NITROIMIDAZOLES IV [1]. SYNTHESIS OF 3,5-DICARBOALKOXY-2,6-DIMETHYL-4-(1-METHYL-5-NITRO-2-IMIDAZOLYL)-1,4-DIHYDROPYRIDINE AND 3,5-DICARBOALKOXY-2,6-DIMETHYL-4-(2-SUBSTITUTED-4-THIAZOLYL)-1,4-DIHYDROPYRIDINE

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Abstract

Different procedures for the syntheses of the title compounds were investigated. The best method for the preparation of the title compounds were the reaction of the readily available 2-formyl-1-methyl-5-nitroimidazole or 2-substituted-4-formylthiazoles with alkyl acetoacetate and alkyl aminocrotonate in boiling alcohol.

Introduction

Calcium ion plays a vital role in a large number of cellular processes, including excitation-contraction and stimulus-secretion [2-4]. The regulation of the intracellular concentration of this ion makes possible the control of such Ca^{2+}-dependent processes. One means of accomplishing this is by the use of agents known as calcium channel antagonists, which inhibit the movement of calcium through certain membrane channels [3, 5, 6].

Structurally diverse groups of organic compounds are known to be effective as calcium antagonists [3, 5, 6]. The most potent class of antagonists comprises derivatives of 1, 4-dihydropyridine of which the most widely known agent is Nifedipine [2,6-dimethyl-3, 5-dicarbomethoxy-4-(2-nitro phenyl)-1, 4-dihydropyridine] [6,7]. These compounds exert a profound negative inotropic effect on heart muscle and a marked relaxation of smooth muscle.

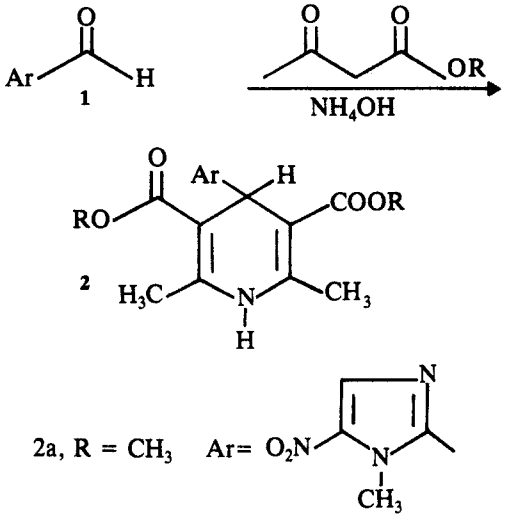
Studies carried out to date suggest that diverse pharmacological activities of these antagonists results from a fundamentally similar mode of action and that they act at specific membrane sites rather than through nonspecific membrane interactions [8, 9].

Structure-activity correlations derived for the dihydropyridine antagonists indicate that the nature and position of the substitution in the aryl group is exceedingly important determinants of activity [10, 12]. The effect of the substituents on activity was observed to be relatively independent of their electronic character but correlated well with a parameter, B_1, reflecting their size.

In addition, the considerable biological importance of imidazoles has stimulated much work on this heterocycle [13-17]. It was also shown that substituted nitroimidazolythiadiazoles and nitroimidazolyloxadiazoles have biological activities [18-20]. We have decided to substitute the phenyl ring of nifedipine with nitroimidazolyl and thiazolyl rings in order to study their biological activities.

Results and Discussion

Most of dihydropyridines (2) were prepared by the classical procedure of Hantzch [21], in which the corresponding aldehyde (1) is reacted with acetoacetic ester and ammonium hydroxide (Scheme 1). The reaction of 2-formyl-1-methyl-5-nitroimidazole with methyl acetoacetate and ammonia gave the desired compound 2a in 50% yield.



Scheme 1

Collie[22] prepared dihydropyridines (2) (Scheme 2), by reacting aminocrotonic ester (3) with aldehyde under acidic conditions. However, the reaction of methyl aminocrotonate with 1a did not give the desired compound 2a in good yield.

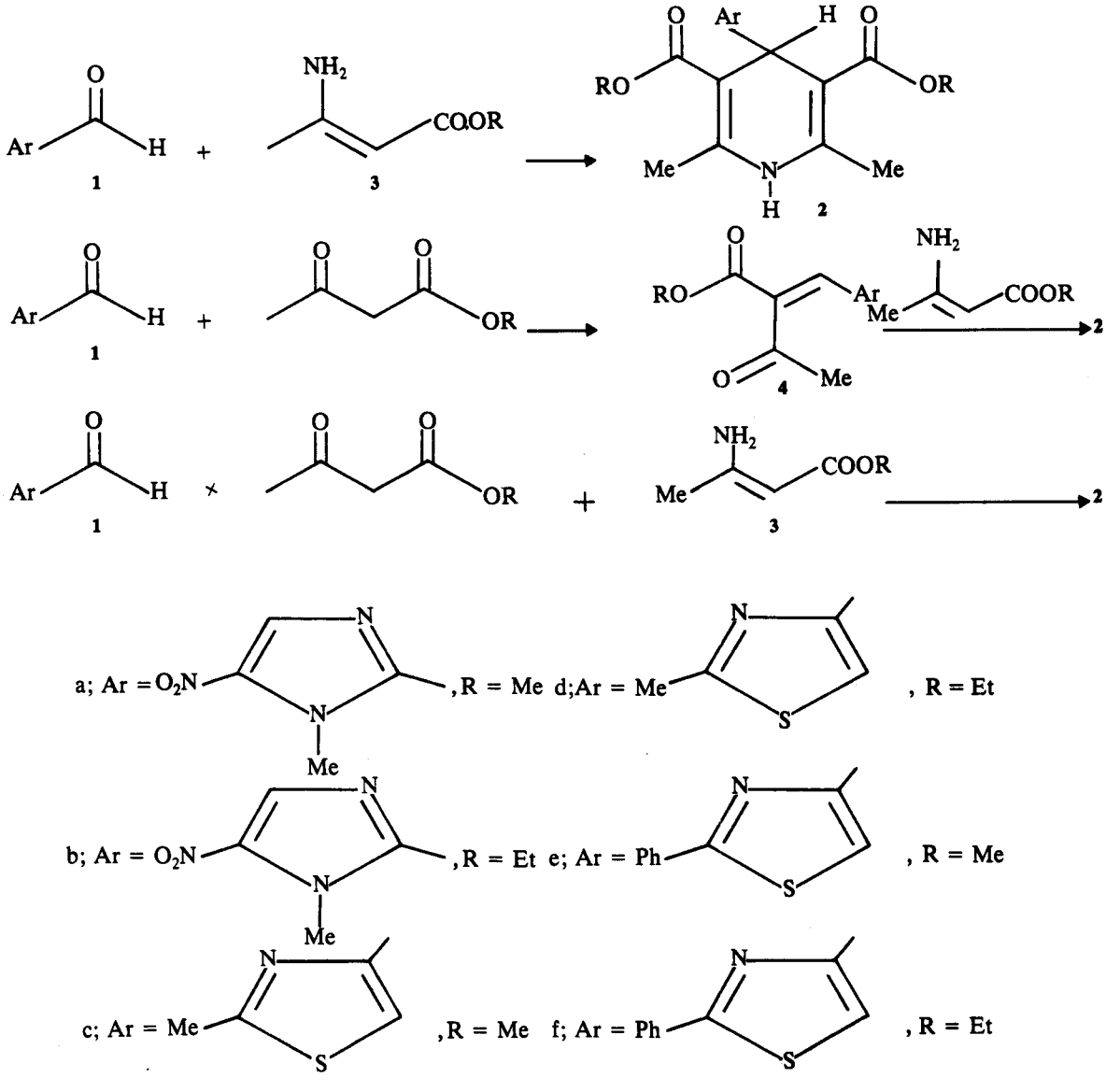
In a more recent method Meyer *et.al* [23] prepared dihydropyridine by the action of aryl aldehyde on alkyl acetoacetate which gave aralkylidenacetoacetic ester (4). The ester (4) resulting from this reaction was reacted with aminocrotonic ester (3) to give the desired compound 2. The reaction of compound 1a with methyl acetoacetate gave compound 4a in low yield [24]. Therefore this procedure for the preparation of compound 2a did not seem to be feasible.

Finally, the most recent synthetic route for dihydropyridine 2 was reported by Dagnino *et al.* [25]. The reaction route involved condensation of alkyl acetoacetate, alkyl aminocrotonate and arylaldehyde to furnish the desired compound in good yield. According to the latter method we could prepare compounds 2b-2f in 50-60% yields.

The primilary pharmacological evaluation of compound 2a showed that the latter has interesting calcium antagonistic activity. The detailed pharmacological activities of all compounds (2a-2f) are under investigation and will be published elsewhere.

Experimental Section

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. The IR spectra were obtained using a Parkin-Elmer Model 267 spectrograph



Scheme 2

(potassium bromide disks). The NMR spectra were recorded on a Varian T-60 spectrometer and chemical shifts (δ) are in ppm relative to internal tetramethylsilane. Mass spectra were run on a Varian Model MAT MS – 311 spectrometer at 70 ev.

Cis and *trans* Methyl ß-(1-Methyl-5 nitro-2-omidazolyl) methylideneacetoacetate (4a).

To a strirring solution of 2-formyl-1-methyl-5-nitroimidazole (155 mg, 1 mmol), methyl acetoacetate (116 mg, 1 mmol) at – 5°C 3 drops of pyridine was added. The solution was let to stand at – 5°C for 4 days and then at r.t. for 5 days. The precipitate was filtered and crystallized from ethyl acetate to give 51 mg (20%) of 4a, mp 143-155°C; IR: 3120 (H – C_4 imidazole), 1742 (C=O ester), 1675 (C=O ketone), 1370 and 1520 cm^{-1} (NO_2); NMR (DMSO-d_6): 7.60 (s, 1H, H_4 imidazole), 6.93 (s, 1H, CH=), 3.86 (s, 3H, NCH_3), 3.70 and 3.64 (2s, 3H, OCH_3), 2.40 and 2.63 (2S, 3H, $COCH_3$); ms: m/e (%) 253 (M^+, 98), 239 (100), 222 (94), 211 (95), 194 (47), 192 (63), 180 (95), 167 (54), 155 (52), 153 (96), 134 (58), 124 (42), 101 (42), 80 (47), 53 (79), 43 (96) and 42 (96).

Anal.Calcd. for $C_{10}H_{11}N_3O_5$: C,47.43; H, 4.35; N, 16.60.

Found: C, 47.61; H, 4.42; N, 16.42.

3,5-Dicarbomethoxy-2,6-dimethyl-4-(1-methyl-5-nitro-2-imidazolyl)-1,4-dihydropyridine (2a).

To a stirring solution of 1a (1.55 g, 0.01 mol), methyl acetoacetate (23 mol) in methanol (6 ml) conc. ammonia (1.1 ml) was added. The solution was refluxed for 5 hrs. After cooling the precipitate was filtered and recrystallized from methanol to give 1.4 g (40%) of 2a; mp>300°C; IR: 1710 (C=O ester), 1675 (C=C), 1370 and 1530 cm^{-1} (NO_2); NMR (DMSO-d_6): 8.16 (s, 1H, H_4 imidazole), 5.23 (s, 1H, H_4), 3.69 (s, 6H, OCH_3), 3.60 (s, 3H, NCH_3) and 2.4 (s, 6H, CH_3); ms: m/e (%) 350 (M^+, 68), 335 (11), 320 (10), 291 (57), 259 (84), 224 (100), 213 (14), 192 (21), 165 (11), 149 (11), 132 (10), 106 (10), 77 (11), 59 (10) and 42 (18).

Anal. Calcd. for $C_{15}H_{18}N_4O_6$: C, 51.43; H, 5.14; N, 16.00.

Found: C, 51.35; H, 5.02; N, 16.14.

3,5-Dicarbomethoxy-2,6-dimethyl-4-(1-methyl-5-nitro-2-imidazolyl)-1,4-dihydropyridine (2b).

To a stirring solution of 1a (1.55 g, 0.01 mol) ethyl acetoacetate (1.3g, 0.01 mol) in ethanol (10 ml) ethyl 3-aminocrotonate (1.29 g, 0.01 mol) was added. The solution was refluxed for 24 hrs. Afer cooling the precipitate was filtered and crystallized from ethyl acetate to give 1.89 g (50%) of 2b; mp 253 – 255°C; NMR (DMSO-d_6): 7.84 (s, 1H, H_4 imidazole), 4.93 (s, 1H, H_4), 3.96 (t, 4H, OCH_2), 3.48 (s, 3H, N – CH_3), 2.18 (s, 6H, CH_3) and 1.08 (s, 6H, CH_3); ms: m/e (%) 378 (M^+, 100), 363 (17), 333 (43), 317 (10) 306 (99), 289 (10), 259 (100), 252 (97), 224 (24), 213 (26), 206 (27), 196 (68), 177 (18), 150 (24), 106 (19) and 42 (15).

Anal. Calcd. for $C_{17}H_{22}N_4O_6$: C, 53. 97; H, 5.82; N, 14.81. Found: C, 53.85; H, 5.93; N, 14.72

3,5-Dicarbomethoxy-2,6-dimethyl-4-(2-methyl-4-thiazolyl)-1,4-dihydropyridine (2c).

Starting from 2-methyl-4-formylthiazole (1c) [26], methyl acetoacetate and methyl 3-aminocrotonate compound 2c was prepared similar to 2b in 52% yield; mp 253 – 255°C; NMR (CF_3COOH): 6. 95 (s, 1H, H_5 thiazole); 5.0 (s, 1H, H_4), 3.50 (s, 6H, OCH_3), 2.63 (s, 3H, CH_3) and 2.03 (s, 6H, CH_3); ms:m/e (%): 322 (M^+, 95), 307 (19), 291 (40), 290 (28), 263 (96), 247 (79), 224 (107), 203 (14), 40 (37), 162 (21), 149 (26), 134 (15), 121 (14), 106 (11), 77 (11), 59 (15), 57 (14) and 42 (14).
Anal. Calcd. for $C_{15}H_{18}N_2O_4S$: C, 55.90; H, 5.59; N, 8.70. Found: C, 55.86; H, 5.74;N, 8.50

3, 5-Dicarbomethoxy-2, 6-dimethyl-4-(2-methyl-4-thiazolyl)-1,4-dihydropyridine (2d)

This compound was prepared from 1c, ethyl acetoacetate and ethyl 3-aminocrotonate in 55% yield; mp 206 – 208°C; IR: 1695(C=O ester), 1670 cm^{-1} (C=C); NMR (DMSO-d_6): 6.60 (s, 1H, H_5 thiazole), 5.00 (s, 1H, H_4), 3.93 (q, 4H, OCH_2), 2.42 (s, 3H, CH_3) and 2.10 (s, 6H, CH_3); ms: m/e (%) 350 (M^+, 97), 335 (48), 306 (94), 305 (93), 277 (98), 259 (26), 252 (100)), 250 (63), 248 (30), 233 (55), 231 (93), 224 (91), 205 (55), 196 (92), 190 (14), 179 (23), 163 (31), 150 (30), 138 (10), 106 (10) and 42 (14).
Anal. Calcd. for $C_{17}H_{22}N_2O_4S$: C, 58.29; H, 6.29; N, 8.0. Found: C, 58. 42; H, 6.12;N, 8.15.

3,5-Dicarbomethoxy-2,6-dimethyl-4-(2-phenyl-4-thiazolyl)-1-4-dihydropyridine (2e).

This compound was prepared from 2-phenyl-4-formylthiazole 1e, methyl acetoacetate and methyl 3-aminocrotonate similar to 2c in 58% yield, mp 177-179°C; IR: 1700 (C=O ester), 1650 cm^{-1} (C=C); NMR (DMSO-d_6): 7.86 (m, 2H, aromatic), 7.40 (m, 3H, aromatic), 6.88 (s, 1H, H_5 thiazole), 5. 33 (s, 1H, H_4), 3.73 (s, 6H, OCH_3) and 2.33 (s, 3H, CH_3); ms: m/e (%) 384 (M^+, 38), 325 (40), 293 (20), 224 (100), 192 (40), 162 (31), 149 (28), 134 (15), 121 (36), 104 (14), 77 (20), 59 (10) and 57 (10).
Anal. Calcd. for $C_{20}H_{20}N_2O_4S$: C, 62. 50; H, 5.21; N, 7.29. Found: C, 62. 38; H, 5.40; N, 7. 34.

3,5-Dicarbomethoxy-2,6-dimethyl-4-(2-phenyl-4-thiazolyl)-1, 4-dihydropyridine (2f).

This compound was prepared from 1e, ethyl acetoacetate and ethyl 3-aminocrotonate similar to 2e in 58% yield, mp 253-257°C, IR: 1700 (C=O ester), 1650 (C=C); NMR (DMSO-d_6): 7.90 (m, 2H, aromatic), 7.50 (m, 3H, aromatic), 7.05 (s, 1H, H_5 thiazole), 5. 22 (s, 1H, H_4), 4.08 (q, 4H, OCH_2), 2.21 (s, 6H, CH_3), and 2.1 (t, 6H, CH_3); ms:m/e (%) 412 (M^+, 99), 397 (22), 367 (45), 339 (98), 311 (17), 293 (50), 252 (100), 224 (25), 196 (56), 162 (11), 150 (10), 121 (12), and 43 (11).
Anal. Calcd. for $C_{22}H_{24}N_2O_4S$: C, 64.08; H, 5.83; N, 6.80.

Found: C, 64. 22; H, 5.67; N, 6.68

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