 g, 10 mmol) and propionitrile (0.88 g, 16 mmol). Yield: 6.00 g (89 %) of pale yellow crystals; mp 172-174°C (dec). IR (KBr): 2934, 1570,1258, 1214; ^{1}H NMR (CD_3CN) δ: 1.38 (t, J =

7.40 Hz, 3H, CH_3), 3.02 (q, J = 7.40 Hz, 2H, CH_2), 3.61 (t, J = 6.69 Hz, 2H, CH_2), 4.88 (t, J = 6.69 Hz, 2H, OCH_2), 7.01~8.12 (m, 8H, Ar-H); ^{13}C NMR (CD_3CN) δ: 9.60 (CH_3), 19.98 (CH_2), 28.07 (CH_2), 77.10 (OCH_2), 122.90, 123.41, 124.53, 127.92, 130.85, 133.94, 135.62, 141.87, 149.40, 152.13, 162.06, 166.34. Anal. calcd. for $C_{18}H_{17}Cl_6N_4O_3Sb$ (%): C, 32.18; H, 2.55; N, 8.34. Found: C, 32.09; H, 2.53; N, 8.28.

2-Benzyl-4,5-dihydro-1-(4-nitrophenyl)-1*H*-1,2,4-triazolo[3,2-d][1,5]benzoxazepinium Hexachloroantimonate (**5f**): From **2b** (3.18 g, 10 mmol) and benzyl cyanide (1.87 g, 16 mmol). Yield: 6.31 g (86 %) of pale yellow crystals; mp 170 °C (dec). IR (KBr): 2931, 1550, 1234, 1210; ^1H NMR (CD_3CN) δ: 3.53 (t, J = 6.78 Hz, 2H, CH_2), 4.43 (s, 2H, $PhCH_2$), 4.93 (t, J = 6.78 Hz, 2H, OCH_2), 7.06~8.01 (m, 13H, Ar-H). Anal. calcd. for $C_{23}H_{19}Cl_6N_4O_3Sb$ (%): C, 37.64; H, 2.61; N, 7.63. Found: C, 37.60; H, 2.58; N, 7.57.

9-Chloro-4,5-dihydro-2-ethyl-1-(4-nitrophenyl)-1*H*-1,2,4-triazolo[3,2-d][1,5]-benzoxazepinium Hexachloroantimonate (**5g**): From **2d** (3.52 g, 10 mmol) and propionitrile (0.88 g, 10 mmol). Yield: 6.00 g (85 %) of pale yellow crystals; mp 176-178°C (dec). IR (KBr): 2934, 1570,1258, 1214; ^1H NMR (CD_3CN) δ: 1.40 (t, J = 7.38 Hz, 3H, CH_3), 3.04 (q, J = 7.38 Hz, 2H, CH_2), 3.63 (t, J = 7.41 Hz, 2H, CH_2), 4.88 (t, J = 7.40 Hz, 2H, OCH_2), 7.03~8.10 (m, 7H, Ar-H). Anal. calcd. for $C_{18}H_{16}Cl_7N_4O_3Sb$ (%): C, 30.61; H, 2.28; N, 7.93. Found: C, 30.58; H, 2.22; N, 7.87.

2-Benzyl-9-chloro-4,5-dihydro-1-(4-nitrophenyl)-1*H*-1,2,4-triazolo[3,2-d][1,5] benzoxazepinium Hexachloroantimonate (**5h**): From **2d** (3.52 g, 10 mmol) and benzyl cyanide (1.87 g, 16 mmol). Yield: 6.61 g (86 %) of pale yellow crystals; mp 174-175 °C (dec). IR (KBr): 2927, 1564, 1234, 1211; ^1H NMR (CD_3CN) δ: 3.55 (t, J = 7.39 Hz, 2H, CH_2), 4.41 (s, 2H, $PhCH_2$), 4.95 (t, J = 7.39 Hz, 2H,

OCH_2), 7.10~8.02 (m, 12H, Ar-H). Anal. calcd. for $C_{23}H_{18}Cl_7N_4O_3Sb$ (%): C, 35.95; H, 2.36; N, 7.29. Found: C, 35.91; H, 2.38; N, 7.21.

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