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SYNTHESIS OF NOVEL 3-(4-SUBSTITUTEDARYLOXYMETHYL) OXETAN-3-YLAMINES

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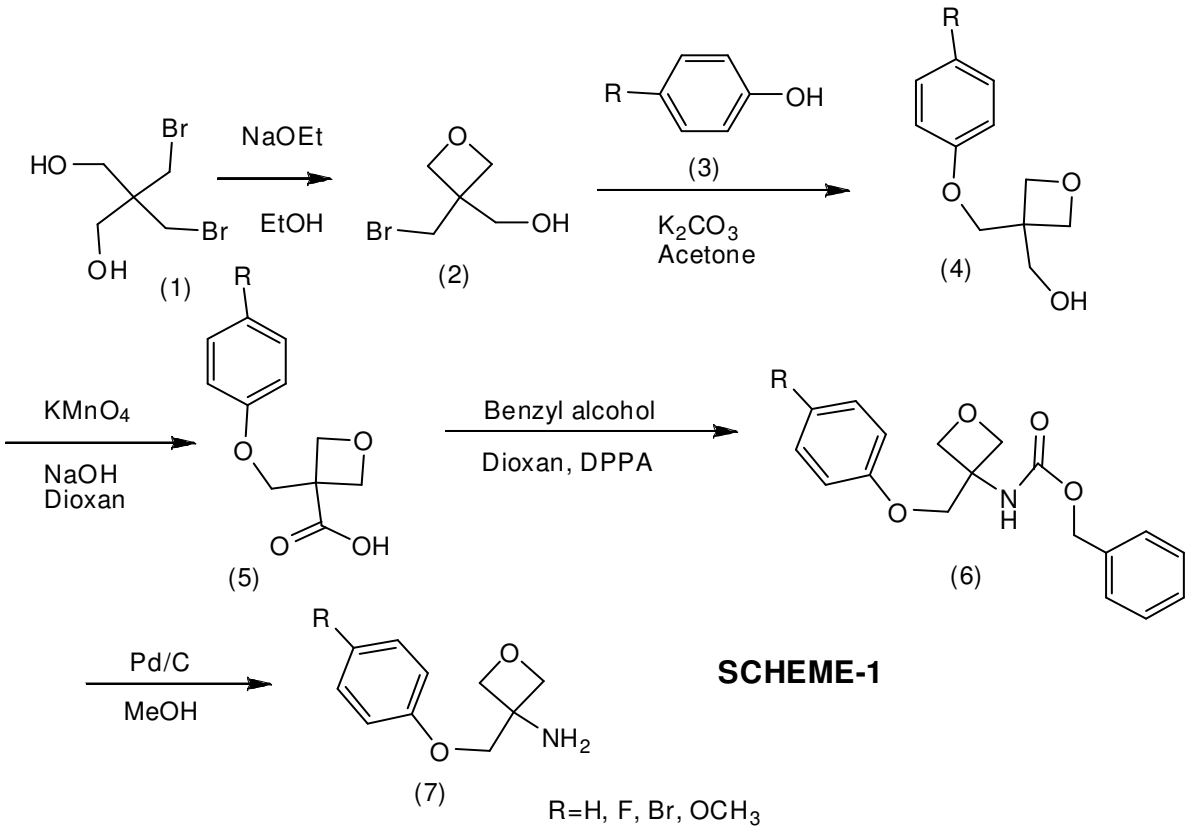
2,2-Bis (bromomethyl) propane-1,3-diol (**1**) was cyclized in the presence of sodium ethoxide at room temp to obtain (3-(bromomethyl) oxetan-3-yl) methanol (**2**) which was treated with various phenols (**3**) to yield (3-(aryloxymethyl) oxetan-3-yl) methanol (**4**). The latter, on oxidation with $KMnO_4$ in aq. NaOH containing dioxan gave the corresponding carboxylic acid derivatives **5.5** with benzyl alcohol containing Diphenyl Phosphoryl Azide (DPPA) gave 3-(4-substitutedaryloxymethyl) oxetan-3-ylamines (**7**) via N-CBz protected aminooxetanes (**6**).

Oxetanes are an essential group of four-membered cyclic ethers that can undergo a broad range of chemical transformations[1]. This ring system has been found to be present in pharmaceutically key natural products such as Paclitaxel[2], Taxotere[3], Oxetanocin-A[4], Mitrephorene[5] and Merrilactone[6]. Simple and yet selective methods for synthesis of the stressed structure are active areas of research. Additionally, oxetange ring containing compounds are essential industrial medicinal agents[7]. Thus, the requirement of differently substituted synthetic oxetanes is quite high. The strained 4-membered ring of oxetane is a strong hydrogen bond acceptor and can be used to develop the solubility of a molecule without compromise on its metabolic stability. Oxetane synthons have been used newly in the preparation of pharmacologically energetic molecules. 3-Hydroxyoxetane is the key precursor for the preparation of a broad range of 3-substituedoxetanes[8].

In view of these observations and keeping in view of our interest in the study of new heterocyclic compounds[9,10], it was considered worthwhile to study the synthesis of 3-(4-substituted aryloxymethyloxetan-3-ylamines).

The synthesis of 3,3-disubstituedoxetane started with cyclizaton of 2,2-bis(bromomethyl) propane-1,3-diol (**1**) in the presence of sodium ethoxide in ethanol to obtain 3-(bromomethyl) oxetan-3-yl) methanol (**2**). The structure of **2** was confirmed from its spectral data. Thus, its IR (neat) spectrum showed a medium but broad peak at 3360 due to –OH group. Its ^{1}H NMR ($CDCl_3$/TMS) spectrum showed signals at δ 2.6 (bs, 1H, OH), 3.70 (s, 2H, CH_2Br), 4.00 (s, 2H, CH_2OH), 4.45 (s, 4H, oxetane ring). Its mass spectrum showed the molecular ion peak at m/z 182 ($M^{+\cdot}$+1), corresponding to a moleculer mass of 181 when recorded in the Q+1 mode. To avoid the use of the strong base (like NaH) in DMF procedure[11] and to improve the low yield in alkylation reactions, an alternate procedure was adopted. Thus, the alkylated compound **4**a was prepared by reaction of 3-(bromomethyloxetan-3-yl) methanol (**2**) with phenol (**3**a, i.e., R=H) in the presence of a mild base like K_2CO_3 in acetone at room temp. The product obtained was assigned the structure **4**a on the basis of its spectral data. Thus, its IR (neat) spectrum showed a medium but broad peak at 3400 due to –OH group. Its ^{1}H NMR ($CDCl_3$/TMS) spectrum showed signals at 3.60 (s, 2H, CH_2OH), 4.10 (s, 2H, CH_2OAr), 4.40 (m, 4H, oxetane ring), 6.90 (m, 3H, ArH), 7.30 (m, 2H, ArH). Its mass spectrum showed the molecular ion peak at m/z 195 ($M^{+\cdot}$+1), corresponding to a molecular mass of 194 when recorded in the Q+1 mode. The above reaction of **2** with phenol (**3**a) has been found to be a general one and has been extended to prepare other derivatives of **4** through the sequence **3**(b-d) → **4**(b-d).

(3-Phenoxymethyloxetan-3-yl) methanol (**4**a) on oxidation with $KMnO_4$ in aq. NaOH in dioxan gave the corresponding 3-phenoxymethyloxetan-3-yl-carboxylic acid (**5**a, i.e., **5**, R=H). The structure of **5**a was confirmed by its spectral data. Thus, its IR (KBr) spectrum showed a medium & broad peak at ~3310 due to the –OH group and a strong, sharp peak at 1640 (C=O) group. Its ^{1}H NMR ($CDCl_3$/TMS) spectrum showed signals at 4.40 (s, 2H, CH_2OAr), 4.70 (d, 2H, oxetane ring), 5.10 (d, 2H, oxetane ring), 6.90 (m, 3H, ArH), 7.10 (m, 2H, ArH). Its mass spectrum



SCHEME-1

showed the molecular ion peak at m/z 208 ($M^{+\cdot}$+1), corresponding to a molecular mass of 207 when recorded in the Q+1 mode. The above reaction of **4**a with $KMnO_4$ has been found to be a general one and has been extended to prepare other derivatives of **5** through the sequence **4**(b-d) → **5**(b-d).

The reaction of **5**a with diphenylphosphoryl azide (DPPA), TEA and benzyl alcohol in dioxan afforded the corresponding (3-phenoxymethyloxetan-3-yl) carbamic acid benzyl ester (**6**a, i.e. **6**, R=H). Structure of this product was confirmed by spectral data. Thus, its IR (KBr) spectrum showed a medium & broad peak at ~3540 due to -NH group and a strong, sharp peak at 1730 (C=O). Its ^{1}H NMR ($CDCl_3$/TMS) showed signals at 4.30 (s, 2H, CH_2O- Ar), 4.60 (d, 2H, oxetane ring), 4.90 (d, 2H, oxetane ring), 5.20 (s, 2H, CH_2-Ar), 7.10-7.50 (m, 10H, ArH). Its mass spectrum showed the molecular ion peak at m/z =314 (M^++1), corresponding to a molecular mass of 313 when recorded in the Q+1 mode. The above reaction of **5**a with DPPA has been found to be a general one and has been extended to prepare other derivatives of **6** through the sequence **5**(b-d) → **6**(b-d).

In continuation of this sequence of reactions, a simple deprotection reaction by treatment with 10% Pd/C in MeOH gave 3-phenoxymethyloxetan-3-ylamine (**7**a, i.e. **7**, R=H). Thus, its IR (KBr) spectrum showed a broad peak at 3420 as an unsplit doublet due to –NH_2 group. ^{1}H NMR ($CDCl_3$/TMS) spectrum showed signals at 4.20 (s, 2H, CH_2OAr), 4.50 (d, 2H, oxetane ring), 4.70 (d, 2H, oxetane ring), 6.80 (d, 2H, ArH), 6.90 (t, 1H, ArH), 7.40 (t, 2H, ArH). Its mass spectrum showed the molecular ion peak at m/z 180 ($M^{+\cdot}$+1), corresponding to a molecular mass of 179 when recorded in the Q+1 mode. The above reaction involving deprotection of **6**a has been found to be a general one and has been extended to prepare other derivatives of **7** through the sequence **6**(b-d) → **7**(b-d).

All the above reactions are nicely depicted in the Scheme-1.

Experimental

Melting points are uncorrected and were determined in a Polman Melting Point apparatus. Purity of the compounds was checked on thin layer chromatography (TLC) plates coated with silica gel G in the solvent system ethyl acetate : hexane. The spots were observed under iodine vapors or UV light. IR spectra were recorded on a Perkin-Elmer 1720 FT-IR spectrometer (KBr Pellets). ^{1}H NMR spectra were recorded on a Bruker AC 300 MHz spectrometer using TMS as internal standard in DMSO-d_6 or in $CDCl_3$

and Mass spectra were recorded on Agilent 6120 Single Quodrupole LCMS instrument giving $M^{+\cdot}$ values either on $M^{+\cdot}+1$ or $M^{+\cdot}-1$ modes.

Synthesis of 2

A solution of **1** (10gm, 0.038 mol) in ethanol (50 ml) was added to a freshly prepared solution of sodium ethoxide (2.5gm, 0.038 mol) in ethanol (25 ml) at RT. The mixture was stirred at RT for 4 hr. After completion of reaction as shown by TLC, salts were filtered. The insoluble salts were washed with cold ethanol (25 ml) and the combined ethanolic filtrate concentrated under reduced pressure to obtain a colourless liquid as residue. Yield : 4.5 gm (65%). [Found : C, 33.01, H, 5.10 $C_5H_9BrO_2$ requires C, 33.17, H, 5.00%].

Synthesis of 4(a-d) : General procedure

A mixture of **2** (0.02 mol), K_2CO_3 (0.04 mol) and the respective phenols **3**(a-d) (0.02 mo) was refluxed for 20 hr. On completion of the reaction, which was monitored by TLC, the mixture was cooled to RT and salts were filtered. The insoluble salts were washed with acetone (20 ml) and the acetone filtrate was concentrated under reduced pressure to obtain a crude residue. The latter was dissolved in dichloromethane (100 ml) and washed with water (50 ml). The organic layer was dried over anhyd. Na_2SO_4, filtered and concentrated under reduced pressure to obtain a crude product which was purified by column chromatography using EtOAc/Hexane as eluent to obtain the pure **4**.

4a (i.e. **4**, R=H); Yield : 4.5gm (80%); Colourless thick liquid. [Found : C, 67.91, H, 7.07 $C_{11}H_{14}O_3$ requires C, 68.02, H, 7.27%].

4b (i.e. **4**, R=F): Yield : 5.1 gm (87%); Colourless thick liquid; IR (neat): 3450 (OH); ^{1}H NMR ($CDCl_3$/TMS): δ 3.70 (s, 2H, CH_2OH), 4.60 (s, 2H, CH_2OAr), 4.90 (m, 4H, oxetane ring), 7.20 (m, 2H, ArH), 7.50 (m, 2H, ArH); LCMS :m/z 213 ($M^{+\cdot}+1$). [Found : C, 62.22, H, 6.12 $C_{11}H_{13}FO_3$ requires C, 62.26, H, 6.17%].

4c (i.e. **4**, R=Br); Yield 6.5gm (86%); Colourless thick liquid; IR (neat): 3550 (OH); ^{1}H NMR ($CDCl_3$/TMS): 3.60 (s, 2H, CH_2OH), 4.30 (s, 2H, CH_2OAr), 4.70 (m, 4H, oxetane ring), 7.10 (m, 2H, ArH), 7.40 (m, 2H, ArH); LCMS : m/z 274 ($M^{+\cdot}+1$). [Found : C, 48.34, H, 4.60 $C_{11}H_{13}BrO_3$ requires C, 48.37, H, 4.80%].

4d (i.e. **4**, R=OCH_3); Yield : 6.5gm (86%); Colourless thick liquid; IR (neat): 3540 (OH); ^{1}H NMR ($CDCl_3$/TMS): 3.20 (s, 3H, OCH_3), 3.60 (s, 2H, CH_2OH), 4.30 (s, 2H, CH_2OAr), 4.80 (m, 4H, oxetane ring), 7.30 (m, 2H, ArH), 7.60 (m, 2H, ArH); LCMS : m/z 225 ($M^{+\cdot}+1$). [Found : C, 64.21, H, 7.12 $C_{12}H_{16}O_4$ requires C, 64.27, H, 7.19%].

Synthesis of 5(a-d) : General procedure

Solid $KMnO_4$ (0.07 mol) was added portion-wise to a mixture of **4**(a-d) (0.02 mol), NaOH (0.04 mol), dioxan (50 ml) and water (25 ml). The mixture was stirred for 4 hr at RT. After completion of the reaction, the mixture was diluted with water, filtered through high flow and the pH of filtrate adjusted to ~3.0. The filtrate was extracted with ethyl acetate (3x100 ml) and the combined organic layers washed with water, dried over anhyd.Na_2SO_4. The organic layer was filtered & concentrated under reduced pressure to obtain a crude residue which was suspended in hexane. The resulting precipitated solid was filtered and washed with hexane to obtain pure oxetane acid **5**.

5a (i.e. **5**, R=H); Yield: 3.5gm (83%); M.P. 126-128^0. [Found : C, 63.15, H, 5.61, $C_{11}H_{12}O_4$ requires C, 63.45, H, 5.81%].

5b (i.e. **5**, R=F); Yield : 4.5gm (84%), M.P. 104-106^0; IR (KBr): 3317 (OH) 1640 (C=O). ^{1}H NMR ($CDCl_3$/TMS): 4.40 (s, 2H, CH_2OAr), 4.70 (d, 2H, oxetane ring), 5.10 (d, 2H, oxetane ring), 6.90 (m, 2H, ArH), 7.10 (m, 2H, ArH); LCMS : m/z 227 ($M^{+\cdot}+1$). [Found : C, 58.11, H, 4.70 $C_{11}H_{11}FO_4$ requires C, 58.41, H, 4.90%].

5c (i.e. **5**, R=Br); Yield : 4.8gm (84%); M.P. 134-136^0; IR (KBr): 3340 (OH), 1640 (C=O); ^{1}H NMR ($CDCl_3$/TMS): 4.40 (s, 2H, CH_2OAr), 4.80 (d, 2H, oxetane ring), 5.30 (d, 2H, oxetane ring), 7.50 (m, 2H, ArH), 7.80 (m, 2H, ArH); LCMS : m/z 288 ($M^{+\cdot}+1$). [Found : C, 45.92, H, 3.56 $C_{11}H_{11}BrO_4$ requires C, 46.02, H, 3.86%].

5d (i.e. **5**, R=OCH_3); Yield : 4.8gm (82%); M.P. 110-112^0; IR (KBr): 3360 (OH), 1640 (C=O); ^{1}H NMR ($CDCl_3$/TMS): 3.30 (s, 3H, OCH_3), 4.30 (s, 2H, CH_2OAr), 4.70 (d, 2H, oxetane ring), 5.40 (d, 2H, oxetane ring), 7.10 (m, 2H, ArH), 7.40 (m, 2H, ArH); LCMS : m/z 239 ($M^{+\cdot}+1$). [Found : C, 60.10, H, 5.62 $C_{12}H_{14}O_5$ requires C, 60.50, H, 5.92%].

Synthesis of 6(a-d) : General procedure

A mixture of **5** (0.01 mol), diphenylphosphoryl azide (0.012 mol), benzyl alcohol (0.01 mol), TEA (0.02 mol) and dioxan (25 ml) was refluxed for 4 hr. After completion of reaction, the mixture was concentrated under reduced pressure, giving a crude residue which was purified by column chromatography after elution with 20% ethyl acetate: hexane to obtain pure **6**.

6a (i.e. **6**, R=H); Yield : 4.5 gm (86%); Colourless thick liquid. [Found : C, 68.79, H, 6.01, N, 4.27 $C_{18}H_{19}NO_4$ requires C, 68.99, H, 6.11, N, 4.47%].

6b (i.e. **6**, R=F); Yield : 5.5gm (84%); Colourless thick liquid; IR (neat): 3520 (NH), 1720 (C=O); ^{1}H NMR ($CDCl_3$/TMS): 4.30 (s, 2H, CH_2OAr), 4.60 (d, 2H, oxetane ring), 4.90 (d, 2H, oxetane ring), 5.20 (s, 2H, CH_2-Ar), 6.90-7.30 (m, 4H, ArH), 7.50-7.90 (m, 5H, ArH); LCMS : m/z 332 ($M^{+\cdot}$+1). [Found : C, 65.12, H, 5.28, N, 4.13 $C_{18}H_{18}FNO_4$ requires C, 65.25, H, 5.48, N, 4.23%].

6c (i.e. **6**, R=Br); Yield: 6.5gm (86%); M.P. 82-84^0; IR (KBr): 3525 (NH), 1720 (C=O); ^{1}H NMR ($CDCl_3$/TMS): 4.30 (s, 2H, CH_2OAr), 4.60 (d, 2H, oxetane ring), 5.10 (d, 2H, oxetane ring), 5.30 (s, 2H, CH_2-Ar), 7.10-7.40 (m, 4H, ArH), 7.60-7.90 (d, 5H, ArH); LCMS : m/z 393 ($M^{+\cdot}$+1). [Found : C, 55.02, H, 4.53, N, 3.34 $C_{18}H_{18}BrNO_4$ requires C, 55.12, H, 4.63, N, 3.57%].

6d (i.e. **6**, R=OCH_3); Yield : 6.9 gm (85%); M.P. 90-92^0; IR (KBr): 3510 (NH), 1730 (C=O); ^{1}H NMR ($CDCl_3$/TMS): 3.30 (s, 3H, OCH_3), 4.30 (s, 2H, CH_2OAr), 4.40 (d, 2H, oxetane ring), 4.90 (d, 2H, oxetane ring), 5.30 (s, 2H, CH_2-Ar), 6.90-7.10 (m, 4H, ArH), 7.40-7.60 (d, 5H, ArH); LCMS : m/z 344 ($M^{+\cdot}$+1). [Found : C, 66.24, H, 6.02, N, 4.01 $C_{19}H_{21}NO_5$ requires C, 66.46, H, 6.16, N, 4.08%].

Synthesis of 7a-d : General procedure

A mixture of **6** (0.01 mol) and 10% Pd/C (0.01 gm) in methanol (20 ml) was stirred for 4 hr at RT. After completion of reaction, the mixture was filtered through a bed of high-flow. The filter bed was washed with methanol and the filtrate concentrated under reduced pressure to obtain a crude residue. The latter was treated with hexane and the separated solid was filtered & washed with hexane to obtain the final product **7**.

7a (i.e. **7**, R=H); Yield 2.1gm (91%); M.P. 45-47^0. [Found : C, 68.91, H, 7.11, N, 7.92 $C_{10}H_{13}NO_2$ requires C, 67.02, H, 7..31, N, 7.82%].

7b (i.e. **7**, R=F); Yield: 3.2gm (87%); M.P. 55-57^0; IR (KBr): 3410 (NH_2); ^{1}H NMR ($CDCl_3$/TMS): 4.30 (s, 2H, CH_2O-Ar), 4.70 (d, 2H, oxetane ring), 4.90 (d, 2H, oxetane ring), 7.40 (d, 2H, ArH), 7.70 (d, 2H, ArH), LCMS : m/z 198 (M^++1). [Found : C, 60.60, H, 6.03, N, 7.02 $C_{10}H_{12}FNO_2$ requires C, 60.90, H, 6.13, N, 7.10%].

7c (i.e., **7**,R=Br): Yield : 3.8 gm (92%); M.P. 60-62^0; IR(KBr): 3420 (NH_2); ^{1}H NMR ($CDCl_3$/TMS): 4.40 (s, 2H, CH_2OAr), 4.80 (s, 2H, oxetane ring), 5.10 (d, 2H, oxetane ring), 7.50 (d, 2H, ArH), 7.80 (d, 2H, ArH); LCMS : m/z 259 ($M^{+\cdot}$+1). [Found : C, 46.33, H, 4.49, N, 5.13 $C_{10}H_{12}BrNO_2$ requires C, 46.53, H, 4.69, N, 5.43%].

7d (i.e. **7**, R=OCH_3); Yield : 3.9gm (92%); M.P. 57-59^0; IR (KBr): 3425 (NH_2); ^{1}H NMR ($CDCl_3$/TMS): 3.30 (s, 3H, OCH_3), 4.30 (s, 2H, CH_2OAr), 4.70 (d, 2H, oxetane ring), 5.10 (d, 2H, oxetane ring), 7.10 (d, 2H, ArH), 7.40 (d, 2H, ArH); LCMS : m/z 210 ($M^{+\cdot}$+1). [Found : C, 63.11, H, 7.03, N, 6.49 $C_{11}H_{15}NO_3$ requires C, 63.14, H, 7.23, N, 6.69%].

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