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CONVENIENT SYNTHESIS OF 1-OXA-3,8-DIAZASPIRO [4,5] DECAN-2-ONES.

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ABSTRACT: Synthesis of 1-oxa-3,8-diazospiro [4,5] decan-2-ones from 4-pyridone by addition of trimethylsilyl cyanide.

Continuing our interest in the synthesis of new antihypertensive agents (1), the syntheses of 9-substituted-1-oxa -3,8-diazaspiro [4,5]- decan-2-ones reported by Clark and co-workers (2,3) intrigued us. They are structurally related to the antihypertensive agent indoramine (4), a known post-synaptic α_1 adrenoceptor blocker. Our synthetic goal was to incorporate similar diazaspiro-[4,5]- decane-2-ones into molecules with the required quinazolinedione (1), and study their potential antihypertensive and other biological properties. Clark and co-workers had synthesized the diazospiro system starting from 1-benzyl-4-piperidone by addition of ethyllithioacetate followed by hydrazine and Curtius rearangement to give an acylhydrazide, subsequent treatment of which with HNO_2 led to the diazospiro compound (3).

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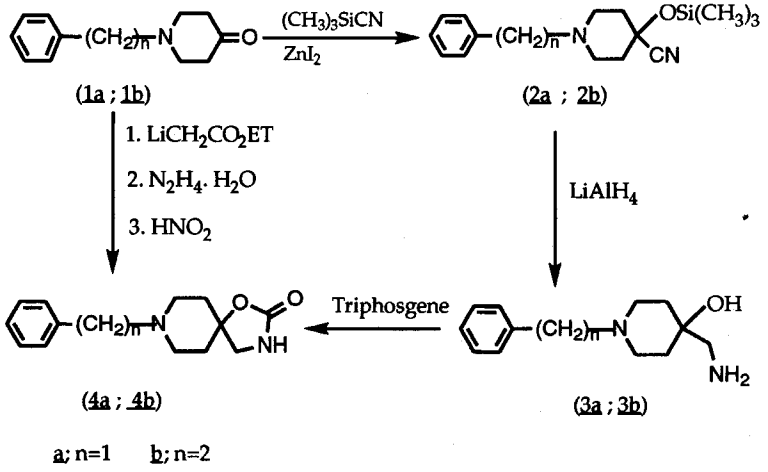
Here we wish to report a convenient alternative synthesis of the diazospiro system by adding trimethysilyl cyanide to (1a) in the presence of catalytic amounts of zinc iodide to give the adduct (2) (7,8), which was reduced with LAH to give the amino alcohol (3), and subsequently ring closed with triphosgene to give the desired compound (4a) in 72% yield from (3). Using the same technique we also converted 1-(2-phenylethyl)-4-piperidone (1b) to Fenspiride (4b), a bronchodilator blocker (9,10).



EXPERIMENTAL

Melting points were obtained on a Gallenkamp apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer FT-IR 1750 spectrophotometer. The proton nuclear magnetic resonance spectra were recorder on a Chemagnetic 200 MHz and Varian EM-390 90 MHz. Mass spectra were obtained on a Finnigan 3000 at 70 eV by direct insertion and data processed using the Teknivent system.

1-Benzyl-4-Cyano-4-Trimethylsilyloxipiperidone(2a):
Trimethylsilyl cyanide (2.66mL,0.019moles) was added dropwise to 1-benzyl-4-piperidone (3.32g,0.012moles) containing Zinc Iodide (≈50 mg) at 0°C. The mixture was stirred at 0°C for 3h and then heated at 60°C for additional 3h and the final product was distilled bulb-to-bulb using a Buchi-Kugelrohr oven at 165°C/4mmHg to give a clear liquid (4.65g, 91%). IR(KBr): 3090, 3060, 3020, 2960, 2810, 2760,1495,1250,1100, 870, 840 cm-1. ^{1}H NMR ($CDCl_3$): ∂ 7.31 (s,5H, Ar-H), 3.50(s,2H,Ar-CH_2), 3.01-1.81(m,8H,CH_2), 0.24(s,9H, CH_3-Si)ppm. ^{13}C NMR ($CDCl_3$): ∂175.17, 138.20, 128.80, 128.15, 127.03, 68.89, 62.44, 61.85, 49.38, 38.63,1.29 ppm. EM(m/e): 288(27), 260(23), 197(47), 91(100).

1-Benzyl-4-Aminomethyl-4-Piperidinol(3a):
$LiAlH_4$ (7mL,7.0mmoles in ether) was added dropwise to a stirred ice-cold solution of compound (2a) (1.54g, 5.3 mmoles) in ether (20mL). After 2h stirring, NaOH (20%) was added and the organic layer was decanted, the residue was further triturated with ether (30mL) and the combined organic phase was dried (Na_2SO_4) and removal of solvent gave a low melting solid (0.91g, 78%). mp. 72-73°C. IR(KBr): 3400, 3080, 3060 3030, 2930, 2810, 2760, 1600, 1450,1050, 970, 740, 690cm-1. ^{1}H NMR ($CDCl_3$): ∂7.3(s,5H, Ar-H), 3.60(s,2H,Ar-CH_2), 3.58(s,1H,OH), 2,70-2.20 (m,10H,CH_2), 1.60(bs,2H, -NH_2)ppm. EM(m/e): 220(6), 190(26), 111(74), 91(100).

8-Benzyl-1-Oxa-2-Oxo-3,8-Diazospiro [4,5] Decane(4a):
Triphosgene (0.12g, 4.0mmoles) in dry dichlorometane (10mL) was added dropwise to a stirred solution of amino alcohol (3a) (0.99g, 4.1mmoles) in dichloromethane (25mL) at RT for 2h. The reaction was neutralized by addition of NaOH (1%, 20mL) and the organic layer was washed with water and dried ($MgSO_4$). Removal of solvent under reduced pressure gave a solid (0.801g, 72%). mp. 170-171°C. IR(KBr): 3290, 3020, 2920, 2800, 2760, 1750, 1700, 1440, 1250, 1150 cm-1. ^{1}H NMR ($CDCl_3$): ∂ 7.20(s,5H, Ar-H), 5.80(bs,1H, NH) 3.60(s,2H,Ar-CH_2),

3.4(s,2H,CH_2-N-CO), 2.60(m,4H,CH_2-N), 1.90(m,4H,CH_2-) ppm. EM(m/e): 246(5), 245(3), 169(12), 155(24), 91(100). Analysis. Calcd. for $C_{14}H_{18}O_2N_2$: C,68.29; H, 7.31. Found: C, 68.48; H, 7.62 %.

The method described above were also used to synthesise compounds (2b), (3b) and (4b).

1-(2-Phenethyl)-4-Cyano-4-Trimethylsilyloxipiperidine(2b): bp. 165°C /4mmHg. IR(KBr): 3080, 3060, 3020, 2950, 2810, 2780, 2220, 1600, 1495, 1470, 1450, 1340, 1250, 1150, 1100, 870, 840 cm^{-1}. ^1H NMR ($CDCl_3$): ∂ 7.20 (m,5H, Ar-H), 2.96-1.83(m,12H,CH_2), 0.25(s,9H, CH_3-Si)ppm. EM(m/e): 287(4), 211(100), 112(12).

1-(2-Phenylethyl)-4-aminomethyl-4-piperidinol(3b): IR(KBr):3440, 3080, 3060 3030, 2940, 2810, 1600, 1500,1460, 970, 740, 690 cm^{-1}. ^1H NMR ($CDCl_3$): ∂ 7.34 (m,5H, Ar-H), 2.86(m,14H,CH_2), 3.65(s,1H,OH), 1.58(bs,2H, -NH_2) ppm. EM(m/e): 234(6), 204(11), 144(83), 126(89), 112(62), 91(88), 77(90), 68(100).

8-(Phenethyl)-1-Oxa-2-Oxo-3,8-Diazospiro[4,5] Decane(4b): (1.087g, 69%). mp. 143-145°C. IR(KBr): 3260, 3020, 2920, 2810, 2760, 1740, 1490,1320, 1250, 1150,1090, 970, cm-1. ^1H NMR ($CDCl_3$): ∂ 8.28(bs,1H,NH), 7.53-7.11(m,5H,Ar-H), 3.75-2.12(m,14H,CH_2) ppm. EM(m/e): 260(.1),169(100), 96(29). Analysis. Calcd. for $C_{15}H_{20}O_2N_2$: C, 69.23; H, 7.69. Found: C,67.27; H,7.47 %.

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REFERENCES:

1) R. Cortez, I.A. Rivero, R. Somanathan, G. Aguire, F. Ramirez and E. Hong, Synthetic Communications., 21, 285 (1991).

2) R.D. Clark, J.M. Caroon, D.B. Repke, A.M. Strosberg, S.M. Bitter, M.D. Okada, A.D. Michel and R.L. Whiting, J. Med. Chem., 26, 855 (1983).

3) J.M. Caroon, R. Clark, A.F. Kluge, J.T. Nelson, A.M. Strosberg, S.H. Unger, A.D. Michel and R.L. Whiting, J. Med. Chem., 24, 21320 (1981).

4) J.L. Archibald, B.J. Alps, J.F. Cavalla and J.L. Jackson, J. Med. Chem., 14, 1054 (1971).

5) D.A. Evans, G.L. Carroll and L.K. Truesdale, J. Org. Chem., 39, 914 (1974).

6) R. Somanathan, H.R. Aguilar, G.R. Ventura and K.M. Smith, Synthetic Communications., 13, 273 (1983).

7) Dutch Patent 6,504,602 (1965). CA, 64, 12679d (1966).

8) The Organic Chemistry of Drug Synthesis, Vol. 2, pp.291 (1977) Eds. D. Lednicer and L.A. Mitscher, John Wiley & Sons, NY.

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