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A new and convenient synthesis of 13,16-diazaestrone analogs

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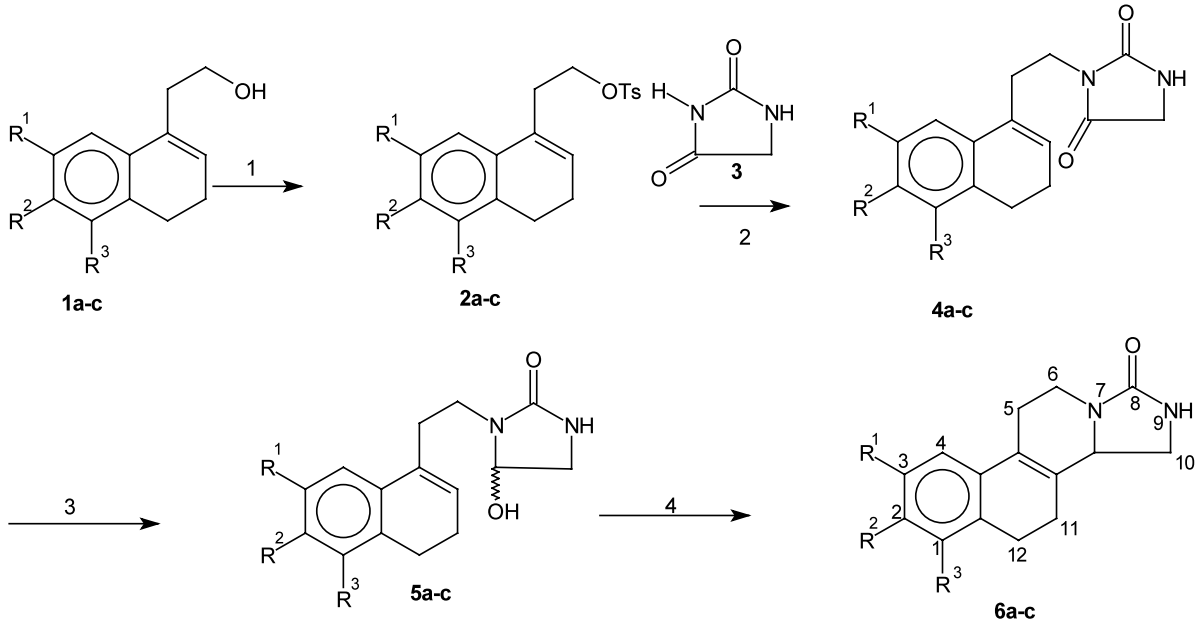
Abstract—Imidazolidine-2,4-dione was chemoselectively *N*-alkylated at the imidic NH with several 2-(3,4-dihydro-1-naphthalenyl)ethyl-4-methylphenylsulphonates to give the corresponding imides for the first time which on selective reduction at one of the carbonyl groups followed by cyclization in PPA gave the corresponding title compounds.

Several azasteroids[1–7] have been synthesised due to their potential biological properties.[8–10] Moreover some of the diazasteroids exhibit analgesic[2] and cardiotonic and hypotensive activity.[11] Though many azasteroids have been reported, the title compounds have not yet been synthesised. We now wish to report the first syntheses of the title compounds.

Towards this end, 2-(3,4-dihydro-1-naphthalenyl)-ethanols **1a–c** were converted to the corresponding 4-methylphenylsulphonates[12] **2a–c**. Imidazolidine-2,4-dione **3** was then chemoselectively *N*-alkylated at the imidic NH with **2a–c** using K_2CO_3 in DMF under reflux for 90 min to give the corresponding seco-azasteroids[13] **4a–c** for the first time. Selective reduction of **4a–c** at one of the carbonyl groups employing $NaBH_4$ in MeOH under reflux for 6 h afforded the corresponding hydroxy lactams[14] **5a–c** which on heat-



Scheme 1. *Reagents and conditions*: (1) *p*-TsCl, $CHCl_3$, C_5H_5N; (2) K_2CO_3/DMF, reflux, 90 min; (3) $NaBH_4$, MeOH, reflux, 6 h; (4) PPA, stream bath, 6 h.

Keywords: 4-methylphenylsulphonylation; chemoselective *N*-alkylation; imide reduction; cyclization; 13,16-diazasteroids.

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Table 1.

Compound	R^1	R^2	R^3	mp[a] (°C)	Yield[b] (%)
2a	H	H	H	51 (lit[1] mp 51.5–53)	85
2b	CH_3	H	H	Oil	84
2c	H	H	Cl	Oil	84
4a	H	H	H	98–100	76
4b	CH_3	H	H	74–76	72
4c	H	H	Cl	Oil	67
5a	H	H	H	Oil	48 (24)[c]
5b	CH_3	H	H	126–128	44 (22)[c]
5c	H	H	Cl	Oil	44 (25)[c]
6a	H	H	H	202	67
6b	CH_3	H	H	197–199	60
6c	H	H	Cl	184–186	39

[a] Melting points are uncorrected.
[b] Yield refers to purified product.
[c] % of starting material recovered.

ing in PPA on a steam bath for 6 h underwent intramolecular cyclization to afford the corresponding title compounds[15] **6a–c** (Scheme 1).

The required 2-(3,4-dihydro-1-naphthalenyl)ethanols **1a–c** were prepared by the Reformatsky reaction[1] on the corresponding 2*H*-3,4-dihydro-1-naphthalenones with ethyl bromoacetate followed by the reduction[16] of the β–γ unsaturated esters with $NaBH_4$ in PEG-400 at 65°C. The physical constants and yields of the compounds synthesized are listed in Table 1.

In conclusion, the present work provides the first synthesis of the title compounds **6a–c** starting from **2a–c** which involves chemoselective *N*-alkylation of **3** at the imidic NH with **2a–c** followed by selective reduction of **4a–c** and finally cyclization of **5a–c** in PPA. Thus the method for the synthesis of title compounds **6a–c** is short, general and utilizes easily accessible materials.

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12. General procedure for the synthesis of 4-methylphenylsulphonates **2**:
To a well-stirred mixture of 4-methylphenylsulphonyl chloride (1.045 g, 5.5 mmole) and dry pyridine (1.58 g, 20 mmole) in dry $CHCl_3$ (25 cm^3) was added alcohol **1** (5 mmole) in dry $CHCl_3$ (10 cm^3) at 10°C (for **1a**) and at rt (for **1b–c**) during a period of 15 min. After the addition was completed, the mixture was stirred for an additional 3 h at the same temperature. The reaction mixture was then poured onto a mixture of ice and conc. HCl (50 cm^3) and the organic layer was separated. The aqueous layer was extracted with $CHCl_3$ (3×25 cm^3) and the combined $CHCl_3$ layer washed with 10% Na_2CO_3 (2×25 cm^3), water (2×25 cm^3) and then dried (anhyd. Na_2SO_4). After the evaporation of the solvent, a brown residue was obtained which was purified by column chromatography [silica gel, pet. ether:$CHCl_3$ (80:20)] to afford the corresponding 4-methylphenylsulphonate **2**.
2-(3,4-Dihydro-1-naphthalenyl)ethyl-4-methylphenylsulphonate **2a**:
IR (KBr): 1180, 1360 (S=O str.) cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz): $\delta = 2.0–2.97$ (9H, m), 4.15 (2H, t, $J=7$ Hz, O–CH_2), 5.8 (1H, t, $J=5$ Hz, C–C=H), 6.8–7.66 (8H, m, Ar-H); UV ($CHCl_3$): λ_{max}, nm (log ε) = 261 (3.90).
2-(3,4-Dihydro-7-methyl-1-naphthalenyl)ethyl-4-methylphenylsulphonate **2b**:
IR (oil film): 1180, 1360 (S=O str.) cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz): $\delta = 2.0–2.93$ (12H, m), 4.1 (2H, t, $J=7$ Hz, O–CH_2), 5.76 (1H, t, $J=5$ Hz, C=C–H), 6.8–7.6 (7H, m, Ar–H); UV ($CHCl_3$): λ_{max}, nm (log ε) = 263 (3.91); Anal. calcd for $C_{20}H_{22}O_3S$: C, 70.15; H, 6.48; S, 9.36. Found: C, 70.05; H, 6.53; S, 9.33.
2-(5-Chloro-3,4-dihydro-1-naphthalenyl)ethyl-4-methylphenylsulphonate **2c**:

IR (oil film): 1180, 1360 (S=O str.) cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz): $\delta = 2.0$–3.0 (9H, m), 4.1 (2H, t, $J = 7$ Hz, O–CH_2), 5.79 (1H, t, $J = 5$ Hz, C=C–H), 6.8–7.66 (7H, m, Ar–H); UV ($CHCl_3$): λ_{max}, nm (log ε) = 263 (3.90); Anal. calcd for $C_{19}H_{19}O_3ClS$: C, 62.89; H, 5.28; Cl, 9.77; S, 8.84. Found: C, 62.80; H, 5.31; Cl, 9.80; S, 8.80.

13. General procedure for the synthesis of seco-azasteroids **4**: A mixture of 4-methylphenylsulphonate **2** (2 mmole), imidazolidine-2,4-dione **3** (298 mg, 3 mmole), anhyd. K_2CO_3 (1 g) and dry DMF (20 cm^3) was refluxed with stirring for 90 min. The reaction mixture was diluted with water and extracted with EtOAc (4×50 cm^3). The combined EtOAc extracts were washed with water (3×50 cm^3) and then dried (anhydrous Na_2SO_4). Evaporation of the solvent gave a brown residue which was purified by column chromatography [alumina (neutral), $CHCl_3$: MeOH (98:2)] to afford the corresponding seco-azasteroid **4**.

    3-[2-(3,4-Dihydro-1-naphthalenyl)ethyl]imidazolidine-2,4-dione **4a**:

    IR (KBr): 1715,1780 (C=O str.), 3250 (N–H str.) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): $\delta = 2.24$ (2H, m, H3 of dihydronaphthalene ring), 2.72 (2H, t, $J = 6.7$ Hz, H4 of dihydronaphthalene ring), 2.77 (2H, t, $J = 7.0$ Hz, C=C–CH), 3.70 (2H, t, $J = 7.0$ Hz, N–CH), 3.87 (2H, s, CO–CH–N), 5.22 (1H, s, NH), 5.96 (1H, t, $J = 5.0$ Hz, H2 of dihydronaphthalene ring), 7.13–7.23 (3H, m, H5–7 of dihydronaphthalene ring), 7.38 (1H, d, $J = 7.9$ Hz, H8 of dihydronaphthalene ring); MS: $m/z = 256$ (M^+, 50%), 156 (65%), 155 (36%), 141 (70%), 128 (100%), 127 (48%), 115(24%); UV ($CHCl_3$): λ_{max}, nm (log ε) = 264 (3.84); Anal. calcd for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.37; H, 6.24; N, 10.99.

    3-[2-(3,4-Dihydro-7-methyl-1-naphthalenyl)ethyl]imidazolidine-2,4-dione **4b**:

    IR (KBr): 1710, 1780 (C=O str.), 3300 (N–H str.) cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz): $\delta = 2.0$–3.0 (9H, m), 3.66–4.0 (4H, m, N–C–H), 5.9 (1H, t, $J = 5.0$ Hz, C=C–H), 6.5 (1H, s, N–H), 7.0–7.5 (3H, m, Ar–H); MS: $m/z = 270$ (M^+, 90%), 170 (85%), 155 (100%), 143 (67%), 142 (72%), 141 (75%), 128 (67%); UV ($CHCl_3$): λ_{max}, nm (log ε) = 263 (3.94); Anal. calcd for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.36. Found: C, 71.00; H, 6.76; N, 10.39.

    3-[2-(5-Chloro-3,4-dihydro-1-naphthalenyl)ethyl]imidazolidine-2,4-dione **4c**:

    IR (oil film): 1715, 1780 (C=O str.), 3300 (N–H str.) cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz): $\delta = 2.1$–3.1 (6H, m), 3.75–4.1 (4H, m, N–C–H), 5.9 (1H, t, $J = 5.0$ Hz, C=C–H), 6.66 (1H, s, N–H), 7.1–7.4 (3H, m, Ar–H); UV ($CHCl_3$): λ_{max}, nm (log ε) = 260 (3.94); Anal. calcd for $C_{15}H_{15}N_2O_2Cl$: C, 61.97; H, 5.20; N, 9.63; Cl, 12.19. Found: C, 61.90; H, 5.24; N, 9.67; Cl, 12.23.

14. General procedure for the synthesis of hydroxy lactams **5**: To a well-stirred solution of seco-azasteroid **4** (1 mmole) in dry MeOH (50 cm^3) was added gradually sodium borohydride (76 mg, 2 mmole) in dry MeOH (20 cm^3) at rt and the mixture was refluxed with stirring for 6 h. MeOH was removed by distillation and the residue was decomposed with 5% NH_4Cl solution (100 cm^3). It was extracted with $CHCl_3$ (3×25 cm^3). The combined $CHCl_3$ extract was washed with water (2×25 cm^3) and then dried (anhyd. Na_2SO_4). Evaporation of the solvent gave a brown residue which was purified by column chromatography [alumina (basic), chloroform: MeOH (98:2)] to furnish starting seco-steroid **4**. Further elution with chloroform:MeOH (96:4) (500 cm^3) followed by recovery of solvents gave hydroxy lactam **5**.

    1-[2-(3,4-Dihydro-1-naphthalenyl)ethyl]-5-hydroxyimidazolidin-2-one **5a**:

    IR (oil film): 1680 (C=O str.), 3200-3500 (N–H and O–H str.) cm^{-1}; UV ($CHCl_3$): λ_{max}, nm (log ε) = 263 (3.86); Anal. calcd for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02; N, 10.84. Found: C, 69.67; H, 6.98; N, 10.92.

    1-[2-(3,4-Dihydro-7-methyl-1-naphthalenyl)ethyl]-5-hydroxyimidazolidin-2-one **5b**:

    IR (KBr): 1670 (C=O str.), 3200-3500 (N–H str.) cm^{-1}; UV ($CHCl_3$): λ_{max}, nm (log ε) = 263 (3.86); Anal. calcd for $C_{16}H_{20}N_2O_2$: C, 70.56; H, 7.40; N, 10.29. Found: C, 70.47; H, 7.43; N, 10.24.

    1-[2-(5-Chloro-3,4-dihydro-1-naphthalenyl)ethyl]-5-hydroxyimidazolidin-2-one **5c**:

    IR (oil film): 1680 (C=O str.), 3200-3500 (N–H and O–H str.) cm^{-1}; UV ($CHCl_3$): λ_{max}, nm (log ε) = 266 (3.90); Anal. calcd for $C_{15}H_{17}N_2O_2Cl$: C, 61.54; H, 5.85; N, 9.57; Cl, 12.11. Found: C, 61.49; H, 5.89; N, 9.53; Cl, 12.15.

15. General procedure for the synthesis of title compounds **6**: A mixture of hydroxy lactam **5** (50 mg) and PPA (10 g) was heated on a steam bath for 5 h. The reaction mixture was poured onto ice and allowed to stand overnight. It was extracted with EtOAc (3×25 cm^3). The combined EtOAc extracts were washed with 10% Na_2CO_3 (2×25 cm^3), water (2×25 cm^3) and then dried (anhyd. Na_2SO_4). Evaporation of the solvent gave a brown residue which was purified by column chromatography [alumina (basic), chloroform: MeOH (98:2)] to furnish title compounds **6**.

    5,6,10,10a,11,12-Hexahydrobenzo[*f*]imidazo[5,1-*a*]isoquinolin-8[9*H*]-one **6a**:

    IR (KBr): 1700 (C=O str.), 3200 (N–H str.) cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz): $\delta = 2.33$–4.6 (11H, m), 5.6 (1H, s, NH), 6.9–7.4 (4H, m, Ar–H); UV ($CHCl_3$): λ_{max}, nm (log ε) = 264 (3.89); Anal. calcd for $C_{15}H_{16}N_2O$: C, 74.97; H, 6.71; N, 11.66. Found: C, 74.85; H, 6.76; N, 11.59.

    5,6,10,10a,11,12-Hexahydro-3-methylbenzo[*f*]imidazo-[5,1-*a*]isoquinolin-8[9*H*]-one **6b**:

    IR (KBr): 1700 (C=O str.), 3300 (N–H str.) cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz): $\delta = 2.0$–4.33 (14H, m), 5.33 (1H, s, NH), 6.5–7.2 (3H, m, Ar–H); UV ($CHCl_3$): λ_{max}, nm (log ε) = 263 (3.93); Anal. calcd for $C_{16}H_{18}N_2O$: C, 75.76; H, 7.13; N, 11.03. Found: C, 75.87; H, 7.08; N, 11.07.

    1-Chloro-5,6,10,10a,11,12-hexahydrobenzo[*f*]imidazo-[5,1-*a*]isoquinolin-8[9*H*]-one **6c**:

    IR (KBr): 1690 (C=O str.), 3300 (N–H str.) cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz): $\delta = 2.0$–4.5 (11H, m), 5.5 (1H, s, NH), 6.8–7.5 (3H, m, Ar–H); UV ($CHCl_3$): λ_{max}, nm (log ε) = 265 (3.88); Anal. calcd for $C_{15}H_{15}N_2OCl$: C, 65.57; H, 5.50; N, 10.20; Cl, 12.90. Found: C, 65.64; H, 5.46; N, 10.17; Cl, 12.94.

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