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Solvent-free One-pot Synthesis Of Polyhydropyridopyrimidine Derivatives *Via* Hantzsch Condensation Using Sulphamic Acid Catalyst

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ABSTRACT

An efficient Hantzsch condensation of polyhydropyridopyrimidine derivatives was reported via a four-component coupling reaction of aldehydes, barbituric acid, ethyl acetoacetate and ammonium acetate in the presence of H_2NSO_3H under solvent-free conditions. Operational simplicity, use of a reusable, economically convenient catalyst under solvent-free condition is described in this paper.

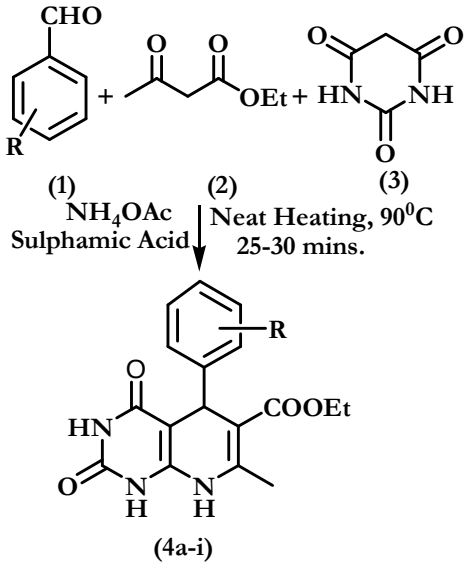
KEYWORDS

Hantzsch condensation;
Sulfamic acid;
Polyhydropyridopyrimidine;
Solvent-free.

INTRODUCTION

4-Aryl 1,4-dihydropyridines(1,4-DHP's) are well known as calcium channel blockers and emerged as one of the most important classes of drugs for the treatment of cardiovascular classes, including hypertension[1]. 1,4-dihydropyridines possess a variety of biological activities, such as vasodilator, bronchodilator, anti-atherosclerotic, antitumor, geroprotective, hepatoprotective and antidiabetic agent[2a-d]. Recent studies have revealed that 1,4-DHP's exhibits several medicinal applications like neuroprotectant[3a] and platelet anti-aggregatory activity[3b], in addition cerebral antischemic activity in the treatment of Alzheimer's disease[3c] and as chemo sensitizer in tumor therapy[3d]. These existing examples clearly demonstrate the remarkable potential of novel DHP derivatives as a source of valuable drug candidates. A recent computational analysis of the comprehensive medicinal chemistry database showed the DHP framework to among the most prolific chemo-type found. Development of drug resistance (intrinsic acquired), remains a clinical obstacle in the chemotherapy in many cancers[4-5]. Among the possible resistance modifiers, the dihydropyridines, calcium antagonists, have been studied extensively as the analog of verapamil[6]. Literature reveals that 1,4-DHP derivatives combined with a single ring have been mostly reported. Thus the synthesis of the heterocyclic nucleus is of continuing interest.

In view of the importance of polyhydroquinolin derivatives, many classical methods for their synthesis were reported[7-12] using conventional heating and refluxing approaches in the presence of an organic solvent. These methods, however, involves long reaction times, harsh reaction conditions, the use of a



(4a-i)

SCHEME 1

TABLE: 1 Synthesis of ethyl, 2, 3, 4, 5, 8-hexahydro-7-methyl 2,4-diono-5-phenyl pyrido[2,3d] pyrimidine-6-carboxylate

Entry	R	Reflux time (min)	Yield (%)[a]	mp/ ^{0}C
4a	H	25	80	244-46
4b	3-Cl	25	85	250-52
4c	4-NO_2	25	87	262-64
4d	4-CH_3	25	85	248-50
4e	3-OCH_3	25	81	254-56
4f	4-OH	25	91	261-63
4g	4-$N(CH_3)_2$	30	90	258-60
4h	Thiophene-2	30	76	260-62
4i	Pyridine-3	30	75	257-59

[a]Isolated % yield

large quantity of volatile organic solvents and generally leading to low yields. Therefore, it is necessary to develop an efficient and versatile method for the preparation of 1,4-dihydropyridines and the progress in this field is remarkable including recently the promotion of microwave[13], TMSCl[14], ionic liquids[15,16] polymers[17,18] and $Yb(OTf)_3$[19].

The multi-component reactions are powerful tools in the modern drug discovery process and allow fast, automated and high throughput generation of organic compounds[20]. The possibility of performing multi-component reactions under solvent-free conditions with sulphamic acid catalyst could enhance their efficiency from an economic as well as an ecological point of view. In recent years safer and reusable catalyst are gaining more importance due to environmental-economic factors. The catalyst is generally of low cost and can be easily handled or removed. Sulphamic acid (H_2NSO_3H), which is a common organic acid with mild acidity, involatality, and incorrosivity, has been studied as an acid catalyst in acetalyzation and ketalyzation reactions[21]. Particularly H_2NSO_3H is insoluble in common organic solvents, and so, its separation and recycling is very easy in catalytic reaction. Herein we would like to report synthesis of Polyhydropyridopyrimidine derivatives**(4a-i)** in presence of sulphamic acid catalyst via an efficient, one-pot condensation aromatic aldehydes**(1)**, barbituric acid**(2)**, ethyl acetoacetate **(3)** and ammonium acetate in excellent yields.

EXPERIMENTAL

Melting points were determined in open capillary tubes and are uncorrected. The purity of compounds was checked by Blaker-Flex silica gel 1B-F(1.55cm) TLC plates, and the spots were detected by UV light absorption. The ^{1}H-NMR spectra were recorded on *Varian* NMR spectrophotometer, model mercury plus(400MHz) and the chemical shifts (δ) are given in ppm relative to signal for TMS as an internal standard. The mass spectra of compound **(4a)**, **(4d)**, **(4f)** recorded on micromass LC-MS system exhibited M^+ values.

Synthesis of ethyl, 2,3,4,5,8-hexahydro-7-methyl 2,4-diono-5-phenyl pyrido[2,3d] pyrimidine-6-carboxylate(4a)

A mixture of benzaldehyde(1mmol), barbituric acid(1mmol), ethyl acetoacetate(1mmol), ammonium acetate(1.5mmol) and sulphamic acid(19mg) was heated at 90^{0}C with stirring for 25 minutes and the solid product gradually formed. After completion of the reaction as indicated by TLC, the resulting solid product was treated with EtOAC followed by water and a Brine solution and dried with anhydrous Na_2SO_4. The solution was concentrated in vacuum to afford the crude product. The pure product was obtained by further recrystallization using absolute alcohol. M.p 243-245^{0}C,^{1}H-NMR ($CDCl_3$,400MHz): δ(ppm) 5.8(s, 2H, -NH), 3.5(q, 2H, -OCH_2CH_3), 1.2(t, 3H, -CH_2CH_3), 2.2(s, 3H, Ar-CH_3), 7.3-7.5(s, 5H, Ar-H), Mass m/z 295, 294, 294, 236, 161, 84, 48.

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Ethyl, 2, 3, 4, 5, 8-hexahydro-7-methyl 2, 4-diono-5-phenyl pyrido[2,3d]pyrimidine-6-carboxylate (4a)

M.p. 261-263^{0}C,^{1}H-NMR($CDCl_3$,400MHz): δ(ppm) 5.8(s, 2H, -NH), 3.5(q, 2H, -OCH_2CH_3), 1.2(t, 3H, -CH_2CH_3), 2.2(s, 3H, Ar-CH_3), 2.4(s, 3H, Ar-CH_3), 7.2(dd, 2H, Ar-H) 7.3(dd, 2H,Ar-H) Mass m/z 308, 307, 306, 249, 172, 94, 53

CONCLUSION

The experimental procedure is very simple, convenient and has the ability to tolerate a variety of functional group such as methoxy, nitro, hydroxy and halides under these reaction conditions. In conclusion, we have developed a simple, one-pot and efficient method for the synthesis of polyhydropyrid opyrimidine derivatives via modified Hantzsch condensation using a H_2NSO_3H catalyst under solvent-free conditions. The conversion, the experimental simplicity, compatibility with various functional groups, inexpensive catalyst, the high yields, regioselectivity, the shorter reaction times and the easy workup procedure employed, makes this procedure very attractive to synthesize a variety of these derivatives.

REFERENCES

[1] **(a)** F.Bossert, H.Meyer, E.Wehinger; Angew. Chem. Int.Ed.Engl., **20**, 762 **(1981)**.
(b) H.Nakayama, Y.Kasoaka; Heterocycles, **42**, 901 **(1996)**.

[2] **(a)** T.Godfraid, R.Miller, M.Wibo; Pharmocol.Rev., **38**, 321 **(1986)**.
(b) A.Sausins, G.Duburs; Heterocycles, **27**, 269 **(1988)**.
(c) P.P.Mager, R.A.Coburn, A.J.Solo, D.J.Triggle, H.Rothe; Drug Design Discovery, **8**, 273 **(1992)**.
(d) R.Mannhold, B.Jablonka, W.Voigdt, K. Schoenafinger, K.Schravan; Eur.J.Med.Chem., **27**, 229 **(1992)**.

[3] **(a)** V.Klusa; Drugs Fut., **20**, 135 **(1995)**.
(b) R.G.Bretzel, C.C.Bollen, E.Maeser, K.F.Federlin; Am.J.Kidney.Dis., **21**, 53 **(1993)**.
(c) R.G.Bretzel, C.C.Bollen, E.Maeser, K.F.Federlin; Drugs.Fut., **17**, **465 (1992)**.
(d) R.Boer, V.Gekeler; Drugs Fut., **20**, 499 **(1995)**.

[4] H.L.Davis, T.E.Davis; Cancer Treat.Rep., **63**, 809 **(1979)**.

[5] I.Pastan, M.M.N.Gottesman; Engl.J.Med., **316**, 1388 **(1987)**.

[6] H.Tanabe, S.Tasaka, H.Ohmori, N.Gomi, Y.Sasaki, T.Machida, M.Lilo, A.Kiue, S.Naito, M.Kuwano; Bioorg.Med.Chem., **6**, 2219 **(1998)**.

[7] A.Hantzsch; Ann.Chem., **1**, 215 **(1882)**.

[8] J.B.Sainani, A.C.Shah, V.P.Arya; Indian J.Chem.Sect., **B33**, 526 **(1994)**.

[9] V.K.Ahluwalia, B.Goyal, U.J.Das; Chem.Res.Synop., 266 **(1997)**.

[10] S.Margarita, O.Estael, V.Yamila, P.Beatriz, M.Lourdes, M.Nazario, Q.Margarita, S.Carlos, L.S.Jose, N.Hector, B.Norbert, M.P.Oswald; Tetrahedron, **55**, 875 **(1999)**.

[11] V.K.Ahluwalia, B.Goyal, U.J.Das; Chem.Res. Miniprint., **7**, 1501 **(1997)**.

[12] V.K.Ahluwalia, B.Goyal; Indian J.Chem.Sect., **B35**, 1021 **(1996)**.

[13] S.J.Tu, J.F.Zhou, X.Deng, P.J.Cai, H.Wang, J.C.Feng; Chin.J.Org.Chem., **21**, 313 **(2001)**.

[14] G.Sabitha, G.S.K.K.Reddy, C.S.Reddy, J.S.Yadav; Tetrahedron Lett., **44**, 4129 **(2003)**.

[15] S.J.Ji, Z.Q.Jiang, J.Lu, T.P.Loa; Synlett, 831 **(2004)**.

[16] R.Sridhar, P.T.Perumal; Tetrahedron., **61**, 2465 **(2005)**.

[17] J.G.Breitenbucher, G.Figliozzi; Tetrahedron Lett., **41**, 4311 **(2000)**.

[18] A.Dondoni, A.Massi, E.Minghini, V.Bertolasi; Tetrahedron, **60**, 2311 **(2004)**.

[19] L.M.Wang, J.Sheng, L.Zhang, J.W.Han, Z.Y.Fan, H.Tian, C.T.Qian; Tetrahedron, **61**, 1539 **(2005)**.

[20] L.Weber; Curr.Med.Chem., **9**, 1241 **(2002)**.

[21] Jin,Tong Shou, Sun Guang, Liyan-Wei, Li Tong-Shuang; Green.Chem., 255-256 **(2002)**.