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Synthesis and Characterization of Some New 1,4-Dihydropyridine Derivatives Containing Dichlorothiazolyl Substituents

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4-Substituted heterocycles or aryl dihydropyridines (DHP) with various C_3, C_5 diesters have calcium channel antagonist activity. In this paper a group of dialkyl, dicycloalkyl and diaryl ester analogues of nifedipine, in which the *ortho* nitro phenyl group at position 4 is replaced by 2,4-dichloro-5-thiazolyl substituent is presented. The Hantzsch condensation of alkyl acetoacetate (**3**) and ammonium acetate with 2,4-dichloro-1,3-thiazole-5-carboxaldehyde (**2**) offered symmetrical dialkyl 1,4-dihydro-2,6-dimethyl-4-(2,4-dichloro-1,3-thiazolyl)-3,5-pyridinedicarboxylates. Whereas condensation of **2** with **3** and **5** gave the asymmetrical dialkyl esters.

Key Words: Dihydropyridines, Dichlorothiazoles,Thiazole synthesis, Nifedipine analogues.

INTRODUCTION

4-Substituted Hantzsch dihydropyridines (DHP) are analogues of NADH coenzymes and an important class of drugs[1], *e.g.*, amilodipine besylate, nifedepine and related dihydropyridines are Ca^{2+} channel blockers (antagonist) and rapidly emerging as one of the most important classes of drugs for the treatment of cardiovascular diseases including hypertension[2,3].

In the human body, it has been observed that these compounds undergo oxidation to form pyridine derivatives. These oxidized compounds are largely devoid of the pharmacological activity of the parent compounds[4]. Sadegi[5,6] illustrated that dihydropyridines having aromatic ring in 4-position, in the presence of oxidizing reagents have been oxidized to related pyridines. Thus this observation suggests that these compounds should be prepared in darkness and in the absence of oxidizing material or

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media. Several papers illustrated that C-4 heterocycles substituents of dihydropyridines were potent antagonists[7-9]. The esters structure in 3,5-positions affect the type and amount of pharmacological activity. Dihydropyridines having imidazole and its derivatives in 4-position are very active compounds as calcium channels antagonist[10-12].

In this report, synthesis of a new group of 1,4-dihydropyridine such as dialkyl, dicycloalkyl and diaryl-1,4-dihydro-2,6-dimethyl-4-(2,4-dichloro-1,3-thiazol-5-yl)-3,5-pyridinedicarboxylates, is described. For selection of this heterocycle substituent in 4-position, the following reasons were considered.

1) Bulky substituent in the heterocyclic grouping 5 position was tolerated by receptor[9,10]. **2**) Substitution of chlorine instead of NO_2 in the 4-aryl ring produced active compounds[13]. **3**) With considering the conformational aspects of two rotamers (sp, ap), of the 2,4 dichlorothiazol (Fig. 1) and pharmacologically activity of two forms[2]. **4**) Some heterocycle rings were effective as 4-aryl in dihydropyridine structure[9,10].

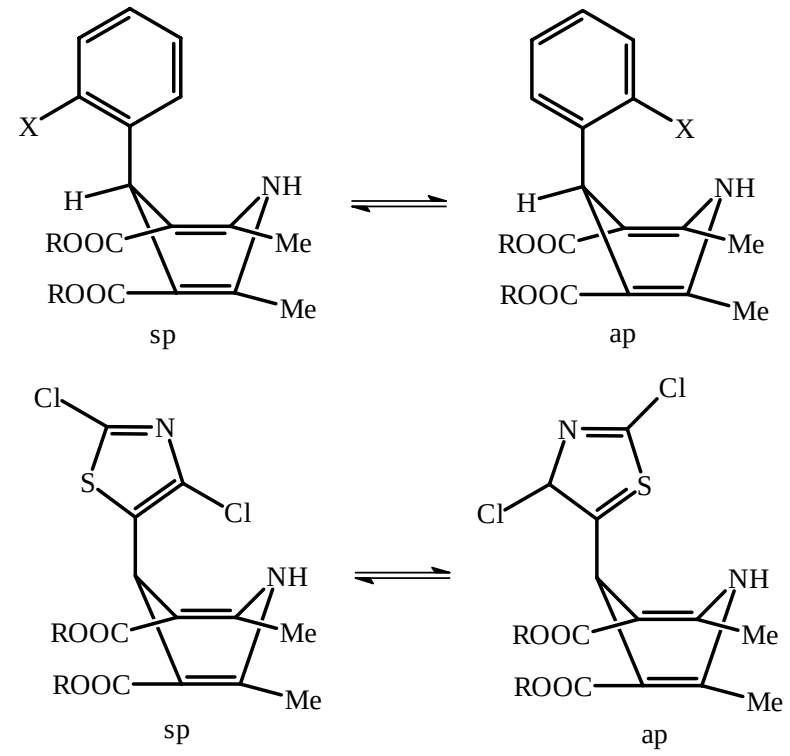


Fig. 1. Conformation of two derivatives of 1,4-dihydropyridine:
A from (7) and B, conformation of one of this study

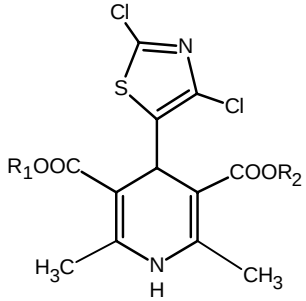
EXPERIMENTAL

Melting points were determined using a Thomas-Hoover capillary apparatus and were uncorrected. ^{1}H NMR spectra were recorded on a Bruker FT-80 spectrometer (Bruker, Rheinstetten, Germany). TMS was used as an internal standard. Infrared spectra were acquired on a Nicolet 550-FT spectrometer (Medison, WI, USA). Mass spectra were measured with a Finigan TSQ-70 spectrometer (Finnigan Mat, Bremer, Germany) at 70 eV. Elemental analyses were carried out with a Perkin-Elmer model 240-C apparatus (Perkin-Elmer, Norwalk, CT, USA). The result of the elemental analyses (C, H, N,) were within ± 0.4 % of the calculated amounts. Methyl and ethyl 3-aminocrotonate were purchased from Sigma-Aldrich Chemie GmbH (Deisenhofen, Germany). Some of the alkylacetoacetates (3-oxobutanoic acid esters) were prepared according to the literature procedure.

Synthesis

Symmetrical **4a-e** and asymmetrical diesters **6a-c** (Table-1) analogues were synthesized according to Fig. 2. The symmetrical analogues 4a-e were prepared by classical Hantzsch condensation[14] in which compound **2** was reacted with 3-oxobutanoic acid ester (**3**) (alkylacetoacetate) and ammonium acetate.

TABLE-1
PHYSICAL AND YIELD DATA FOR SYNTHESIZED COMPOUNDS **4a-e** AND **6a-c**



No.	R_1	R_2	m.f.	m.w.	m.p. (ºC)	Yield (%)
4a	$CH(CH_3)_2$	$CH(CH_3)_2$	$C_{18}H_{22}N_2O_4SCl_2$	433	163-164	57
4b	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	$C_{18}H_{22}N_2O_4SCl_2$	433	Oil	45
4c	$CH(CH_3)_2CH_2$	$CH(CH_3)_2CH_2$	$C_{20}H_{26}N_2O_4SCl_2$	461	122-123	55
4d	$CH_3C_6H_{11}$	$CH_3C_6H_{11}$	$C_{26}H_{36}N_2O_4SCl_2$	543	114-115	50
4e	$CH_2CH_2C_6H_{11}$	$CH_2CH_2C_6H_{11}$	$C_{28}H_{40}N_2O_4SCl_2$	571	Oil	53
6a	CH_3	$CH_2C_6H_5$	$C_{20}H_{18}N_2O_4SCl_2$	453	151-152	32
6b	CH_3	$CH_2C_6H_{11}$	$C_{20}H_{24}N_2O_4SCl_2$	459	97-99	40
6c	CH_3	$CH_2CH_2C_6H_{11}$	$C_{21}H_{26}N_2O_4SCl_2$	473	Oil	28

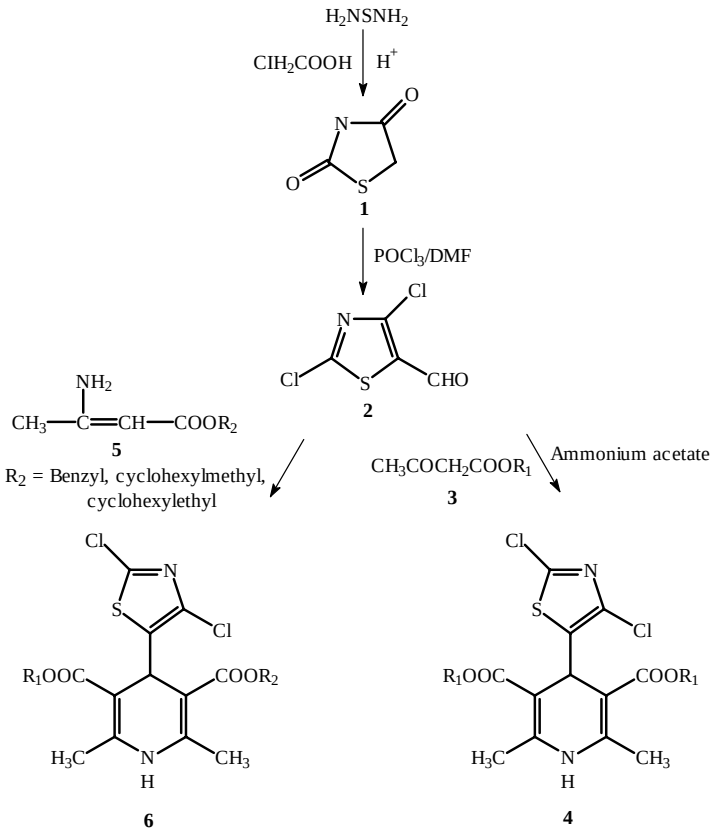


Fig. 2. Synthesis of 1,4-dihydropyridines having symmetrical and asymmetrical C_3,C_5 diesters

The asymmetrical diesters **6a-c** were synthesized according to a modified procedure reported by Meyer *et al.*[15] in which compound **2** was reacted with alkyl acetoacetate (**3**) and alkyl 3-aminocorotonate (**5**). Since these compounds undergo oxidization[5,6], therefore synthesis, collection and purification of the product should be carried out in the absence of oxidizing reagent and in darkness condition. 2,4-Dichloro(1,3-thiazole)-5-carboxaldehyde **2** was prepared in two steps, first chloroacetic acid and thiourea was refluxed for desired time to give 2,4-(1,3-thiazolidine)dione (**1**)[16]. Reaction of **1** with $POCl_3$ and DMF gave the desired aldehyde **2**[17].

3-Oxobutanoic acid esters **3** were synthesized by using 2,3,6-trimethyl-4-H-1,5-dioxine-4-one was used as starting material[18,19]. 3-Ammoniumcrotonates (**5**) were prepared by reaction of 3-oxobutanoic acid ester (**3**) and ammonium acetate[20].

2,4-(1,3-Thiazolidine)dione (1): To stirring solution of thiourea (10.133 g, 0.133 mol) in 100 mL water was added chloroacetic acid (12.613 g, 0.133 mol) in presence of concentrated HCl and was refluxed for 7 h.

The precipitate was collected and crystallized from water to give 13 g (83 %) of **1**, m.p. (123-125)°C ; IR (KBr, cm^{-1}): 1672 ν(CO); ^{1}H NMR (DMSO-d_6, 80 MHz), δ: 1.59 (s, 2H, CH_2), 4.03 (s, 1H, NH); Mass: m/z (%) 117 (M^+, 85), 89 (50), 74 (65), 46 (100) Anal. Calcd. for $C_3H_3NO_2S$: C, 30.76; H, 2.58; N, 11.96, Found: C, 30.70; H, 2.63; N, 12.05.

2,4-Dichloro-5-(1,3-thizole)carboxaldehyde (2): A mixture of compound 1 (10 g, 0.0584 mol) and $POCl_3$ (78.6g, 0.51 mol) in 6.8 mL DMF was refluxed for 6 h. Cooled to room temperature. The product was purified on the column chromatography and was crystallized in methanol to give 8.7 g (56 %) of **2**, m.p. (45-46)°C; IR (KBr, cm^{-1}) : 1690 (CO); ^{1}H NMR ($CDCl_3$, 80 MHz), δ: 9.96 (s, 1H, CHO) ; Mass: m/z (%) 185 (M^+, 80), 182 (100), 154 (37), 152 (43), 91 (53), 79 (32), 57 (30); Anal. Calcd. for $C_4HNOSCl_2$: C, 26.39; H, 0.55; N, 7.69; Found: C, 26.43; H, 0.54; N, 7.72.

Di-isopropyl 1,4-dihydro-2,6-dimethyl-4-(2,4-dichloro-1,3-thiazole-5-yl)-3,5-pyridinedicarboxylate (4a): A Solution of compound **2** (500 mg, 2.7 mmol), ammonium acetate (211.7 mg, 2.75 mmol) and isopropyl 3-oxobutanoate acid ester **3** (0.791 mg, 5.51 mmol) in 30 mL methanol was refluxed for 12 h. The solvent was removed under reduced pressure and residue was crystallized from methanol-water to give 667 mg (57 %) of **4a**, m.p. (163-164)°C; IR (KBr, cm^{-1}): 3333, 3235 ν(NH), 1696 ν(CO); ^{1}H NMR ($CDCl_3$, 80 MHz): δ, 1.21-1.29 (2d, J = 1.2 HZ, 12H, $COOCH(CH_3)_2$), 2.33 (s, 6H, C_2, C_6-CH_3), 5.05 (hepted, 2H, $COOCH(CH_3)_2$), 5.33 (s, 1H, H_4-DHP), 5.84(bs, 1H, NH-DHP); Mass: m/z (%) 432 (M^+, 25), 397 (24), 303 (51), 267 (32), 196 (100), 150 (20), 106 (7), 69 (13); Anal. Calcd. for $C_{18}H_{22}N_2O_4SCl_2$: C, 49.89; H, 5.12; N, 6.46; Found: C, 49.52; H, 5.15; N, 6.39.

Compounds **4b-e** (Table-1) were synthesized similar to **4a**.

Methyl benzyl 1,4-dihydro-2,6-dimethyl-4-(2,4-dichlorothiazole-5-yl)-3,5-pyridinedicarboxylate (6a): A solution of compound 2 (500 mg, 2.7 mmol), methyl 3-oxobutanoate **3** (320 mg, 2.77 mmol) and benzyl 3-aminocrotonate **4** (569 mg, 2.77 mmol) in 30 mL methanol was refluxed for 50 h. The reaction mixture was purified with a silica gel column. The desired compound was crystallized from methanol-water to give 380 mg (32 %) of **6a** m.p. (151-152)°C; IR (KBr, cm^{-1}): 3324, 3240 ν(NH), 1696 ν(CO); ^{1}H NMR ($CDCl_3$, 80 MHz): δ, 2.32 (s, 6H, C_2, C_6-CH_3), 3.66 (s, 3H, $COOCH_3$), 5.15 (s, 1H, H_4-DHP), 5.15 (s, 2H, $COOCH_2Ph$) 5.90 (bs, 1H, NH-DHP), 7.31 (s, 5H, phenyl); Mass: m/z (%) 452 (M^+, 32), 393 (12), 361 (32), 300 (97), 267 (32), 165 (70), 150 (37), 91 (100), 67 (45); Anal. Calcd. for $C_{20}H_{18}N_2O_4SCl_2$: C, 52.99; H, 4.00; N, 6.18; Found: C, 52.72; H, 4.02; N, 6.16.

Compounds **6b-c** (Table-1) were synthesized similarly.

RESULTS AND DISCUSSION

The yield was increased with increasing the reflux time[16] from 4 to 7 h in preparation of compound **1** which was easily purified by crystallization.

For purification of synthesized aldehyde **2**, column chromatography was used with a mixture of petroleum-ether-chloroform (85:15) as mobile phase, which easily yielded to purified compound, comparing to the reported procedure (distillation on high vacuum and at the high temperature)[17].

IR, ^{1}H NMR and mass spectra characterized all of the synthesized compounds. The infrared spectrum of compound **1** shows two bands at 1680 and 1747 cm^{-1}. It seems that 1680 cm^{-1} related to 2-CO and 1747 cm^{-1} to 4-CO groups. Melting points of compounds **4a-g** and **6a-c** were 50-70ºC low in comparison with the products of reports[7,10]. Probably, this could be related to crystal structure and sulfur atom orbitals of compounds.

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