SYNTHESIS OF 2-MONO AND 2,6-DISUBSTITUTED METHYL-1,4-DIHYDROPYRIDINES

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ABSTRACT: *The 2-mono and 2,6-disubstituted methyl-1,4- dihydropyridines were synthesized by reaction of morpholine, thiophenol, 8-hydroxyquinoline, 2-naphthol and 2- mercapto-1-methyl imidazole with the 2-mono bromo and 2,6-dibromo-1,4-dihydropyridines.*

KEY WORDS: *Nitrenedipine analogues, Calcium channel antagonists, 2-mono and 2,6-disubstituted 1,4-dihydropyridines.*

We had reported on the synthesis, structure and biological activity of isoxazole-1,4-dihydropyridines (IDHPs) and 4-aryl-1,4-dihydropyridines [1]. Compounds **1-2** were synthesised and were brominated regioselectively at C_2 and $C_{2,6}$ according to the procedure developed in this lab. [2]. Nucleophilic quenching of the mono and dibrominated derivatives afforded **3-4** and **5** in moderate yields (Scheme), (Table 1).

Preparation of 2-mono and 2,6-disubstituted methyl-3- ethoxycarbonyl-5- methoxycarbonyl-4-(3-nitrophenyl)-1,4-dihydropyridine

General procedure; preparation of 3a

To a solution of **1** or **2** (0.72 g, 2 mmol)in dichloromethane (16.0 mL) at –20 °C was added pyridine (0.3 mL, 3.5 mmol) and pyridinium bromide perbromide (0.78 g , 2.2 mmol). The solution was stirred for 1 hour (–20 °C) and after completion of the reaction, it was diluted with cold CH_2Cl_2 (24.0 mL) and washed with hydrochloric acid (2×20.0 mL of 2M) and then with ice-water (2×20.0 mL). The solution was then dried over anhydrous sodium sulfate and the solvent was removed in vacuo without heating. The yellow residue was diluted with cold anhydrous THF (4.0 mL) and was poured over an ice-cooled solution of the sodium salt of morpholine [derived from morpholine (0.21 mL, 2.4 mmol) and sodium hydride (0.096 g , 2.4 mmol) in 10.0 mL THF] and the mixture was stirred at 0 °C for 2 hours and at room temprature for 3 hours. After completion of the reaction the solvent was removed in vacuo and was diluted with EtOAc (20.0 mL) and washed with hydrochloric acid (20.0 mL of 2M) and brine (2×20.0 mL). The organic layer was dried over anhydrous sodium sulfate. Evaporation of the solvent gave a solid residue. Column chromatography over silicagel 60 (2% EtOAc/CH_2Cl_2) and crystalization from EtOH- hexane gave the desired product (**3a**). Other mono and disubstituted compounds were prepared according to the same procedure for **3a** by using the appropriate nucleophile and the mono and/or dibromo compounds (**1a , b ; 2a , b**).

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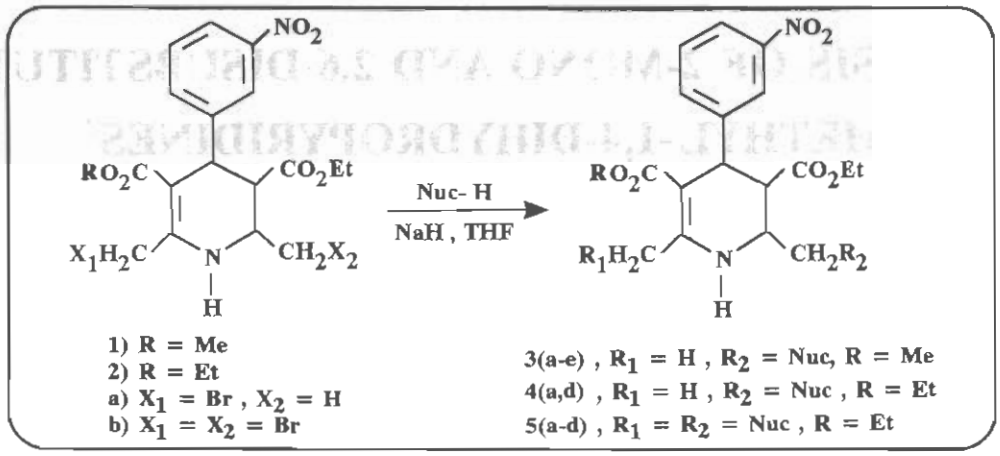

Scheme

Table 1:

Compound	^{1}H NMR δ(*ppm*)	Reacting Nucleophile/amount (mmol)	m.p. (°C)	Yield (%)
$C_{22}H_{27}N_3O_7$ (3a)	$\delta(CDCl_3)$, 60 MHz: 0.66(3H, t), 1.92(3H,s), 2.1 (4H, m), 3.1 (3H, s), 3.2 (4H, m), 3.3(2H, s), 3.6 (2H, q), 4.62 (1H, s), 6.8- 7.6 (4H, m), 7.5(1H, br)	Morpholine (2.4 mmol)	110-111	50
$C_{24}H_{24}N_2O_6S$ (3b)	$\delta(CDCl_3)$, 60 MHz: 1.2(3H,t), 2.2(3H, s), 3.5 (3H, s), 3.9 (2H, q), 4.22-4.38(2H, s), 4.9(1H, s), 6.7(1H, br), 6.9-7.85(4H, m)	Thiophenol (4.8 mmol)	—	76
$C_{27}H_{25}N_3O_7$ (3c)	$\delta(CDCl_3)$, 60 MHz:1.16(3H, t), 2.4(3H, s), 3.5 (3H, s), 4.0 (2H, q), 4.9(1H, s), 5.4(2H, s), 7.0- 8.8 (10H, M), 9.4(1H, br)	8-Hydroxy quinoline(4.8 mmol)	143	61
$C_{28}H_{26}N_2O_7$ (3d)	$\delta(CDCl_3)$, 60 MHz: 1.25(3H, t),2.4(3H, s), 3.6(3H, s), 4.1(2H, q, q, J=8.0 Hz), 5.1(1H, s), 5.3(2H, s), 7.0-8.1 (12H, m)	2-Naphthol (4.8 mmol)	132	48
$C_{22}H_{24}N_4O_6S$ (3e)	$\delta(CDCl_3)$, 60 MHz:1.22(3H, t), 2.3(3H, s), 3.5(3H, s), 3.6 (3H, s, s), 4.1(2H, q), 4.4 (2H, s, s), 5.0 (1H, s), 6.8- 8 (6H, m), 10.2(1H, br)	2-Mercapto-1-methyl-imidazole (4.8 mmol)	—	32
$C_{23}H_{29}N_3O_7$ (4a)	$\delta(CDCl_3)$,80 MHz: 1.2(6H, t, ester 2×CH_3), 2.45(3H, s, allylic CH_3), 2.6(4H, broad, morpholio 2 × CH_2N), 3.8(6H, broad, allylic and morpholio 2 × CH_2O), 4.15(4H, q, ester CH_2), 5.1(1H, s, CH), 7.3-8.1 (5H, m,NH and ArH)	Morpholine (2.56 mmol)	141	51

Table 1: continued.

Compound	^{1}H NMR signal δ[*ppm*]	Reacting Nucleophile/amount (mmol)	m.p. (°C)	Yield (%)
$C_{29}H_{28}N_2O_7$ **(4d)**	$\delta(CDCl_3)$, 80 MHz: 1.32 (6H, dt, ester 2 × CH_3), 2.45 (3H, s, allylic CH_3), 4.15(4H, dq, ester 2 × CH_2), 5.25(1H, s, CH), 5.45(2H, s, allylic CH_2), 7.1(1H, broad s, NH), 7.2-8.25 (4H, m, ArH)	2-Naphthol (2.14 mmol)	162-163	72
$C_{27}H_{36}N_4O_8$ **(5a)**	$\delta(CDCl_3)$, 80 MHz:1.2(6H, t, ester 2×CH_3), 2.6 (8H, broad, morpholio 4 × CH_2N),3.8 (12H, broad t, allylic 2×CH_2 and morpholio 4×CH_2O), 4.15 (4H, q, ester 2×CH_2), 5.1 (1H, s, CH), 7.3- 8.1	Morpholine (8.0 mmol)	189	36
$C_{31}H_{30}N_2S_2O_6$ **(5b)**	$\delta(CDCl_3)$, 400 MHz: 1.2(6H, t, ester CH_3), 4.0 (2H, d, J= 16 Hz allylic CH_2), 4.1 (4H, m, ester 2×CH_2), 4.8(2H, d, J= 16 Hz allylic CH_2), 5.08 (1H, s, CH), 8.2(1H, broad, s, NH), 6.95-8.00 (14H,m, ArH)	Thiophenyl (4.78 mmol)	123-124	86
$C_{31}H_{30}N_2S_2O_6$**(5c)**	$\delta(CDCl_3)$, 80 MHz: 1.3(6H, t, ester 2 × CH_3), 3.8 (1H, s, NH), 4.2(4H, q, ester 2× CH_2), 5.3(1H, s, CH), 5.7(4H, s, allylic CH_2), 7.0-8.5(16H, m, ArH)	8-Hydroxy quinoline(4.78 mmol)	181-182	41
$C_{39}H_{34}N_2O_8$ **(5d)**	$\delta(CDCl_3)$,80 MHz:1.3(6H,t,ester 2×CH_3), 4.2(4H, q, ester 2×CH_2), 5.2(1H, s, CH), 5.5 (4H, s, allylic 2 × CH_2), 7.1-8.1(18H, m, ArH), 8.6(1H, broad s, NH)	9-Naphthol (4.78 mmol)	173-174	51

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