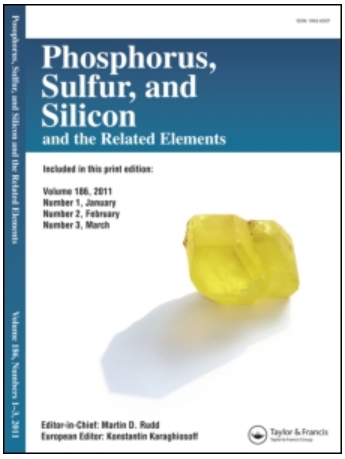

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Synthesis of New 1,4-Dihydropyridine Derivatives Containing Thiazolyl Substituents

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A series of 4-[2-methyl (or aryl) thiazole-4-yl]-2,6-dimethyl-3,5-diacetyl (or dibenzoyl) 1,4-dihydropyridines were synthesized using a modified Hantzsch reaction involving the condensation of the corresponding aldehyde with acetyl acetone or benzoyl acetone. The preparation of the corresponding aldehydes (2-methylthiazole-4-carboxaldehyde and some 2-arylthiazole-4-carboxaldehydes) was achieved by a simplified protocol of the published synthesis.

Keywords 1,4-Dihydropyridines; β-diketones; thiazoles

INTRODUCTION

Development of multidrug-resistance (MDR) in tumor cells remains one of the major clinical obstacles during antitumor chemotherapy against many malignancies.[1] The introduction of potent MDR reversal agents such as NIK-250, N276-9, nicardipine (Figure 1) and other

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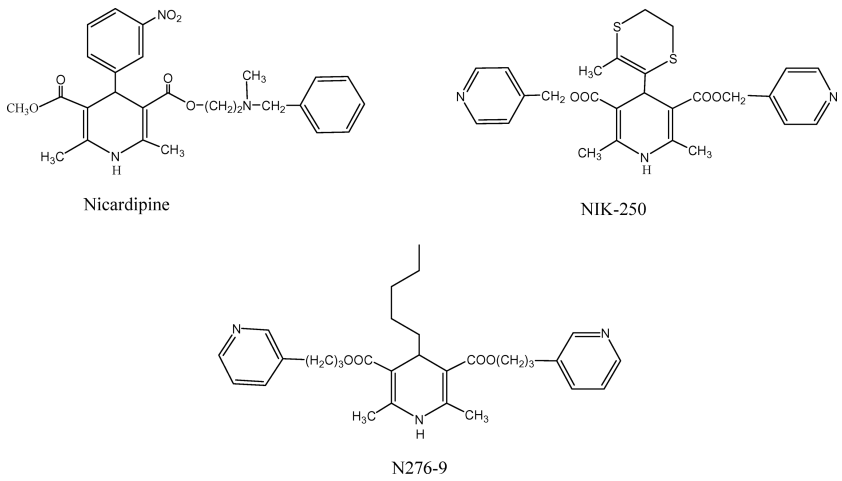


FIGURE 1 Structures of nicardipine, NIK-250, and N276-9.

1,4-dihydropyridines (DHP) stimulated the synthesis of novel dihydropyridine (DHP) derivatives.[2]

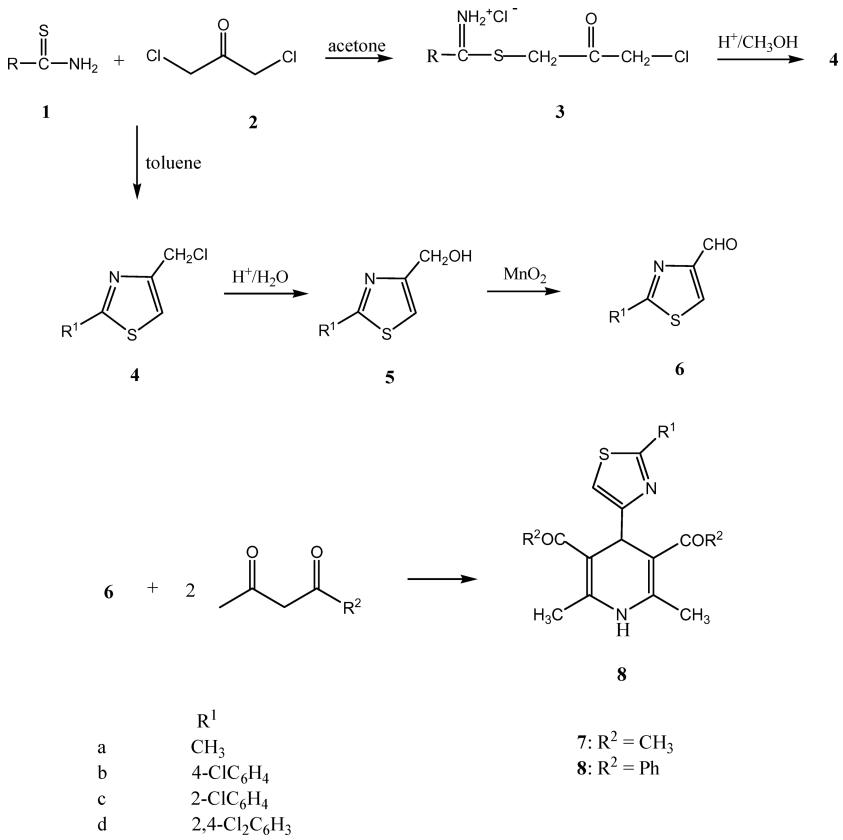
1,4-Dihydropyridines were classically prepared by the Hantzsch reaction[3] (Scheme 1), in which the mixture of an aldehyde, a β-dicarbonyl compound, and ammonia (or ammonium acetate) was refluxed in an alcohol for 12 to 36 h.

A one-pot condensation of an aldehyde with alkyl acetoacetate and ammonia either in acetic acid or refluxing in an alcohol was later developed.[4] The synthesis of dihydropyridines under solvent free conditions also has been recently reported.[5] In all of the reported methods for the preparation of DHPs, an aldehyde was used as source of the substituents in the 4-position.

As a part of our ongoing program to design new DHPs,[6–12] we report the synthesis of 1,4-dihydropyridines having a substituted thiazolyl moiety in the 4-position from the corresponding substituted thiazolyl aldehydes. The latter were prepared by a simplified protocol as shown in Scheme 1.

RESULTS AND DISCUSSION

It has been reported[13,14] that the reaction of substituted thioamides **1** and 1,3-dichloroacetone in acetone provides the intermediates **3**. The latter under acidic conditions gives the 2-substituted 4-chloromethylthiazoles **4**. We found that refluxing compounds **1** and **2**



SCHEME 1

in toluene gives compounds **4** in one step and in good yields. This synthesis could serve as a valuable method to prepare other 2-substituted thiazoles. The hydrolysis of compounds **4** in 50% aqueous sulfuric acid gave the 2-substituted 4-hydroxymethylthiazoles **5**. Oxidation of the latter with activated manganese(IV) oxide gave the corresponding 2-substituted 4-formylthiazoles **6** in excellent yields.

Several syntheses of 1,4-dihydropyridines have been reported. Most of the symmetrical 1,4-dihydropyridine 3,5-diesters were prepared by the well known Hantzsch reaction.[3] For asymmetrical analogues, a modified method was developed by Meyer et al.[15] in which first an aldehyde was condensed with a β-dicarbonyl compound, and then the ring was closed by reaction with alkyl 3-aminocrotonate. Recently, the preparation of 1,4-dihydropyridines under solvent free conditions

was reported.[5] In this case, alkyl acetoacetate and a series of aldehydes were converted to 1,4-dihydropyridines in the presence of ammonium acetate under solvent-free conditions at 80°C. Good to excellent yields were obtained by this method in the case of some aliphatic, aromatic, and heteroaromatic aldehydes. However, condensation of the aldehyde **6** with acetyl and benzoyl acetone under the same conditions gave only low yields of the corresponding dihydropyridines. The condensation reaction between aldehydes and 1,3-cyclohexanedione in the solid state by grinding at room temperature has also been reported.[16] In our case, however, this procedure was also unsuccessful. We could prepare the compounds **7** and **8** through the modified method of Hantzsch reaction. Thus, the reaction of aldehydes **6** with acetyl acetone or benzyl acetone and ammonium acetate in ethanol in darkness and under nitrogen afforded the dihydropyridines **7** and **8** (Table I).

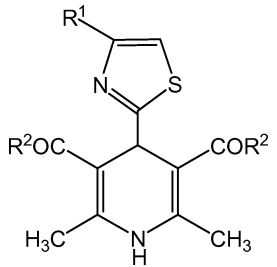
EXPERIMENTAL

Melting points were determined with a Kofler hot stage apparatus and are uncorrected. ^{1}H NMR spectra were obtained with a 400 Varian Unity Plus spectrometer. TMS was used as the internal standard. The IR spectra were recorded with a Nicolet-550 FT-IR spectrophotometer. 4-Chlorothiobenzamide and 2-chlorothiobenzamide were prepared from the corresponding nitrile derivatives as reported.[17] Column chromatography was carried out using silica gel (230–400 mesh). The compounds **5a–d** and **6a–d** were prepared as reported.[13]

Preparation of 4-Chloromethyl-2-methyl (or Aryl) Thiazoles 4: General Procedure

To a magnetically stirred solution of 1,3-dichloroacetone (0.1 mol) in 100 mL of toluene, thioacetamide or the respective 4-substituted thiobenzamide (0.1 mol) was added, and the reaction mixture was refluxed at 110°C for 2–3 h. The course of the reaction was monitored by TLC. After completion of the reaction, the solvent was removed under reduced pressure. To the residue, 200 mL of water was added, and the precipitate formed was filtered. The crude product was crystallized from methanol (10 mL). In the case of thioacetamide, after the addition of water, the mixture was extracted with dichloromethane (2 × 50 mL). The organic phase was dried (sodium sulfate), and the solvent was removed under reduced pressure. Purification was achieved by distillation at 65°C (5 mm Hg) to give pure **4a**.

TABLE I Data for Compounds 7a–d and 8a–d



						Calcd. (%)			Found (%)		
	R^1	R^2	Yield %	mp (°C)	Formula	C	H	N	C	H	N
7a	Me	Me	32	228–230	$C_{15}H_{18}N_2O_2S$	62.04	6.24	9.65	62.30	6.19	9.79
7b	4-ClC_6H_4	Me	36	218–220	$C_{20}H_{19}ClN_2O_2S$	62.09	4.95	7.24	61.91	5.30	7.38
7c	2-ClC_6H_4	Me	33	209–212	$C_{20}H_{19}ClN_2O_2S$	62.09	4.95	7.24	62.11	5.28	7.09
7d	2,4-$Cl_2C_6H_3$	Me	30	202–204	$C_{20}H_{18}Cl_2N_2O_2S$	57.01	4.31	6.64	57.29	4.42	6.50
8a	Me	Ph	33	209–211	$C_{25}H_{22}N_2O_2S$	72.43	5.35	6.75	72.82	5.19	6.89
8b	4-ClC_6H_4	Ph	42	245–247	$C_{30}H_{23}ClN_2O_2S$	70.51	4.53	5.48	70.81	4.21	5.19
8c	2-ClC_6H_4	Ph	41	225–228	$C_{30}H_{23}ClN_2O_2S$	70.51	4.53	5.48	70.39	4.67	5.56
8d	2,4-$Cl_2C_6H_3$	Ph	44	216–218	$C_{30}H_{22}ClN_2O_2S$	66.06	4.65	5.13	66.29	4.93	5.01

4-Chloromethyl-2-methylthiazole (4a)

Yield 70%, ^{1}H NMR ($CDCl_3$): $\delta = 7.13$ (s, 1H, 5-H), 4.60 (s, 2H, CH_2Cl), 2.66 (s, 3H, CH_3). Anal. Calcd. for C_5H_6ClNS (147.63): C 40.68, H 4.10, N 9.49%; Found: C 40.36, H 4.44, N 9.29%.

4-Chloromethyl-2-(4-chlorophenyl)thiazole (4b)

Yield 75%, mp 79–80°C, ^{1}H NMR ($CDCl_3$): $\delta = 4.80$ (s, 2H, CH_2), 7.23 (s, 1H, 5-H), 7.40 (d, $J = 8$ Hz, 2H, arom-H), 7. 68 (d, $J = 8$ Hz, 2H, arom-H). Anal. Calcd. for $C_{10}H_7Cl_2NS$ (244.14): C 49.20, H 2.89, N 5.74%; Found: C 49.44, H 2.59, N 5.91%.

2-Chlormethyl-2-(2-chlorophenyl)thiazole (4c)

Yield 68%, mp 61–63°C, ^{1}H NMR ($CDCl_3$): $\delta = 4.75$ (s, 2H, CH_2), 7.20 (s, 1H, 5-H), 7.37–7.80 (m, 4H, arom-H). Anal. Calcd. for $C_{10}H_7Cl_2NS$ (244.14): C 49.20, H 2.89, N 5.74%; Found: C 49.55, H 2.68, N 5.48%.

2-Chlormethyl-2-(2,4-dichlorophenyl)thiazole (4d)

Yield 76%, mp 69–71°C, ^{1}H NMR ($CDCl_3$): $\delta = 4.75$ (s, 2H, CH_2), 7.15–7.60 (m, 3H, arom-H), 8.20 (d, $J = 8.2$ Hz, 1H, arom-H). Anal. Calcd. for $C_{10}H_6Cl_3NS$ (278.59): C 43.11, H 2.17, N 5.03%; Found: C 43.29, H 2.34, N 5.34%.

Preparation of Diacetyl 1,4-Dihydropyridines 7 and Dibenzoyl 1,4-Dihydropyrines 8: General Procedure

To a solution of **6a–d** (2 mmol) and acetyl acetone or benzoyl acetone (4 mmol) in 20 mL of ethanol, ammonium acetate (2 g) was added. The mixture was refluxed in the dark and under nitrogen atmosphere overnight. After cooling, the solvent was removed under reduced pressure. The mixture was extracted with ethyl acetate (3 × 20 mL). The organic phase was dried (sodium sulfate), the solvent was removed in vacuo, and the crude product was purified by column chromatography using CH_2Cl_2:ethyl acetate (80:20) as eluent. Compounds **7** and **8** were recrystallized from methanol-water (Table I).

4-(2-Methylthiazole-4-yl)-2,6-dimethyl-3,5-diacetyl-1,4-dihydropyridine (7a)

IR (KBr, cm^{-1}): 1665, 3316. ^{1}H NMR ($CDCl_3$): $\delta = 2.30$ (s, 6H, 2,6-CH_3), 2.37 (s, 6H, $COCH_3$), 2.61 (s, 3H, CH_3-thiazole), 5.20 (s, 1H, 4-H), 6.37 (bs, 1H, NH), 6.57 (s, 1H, H-thiazole).

4-[2-(4-Chlorophenylthiazole)-4-yl]-2,6-dimethyl-3,5-diacetyl-1,4-dihydropyridine (7b)

IR (KBr, cm^{-1}): 1669 (CO). ^{1}H NMR ($CDCl_3$): $\delta = 2.33$ (s, 6H, 2,6-CH_3), 2.48 (s, 6H, $COCH_3$), 5.38 (s, 1H, 4-H), 6.90 (bs, 1H, NH), 7.22 (s,

1H, H-thiazole), 7.38 (d, $J = 8.1$ Hz, 2H, arom-H), 7.70 (d, $J = 8.1$ Hz, 2H, arom-H).

4-[2-(2-Chlorophenylthiazole)-4-yl]-2,6-dimethyl-3,5-diacethyl-1,4-dihydropyridine (7c)

IR (KBr, cm^{-1}): 1669 (CO). ^1H NMR ($CDCl_3$): $\delta = 2.34$ (s, 6H, 2,6-CH_3), 2.44 (s, 6H, $COCH_3$), 5.36 (s, 1H, 4-H), 6.40 (bs, 1H, NH), 7.05–7.35 (m, 5H, arom-H).

4-[2-(2,4-Dichlorophenylthiazole)-4-yl]-2,6-dimethyl-3,5-diacethyl-1,4-dihydropyridine (7d)

IR (KBr, cm^{-1}): 1675 (CO). ^1H NMR ($CDCl_3$): $\delta = 2.36$ (s, 6H, 2,6-CH_3), 2.47 (s, 6H, $COCH_3$), 5.36 (s, 1H, 4-H), 6.93 (bs, 1H, NH), 7.21 (s, 1H, H-thiazole), 7.32 (dd, $J = 8$ Hz, $J = 2$ Hz, 1H, arom-H), 7.48 (d, $J = 2$ Hz, 1H, arom-H), 8.14 (d, $J = 8$ Hz, 1H, arom-H).

4-(2-Methylthiazole-4-yl)-2,6-dimethyl-3,5-dibenzoyl-1,4-dihydropyridine (8a)

IR (KBr, cm^{-1}): 1665 (CO). ^1H NMR ($CDCl_3$): $\delta = 1.97$ (s, 6H, 2,6-CH_3), 2.53 (s, 3H, CH_3-thiazole), 5.35 (s, 1H, 4-H), 6.25 (bs, 1H, NH), 6.43 (s, 1H, H-thiazole), 7.29–7.70 (m, 10H, arom-H).

4-[2-(4-Chlorophenylthiazole)-4-yl]-2,6-dimethyl-3,5-dibenzoyl-1,4-dihydropyridine (8b)

IR (KBr, cm^{-1}): 1669 (CO). ^1H NMR ($CDCl_3$): $\delta = 2.30$ (s, 6H, 2,6-CH_3), 5.72 (s, 1H, 4-H), 6.05 (bs, 1H, NH), 6.75 (s, 1H, H-thiazole), 7.20–7.85 (m, 14H, arom-H).

4-[2-(2-Chlorophenylthiazole)-4-yl]-2,6-dimethyl-3,5-dibenzoyl-1,4-dihydropyridine (8c)

IR (KBr, cm^{-1}): 1670 (CO). ^1H NMR ($CDCl_3$): $\delta = 2.03$ (s, 6H, 2,6-CH_3), 5.43 (s, 1H, 4-H), 5.60 (bs, 1H, NH), 6.92 (s, 1H, H-thiazole), 7.20–7.90 (m, 14H, arom-H).

4-[2-(2,4-Dichlorophenylthiazole)-4-yl]-2,6-dimethyl-3,5-dibenzoyl-1,4-dihydropyridine (8d)

IR (KBr, cm^{-1}): 1674 (CO). ^1H NMR ($CDCl_3$): $\delta = 2.03$ (s, 6H, 2,6-CH_3), 5.35 (s, 1H, 4-H), 5.80 (bs, 1H, NH), 6.93 (s, 1H, H-thiazole), 7.15–7.98 (m, 13H, arom-H).

REFERENCES

[1] S. Hasegawa, T. Abe, S. Natio, S. Kotoh, J. Kumazawa, D. R. Hipfner, R. G. Delley, S. P. C. Cole, and M. B. Kuwano, *J. Cancer*., **71**, 907 (1995).
[2] S. Tasaka, H. Ohmri, N. Gomi, M. Iino, T. Machida, A. Kiue, S. Naito, and M. Kuwano, *Bioorg. Med. Chem. Lett*., **11**, 275 (2001).
[3] (a) A. Hantzsch, *Ann. Chem*., **215**, 1 (1882); (b) A. E. Sausins and G. Duburs, *Chem. Heterocycl. Comp.*, **28**, 363 (1992); (c) J. J. Vanden Eynde and A. Mayence, *Molecules*, **8**, 381 (2003); (d) H. Salehi, and Q. X. Guo, *Synthetic Comm.*, **34**, 4349 (2004).
[4] B. Loev and K. M. Snader, *J. Org. Chem*., **30**, 1914 (1965).
[5] M. A. Zolfigol and M. Safaiee, *Synlett*, **5**, 827 (2004).
[6] S. Ghodsi, E. Alipour, M. Amini, R. Miri, K. M. Tagi-Ganji, H. Mirkhani, and A. Shafiee, *Phosphorus, Sulfur, and Silicon*, **181**, 2435 (2006).
[7] A. Davood, N. Mansouri, A. R. Dehpour, H. Shafaroudi, E. Alipour, and A. Shafiee, *Arch. Pharm. Chem. Life Sci*., **339**, 299 (2006).
[8] L. Navidpour, H. Shafaroodi, R. Miri, A. R. Dehpour, and A. Shafiee, *Il Farmaco*, **59**, 261 (2004).
[9] L. Navidpour, R. Miri, and A. Shafiee, *Arzneim. Forsch*., **54**, 499 (2004).
[10] A. Shafiee, N. Rastkari, and M. Sharifzadeh, *Daru*, **12**, 81 (2004).
[11] A. Shafiee, N. Rastkari, and M. Jorjani, *Arzneim. Forsch*., **52**, 537 (2002).
[12] A. Shafiee, R. Rastkary, M. Jorjani, and B. Shafaghi, *Arch. Pharm. Pharm. Med. Chem.,* **2**, 69 (2002).
[13] A. Shafiee, A. Mazloumi, and V. I. Cohen, *J. Heterocycl. Chem*., **16**, 1563 (1979).
[14] E. H. Huntress and K. Pfister, *J. Am. Chem. Soc*., **65**, 1667 (1943).
[15] H. Meyer, F. Bossert, E. Wehinger, K. Stoepel, and W. Voter, *Arzneim. Forsch*., **31**, 407 (1981).
[16] J. Tong-Shou, Z. Jian-Shezhang, W. Ai-Qing, and L. Tong-Shuange, *Synthetic Comm*., **35**, 2339 (2005).
[17] J. Sokakimoto, E. Seydel, and P. Werm, *Arzneim. Forsch*., **12**, 127 (1962).