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### UNPRECEDENTED SYNTHESIS OF HANTZSCH 1,4-DIHYDROPYRIDINES UNDER BIGINELLI REACTION CONDITIONS<sup>\*</sup>

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## UNPRECEDENTED SYNTHESIS OF HANTZSCH 1,4-DIHYDROPYRIDINES UNDER BIGINELLI REACTION CONDITIONS\*

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### ABSTRACT

Hantzsch 1,4-dihydropyridines are synthesized in high yields by a one-pot cyclocondensation of aldehyde,  $\beta$ -ketoester, and urea on the surface of silica gel under microwave irradiation in solvent-free conditions.

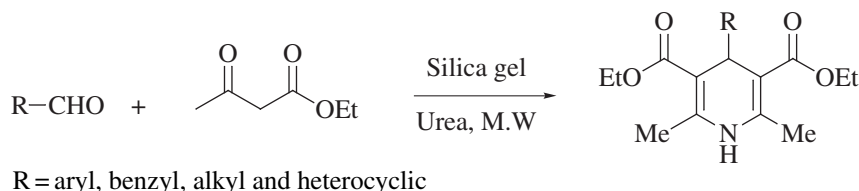
Hantzsch 1,4-DHPs are biologically active compounds that include various vasodilator, antihypertensive, bronchodilator, antiatherosclerotic, hepatoprotective, antitumor, antimutagenic, geroprotective, and antidiabetic agents (1–3). DHPs have found commercial utility as calcium channel blockers (4–6) such as Nifedipine, Nitrendipine, and Nimodipine. A number of DHP calcium antagonists have been introduced as potential drugs for the treatment of congestive heart failure (7,8). Among DHPs with other types of bioactivity, cerebrocrast (9) has been introduced as a neuroprotectant and cognition enhancer. In addition, a number of DHPs

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with platelet antiaggregatory activity have also been discovered (10). However, a number of methods have been reported for the synthesis of DHPs, which suffer from drawbacks like longer reaction times, low to moderate yields, and require highly acidic reaction conditions. Organic reactions on solid supports and those that are associated with microwaves, especially under solvent-free conditions, have attracted much attention. The advantage of these methods over conventional reactions is that they provide greater selectivity, enhanced reaction rates, cleaner reaction products, and operational simplicity, and are eco-friendly. Due to a wide range of biological significance of DHPs, we describe a new and rapid method for the synthesis of DHPs by the cyclocondensation of aldehyde,  $\beta$ -ketoester and urea mediated by silica gel (11,12) under microwaves in dry media (Sch. 1).



*Scheme 1.*

Generally, 1,4-dihydropyridines (13–18) were synthesized by Hantzsch method, which involves cyclocondensation of 1 mol of aldehyde, 2 mol of  $\beta$ -ketoester, and 1 mol of ammonia either in acetic acid at room temperature or refluxing in alcohol for a long time. Surprisingly, under the Biginelli reaction conditions comprising three-component condensation among aldehyde,  $\beta$ -ketoester, and urea, 1,4-dihydropyridines are formed rapidly in high yields on the surface of silica gel under microwave irradiation. However, when KSF clay was used as the catalyst instead of silica gel, pyrimidines were obtained in good yields under present reaction conditions (19).

Several substituted dihydropyridines such as aryl, alkyl, benzyl, and heterocyclic moieties at 4 position are synthesized by the condensation of 1 mol of aldehyde, 2 mol of ethyl acetoacetate, and 1 mol of urea when subjected to microwave irradiation in the presence of silica gel for 3–5 min.

All the reactions were carried out under solvent-free conditions in a open pyrex test tube and were rapid, clean, and high-yielding when compared to those obtained by conventional methods. The results are summarized in Table 1. The reaction procedure is very simple, it involves mixing the reactant on the surface of  $\text{SiO}_2$  and subjecting it to microwaves to afford exclusively good yields of dihydropyridines without the formation of pyrimidines.

In conclusion, we have described a rapid and high-yielding protocol for the synthesis of DHPs in the presence of silica gel under microwave irradiation.



**Table 1.** Microwave-Assisted Synthesis of Hantzsch 1,4-Dihydropyridines

Entry	R <sup>a</sup>	Microwave Irradiation <sup>b</sup>		Conventional Heating <sup>c</sup>		m.p. (°C)/b.p./tarr	
		Time (min)	Yield (%) <sup>d</sup>	Time (h)	Yield (%)	Found	Reported <sup>d</sup> (13–18)
a	Phenyl	3	90	12	50	158–159	156–157
b	$\alpha$ -Naphthyl	5	87	12	55	196–198	195–198
c	2-Thienyl	2	93	12	77	167–168	167–169
d	2-Furyl	2	90	12	47	163–165	164
e	4-ClC <sub>6</sub> H <sub>4</sub>	4	85	12	39	144–145	145–146
f	4-Me <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	4	88	12	47	200–202	203
g	2-MeOC <sub>6</sub> H <sub>4</sub>	3	89	12	15	142–143	138–143
h	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	5	78	12	50	128–129	129–130
i	Benzyl	4	75	12	61	116–118	115–117
j	Isopropyl	5	70	12	61	96–98	97–99
k	<i>n</i> -Hexyl	5	73	12	26	188–190/0.1 mm	189–190/0.1 mm
l	<i>n</i> -Decyl	6	80	–	–	Liquid	–
m	C <sub>6</sub> H <sub>4</sub> CH=CH	4	78	12	50	148–150	148–149
n	3-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	5	82	12	50	162–163	162–164

<sup>a</sup>All products were characterized by IR, <sup>1</sup>H NMR, mass spectra, and by comparison of physical characteristics with authentic samples.

<sup>b</sup>Pulsed irradiation (1 min with 20-s interval) operating at 2450 MHz.

<sup>c</sup>Refluxed in ethanol in the presence of concentrated NH<sub>4</sub>OH.

<sup>d</sup>Isolated yields after column chromatography are reported.

The new procedure is simple, inexpensive, solvent-free reaction condition and eco-friendly, making it a useful alternative to the existing methods.

## EXPERIMENTAL

Aldehyde (10 mmol), ethylacetoacetate (20 mmol), and urea (10 mmol) were thoroughly admixed with silica gel (5 g, Aldrich 200–300 mesh) in solid state using pestle and mortar. The resulting powder was transferred to a 25-mL Erlenmeyer flask and subjected to microwave irradiation (BPL, BMO-700T) for 2–5 min at 650 W. After complete conversion, as shown by TLC, the reaction mass was charged directly on a small silica gel column (60–120 mesh), and eluted with ethyl acetate–hexane (3:7) to afford pure product.

**Entry a.** <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  1.30 (t, 6H,  $J$  = 8.2 Hz), 2.55 (s, 6H), 4.10 (q, 4H,  $J$  = 8.2 Hz), 5.05 (s, 1H), 5.75 (br, s, 1H), 7.25–7.35 (m, 5H). CHN



analysis calcd. for  $C_{19}H_{23}NO_4$ : C, 69.28; H, 7.04; N, 4.25. Found C, 69.15; H, 6.95; N, 4.14.

**Entry b.**  $^1H$  NMR ( $CDCl_3$ ):  $\delta$  0.95 (t, 6H,  $J = 8.2$  Hz), 2.30 (s, 6H), 3.95 (q, 4H,  $J = 8.2$  Hz), 5.55 (br, s, 1H), 5.75 (s, 1H), 7.25–7.50 (m, 4H), 7.60 (d, 1H,  $J = 8.6$  Hz), 7.70 (d, 1H,  $J = 8.6$  Hz), 8.55 (d, 1H,  $J = 8.6$  Hz). CHN analysis calcd. for  $C_{23}H_{25}NO_4$ : C, 72.80; H, 6.64; N, 3.69. Found C, 72.41; H, 6.41; N, 3.55.

**Entry c.**  $^1H$  NMR ( $CDCl_3$ ):  $\delta$  1.25 (t, 6H,  $J = 8.2$  Hz), 2.30 (s, 6H), 2.35 (s, 6H), 4.25 (q, 4H,  $J = 8.2$  Hz), 5.25 (s, 1H), 5.75 (brs, 1H), 6.75–7.05 (m, 3H). CHN analysis calcd. for  $C_{17}H_{21}NO_4S$ : C, 60.88; H, 6.31; N, 4.18. Found C, 60.47; H, 6.23; N, 4.06.

**Entry d.**  $^1H$  NMR ( $CDCl_3$ ):  $\delta$  1.30 (t, 6H,  $J = 8.2$  Hz), 2.40 (s, 6H), 4.30 (q, 4H,  $J = 8.2$  Hz), 5.30 (s, 1H), 5.80 (brs, 1H), 6.80–7.05 (m, 3H). CHN analysis calcd. for  $C_{17}H_{21}NO_5$ : C, 63.94; H, 6.63; N, 4.39. Found C, 63.68; H, 6.42; N, 4.18.

**Entry e.**  $^1H$  NMR ( $CDCl_3$ ):  $\delta$  1.25 (t, 6H,  $J = 8.2$  Hz), 2.35 (s, 6H), 4.15 (q, 4H,  $J = 8.2$  Hz), 5.00 (s, 1H), 5.70 (brs, 1H), 7.15–7.25 (m, 4H). CHN analysis calcd. for  $C_{19}H_{22}ClNO_4$ : C, 62.72; H, 6.09; N, 3.85. Found C, 62.41; H, 5.93; N, 3.53.

**Entry f.**  $^1H$  NMR ( $CDCl_3$ ):  $\delta$  1.25 (t, 6H,  $J = 8.2$  Hz), 2.35 (s, 6H), 3.10 (s, 6H), 4.15 (q, 4H,  $J = 8.2$  Hz), 5.10 (s, 1H), 5.6 (brs, 1H), 7.15–7.75 (m, 4H). CHN analysis calcd. for  $C_{21}H_{28}N_2O_4$ : C, 67.72; H, 7.58; N, 7.52. Found C, 67.41; H, 7.51; N, 7.26.

**Entry g.**  $^1H$  NMR ( $CDCl_3$ ):  $\delta$  1.25 (t, 6H,  $J = 8.2$  Hz), 2.30 (s, 6H), 3.90 (s, 3H), 4.10 (q, 4H,  $J = 8.2$  Hz), 5.10 (s, 1H), 5.80 (brs, 1H), 6.80 (d, 2H,  $J = 8.7$  Hz), 7.4 (d, 2H,  $J = 8.7$  Hz). CHN analysis calcd. for  $C_{20}H_{25}NO_5$ : C, 66.84; H, 7.01; N, 3.90. Found C, 66.42; H, 6.89; N, 3.55.

**Entry h.**  $^1H$  NMR ( $CDCl_3$ ):  $\delta$  1.20 (t, 6H,  $J = 8.2$  Hz), 2.25 (s, 6H), 4.10 (q, 4H,  $J = 8.2$  Hz), 5.05 (s, 1H), 5.70 (brs, 1H), 7.40 (d, 2H,  $J = 8.7$  Hz), 8.10 (d, 1H,  $J = 8.7$  Hz). CHN analysis calcd. for  $C_{19}H_{22}N_2O_6$ : C, 69.95; H, 5.92; N, 7.48. Found C, 60.78; H, 5.79; N, 7.26.

**Entry i.**  $^1H$  NMR ( $CDCl_3$ ):  $\delta$  1.30 (t, 6H,  $J = 8.2$  Hz), 2.55 (d, 2H,  $J = 7.2$  Hz), 4.05 (q, 4H,  $J = 8.2$  Hz), 4.20 (t, 1H), 5.25 (brs, 1H), 6.95–7.35 (m, 5H).



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CHN analysis calcd. for  $C_{20}H_{25}NO_4$ : C, 69.95; H, 7.34; N, 4.08. Found C, 69.59; H, 7.16; N, 3.93.

**Entry j.**  $^1H$  NMR ( $CDCl_3$ ):  $\delta$  0.80 (d, 6H,  $J = 7.0$  Hz), 1.25 (t, 6H,  $J = 8.2$  Hz), 1.5 (m, 1H), 3.90 (d, 1H,  $J = 7.2$  Hz), 4.15 (q, 4H,  $J = 8.2$  Hz), 5.6 (brs, 1H). CHN analysis calcd. for  $C_{16}H_{25}NO_4$ : C, 65.06; H, 8.53; N, 4.74. Found C, 64.93; H, 8.37; N, 4.54.

**Entry k.**  $^1H$  NMR ( $CDCl_3$ ):  $\delta$  0.90 (t, 3H, 8.2 Hz), 1.15 (t, 6H,  $J = 8.2$  Hz), 1.25 (t, 6H,  $J = 8.2$  Hz), 1.45 (m, 2H), 2.30 (s, 6H), 3.85 (t, 1H,  $J = 8.2$  Hz), 4.15 (q, 4H, 8.2 Hz), 5.65 (brs, 1H). CHN analysis calcd. for  $C_{19}H_{31}NO_4$ : C, 67.63; H, 9.26; N, 4.15. Found C, 67.42; H, 9.06; N, 4.03.

**Entry l.**  $^1H$  NMR ( $CDCl_3$ ):  $\delta$  0.90 (t, 3H,  $J = 8.4$  Hz), 1.15 (m, 16H), 1.25 (t, 6H,  $J = 8.4$  Hz), 1.45 (m, 2H), 2.30 (s, 6H), 3.85 (t, 1H), 4.15 (q, 4H,  $J = 8.6$  Hz), 5.65 (brs, 1H). CHN analysis calcd. for  $C_{23}H_{39}NO_4$ : C, 72.04; H, 7.62; N, 3.65. Found C, 71.86; H, 7.39; N, 3.42.

**Entry m.**  $^1H$  NMR ( $CDCl_3$ ):  $\delta$  1.20 (T, 6H,  $J = 8.2$  Hz), 2.45 (s, 6H), 4.15 (q, 4H,  $J = 8.2$  Hz), 5.15 (d, 1H,  $J = 5.4$  Hz), 5.75 (brs, 1H), 6.19 (t, 1H,  $J = 6.0$  Hz), 7.20 (d, 1H,  $J = 16.6$  Hz), 7.25 (m, 5H). CHN analysis calcd. for  $C_{21}H_{24}NO_4$ : C, 71.17; H, 6.83; N, 3.95. Found C, 70.98; H, 6.56; N, 3.74.

**Entry n.**  $^1H$  NMR ( $CDCl_3$ ):  $\delta$  1.25 (t, 6H,  $J = 8.2$  Hz), 2.4 (s, 6H), 4.10 (q, 4H,  $J = 8.2$  Hz), 5.15 (s, 1H), 5.75 (brs, 1H), 7.35 (t, 1H,  $J = 8.8$  Hz), 7.60 (d, 1H,  $J = 8.8$  Hz), 8.0 (d, 1H,  $J = 8.8$  Hz), 8.1 (s, 1H). CHN analysis calcd. for  $C_{19}H_{22}N_2O_6$ : C, 60.94; H, 5.93; N, 7.49. Found C, 60.56; H, 5.76; N, 7.31.

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