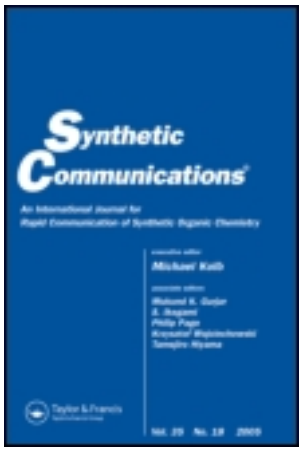

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SYNTHESIS OF HANTZSCH 1,4-DIHYDROPYRIDINES UNDER MICROWAVE IRRADIATION

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SYNTHESIS OF HANTZSCH 1,4-DIHYDROPYRIDINES UNDER MICROWAVE IRRADIATION

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ABSTRACT

Biologically active substituted 1,4-dihydropyridines have been synthesized in excellent yields by the reaction of aldehydes, ethyl or methyl acetoacetic ester and ammonium acetate under microwave irradiation (MWI) within 0.75–3 min.

Substantial reduction in reaction times by many fold and minimisation of thermal decomposition products are the two main advantages offered by microwave heating in chemical reactions. This has resulted in an increased number of research articles published during the last decade in the field of organic synthesis, demonstrating the suitability of microwave heating in synthesising various compounds of commercial importance.[1–7]

The conventional methods for the preparation of Hantzsch 1,4-dihydro-pyridines from various aliphatic and aromatic aldehydes, β keto ester and ammonia reported by earlier workers[8–12] involved prolonged reaction

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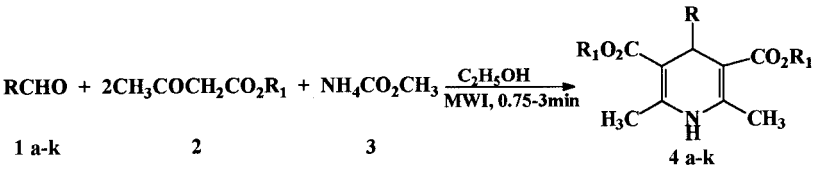
times under refluxing conditions and moderate yields. Considering the growing importance in this class of compounds which possess biological activities like antihypertensive,[13] treatment of benign prostatic hyperplasia,[14] overcoming multidrug resistance encountered in cancer chemotherapy[15] etc. and the advantages offered by microwave irradiation that has been successfully employed in several organic synthesis, we planned to prepare Hantzsch 1,4-dihydropyridines and their derivatives under microwave irradiation in good yields.

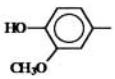
The reaction of 1 eq. of formaldehyde (**1a**), 2 eq. of ethyl acetoacetate (**2**) with 1 eq. of ammonium acetate (**3**) in 10 ml of ethanol was subjected to microwave irradiation for 45 s in a domestic (BPL-SANYO) microwave oven with a pulse of 15 s each.[16] The reaction was carried out at a power level of 80 which corresponds to an output power of 580 W. The product (**4a**) was obtained as a light yellow solid in 96% yield (Scheme 1). The yield obtained with other substituted aldehydes are given in Table 1.



Scheme 1.

Alajarin et al.[17] have reported the synthesis of 1,4-dihydropyridines under microwave irradiation with moderate yields but much lower compared to our results. Aqueous ammonium hydroxide and ethanol used by the previous authors have been replaced with ammonium acetate in alcohol in the present investigation which might have enhanced the yields. The loss of ammonia during heating could be minimised by using ammonium acetate thereby improving the yields. Further we have attempted the reaction in an open glass conical flask (250 ml) in place of teflon vessel and microwave digestion bomb used by Alajarin et al. for a period of 0.75–3 min with intermittent cooling. Although we have carried out the experiments at a higher output power (580 W) no untoward incident occurred during our investigations indicating that no special precautionary measures are needed for this experiment. Usage of higher output power during the reactions has considerably reduced the reaction time and enhanced the yield compared to earlier studies.

Table 1. Synthesis of Hantzsch 1,4-Dihydropyridines Under MWI

Entry	Substrates R	Substrates R_1	Products[a] 4a–k	Time (in min)	Yield (%)
1	H	CH_3CH_2-	**4a**[b]	0.75	96
2	C_6H_5-	CH_3CH_2-	**4b**[b]	2	91
3	*m*-$NO_2C_6H_4$-	CH_3-	**4c**	2	89
4	*o*-$NO_2C_6H_4$-	CH_3-	**4d**	2	84
5	*m*-$NO_2C_6H_4$-	CH_3CH_2-	**4e**	2	93
6	*p*-ClC_6H_4-	CH_3CH_2-	**4f**	2	90
7	*o*-ClC_6H_4-	CH_3-	**4g**	2	86
8	*p*-$CH_3C_6H_4$-	CH_3-	**4h**	3	88
9	*p*-$OCH_3C_6H_4$-	CH_3-	**4i**	3	66
10		CH_3CH_2-	**4j**	3	69
11		CH_3CH_2-	**4k**	2	94

[a]Products were characterized by ^{1}H NMR, ^{13}C NMR, IR, Mass spectra and CHN analysis.
[b]The products were also prepared in 5g scale under MWI.

In conclusion, this paper describes a simple and convenient method for the synthesis of substituted Hantzsch 1,4-dihydropyridines under microwave irradiation in excellent yields and shorter reaction times compared with previous methods which involve longer reaction times under refluxing conditions with moderate yields.

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GENERAL PROCEDURE

0.5 g (3.3 mmol, 1 eq.) of *m*-nitrobenzaldehyde, 0.86 g (6.6 mmol, 2 eq.) of ethyl acetoacetate and 0.26 g (3.3 mmol, 1 eq.) of ammonium acetate in 10 ml of ethanol taken in a conical flask was subjected to microwave irradiation for 2 min in a domestic microwave oven with a pulse of 15 s each and allowed to stand at room temperature. To facilitate crystallization of the compounds, the reaction mixture was scratched with a glass rod. Yellow crystals of 2,6-Dimethyl-3,5-dicarboethoxy-4-(*m*-nitrophenyl)-1,4-dihydropyridine (**4e**) were formed. The solid product obtained was washed with 20% ethyl acetate pet-ether (bp. 60–80°C) mixture. The yield was 93%, mp. 163–164°C (lit. 164–165°C). The product was recrystallized from ethanol. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.13 (s, 1H), 8.02 (d, 1H, $J = 7.5$ Hz), 7.66 (d, 1H, $J = 7.5$ Hz), 7.40 (d, 1H, $J = 8.7$ Hz), 6.16 (s, 1H), 5.10 (s, 1H), 4.10 (q, 4H), 2.36 (s, 6H), 1.24 (t, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 167.2, 150.0, 148.1, 145.0, 134.5, 128.6, 123.1, 121.3, 103.2, 60.0, 40.0, 19.5, 14.2; MS *m*/*z*: 374 (M^+); IR (KBr): 3404, 3328, 1674, 1633, 1590, 1529, 1105, 857 cm^{-1}.

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REFERENCES

1. Bose, A.K.; Manhas, M.S.; Ghosh, M.; Raju, V.S.; Tabei, K.; Orbanczyk-Lipkowska, Z. Heterocycles **1990**, *30*, 741.
2. (a) Villemin, D.; Benalloum, A. Synth. Commun. **1991**, *21*, 1; (b) Babu, G.; Perumal, P.T. Synth. Commun. **1997**, *27*, 3677.
3. Latouch, L.; Texier-Boullet, F.; Hamelin, J. Tetrahedron Lett. **1991**, *32*, 1179.
4. Abdallah-Ei Ayoubi, S.; Texier-Boullet, F.; Hamelin, J. Synthesis **1994**, 258.
5. Soniente, A.; Spinella, A.; DeRosa, M.; Giordano, M.; Scettri, A. Tetrahedron Lett. **1997**, *38*, 289.
6. Selvi, S.; Perumal, P.T. Synth. Commun. **2000**, *30*, 3925.
7. Alterman, M.; Hallberg, A. J. Org. Chem. **2000**, *65*, 7984.
8. Anderson, A.G., Jr.; Berkelhammer, G. J. Am. Chem. Soc. **1958**, *80*, 992.

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

9. *Practical Heterocyclic Chemistry*, Fitton, A.O., Smalley, R.K., Ed.; Academic Press, New York, 1968, p. 68.
10. Phillips, A.P. J. Am. Chem. Soc. **1949**, *71*, 4003.
11. Bossert, F.; Vater, W. S. African patent 68 01 482, 07, 1968; Chem. Abstr. **1969**, *70*, 96641d.
12. Maquestiau, A.; Mayence, A.; Eynde, J.-J.V. Tetrahedron Lett. **1991**, *32*, 3839.
13. Janis, R.A.; Triggle, D.J. J. Med. Chem. **1983**, *26*, 775.
14. Wong, W.C.; Chiu, G.; Wetzel, J.M.; Marzabadi, M.R.; Nagarathnam, D.; Wang, D.; Fang, J.; Miao, S.W.; Hong, X.; Forray, C.; Vaysse, P.J.-J.; Branchek, T.A.; Gluchowski, C.; Tang, R.; Lepor, H. J. Med. Chem. **1998**, *41*, 2643.
15. Nogec, I.; Kohno, K.; Kikuchi, J.; Kuwano, M.; Akiyama, S.-I.; Kiue, A.; Suzuki, K.-I.; Yoshida, Y.; Cornwell, M.; Pastan, M.; Gottesman, M. Biochem. Pharmacol. **1989**, *38*, 519.
16. The domestic microwave oven, BPL microwave cooking system model BMO-700T manufactured by BPL-SANYO utilities and appliances Ltd., Bangalore, India was used in the present studies. The oven has variable timing cycles from 1 s to 99 min and 99 s and heating cycles from 155 to 700 W of power output which can be varied by selecting power levels ranging from 10 to 100. The over all dimensions of the domestic oven is 525(W) × 419(D) × 281(H) mm with a chamber of 350(W) × 370(D) × 208(H) mm. The microwave frequency is 50 Hz and the oven capacity is 26 lit.
17. Alajarin, R.; Vaquero, J.J.; Garcia Navio, J. L.; Alvarez-Builla, J. Synlett **1992**, 297.

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