Pergamon

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Tetrahedron Letters 44 (2003) 4129–4131

TETRAHEDRON LETTERS

A novel TMSI-mediated synthesis of Hantzsch 1,4-dihydropyridines at ambient temperature☆

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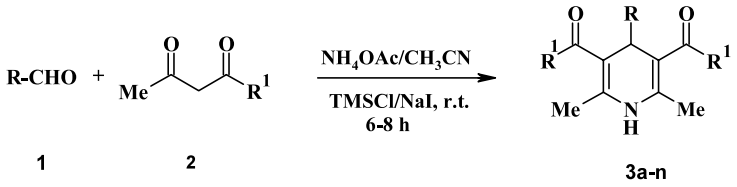
Received 10 February 2003; revised 13 March 2003; accepted 21 March 2003

Abstract—The synthesis of various substituted Hantzsch 1,4-dihydropyridines has been achieved using the classical Hantzsch procedure and modified Hantzsch conditions for the first time at room temperature in the presence of iodotrimethylsilane (TMSI) generated in situ in CH_3CN, in excellent yields.

Hantzsch 1,4-dihydropyridines (1,4-DHPs) are well known as Ca^{2+} channel blockers, and have emerged as one of the most important classes of drugs for the treatment of cardiovascular diseases, including hypertension.[1] The DHP heterocyclic ring is a common feature of various bioactive compounds such as vasodilator, bronchodilator, antiatherosclerotic, antitumor, geroprotective, hepatoprotective and antidiabetic agents.[2] Recent studies have revealed that 1,4-DHPs exhibit several other medicinal applications which include neuroprotectant[3a] and platelet anti-aggregratory activity,[3c] in addition to acting as a cerebral antiischemic agent in the treatment of Alzheimer's disease[3c] and as a chemosensitizer in tumor therapy.[3d] These 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 found the DHP framework to be among the most prolific chemotypes found. Thus, the synthesis of this heterocyclic nucleus is of continuing interest. The success of these calcium antagonists has led to the development of novel synthetic strategies to improve their classical methods of preparation. Microwave activation stands among the alternative routes proposed during the past decade due to the drastic reduction of reaction times.[4] More than a century ago the first 1,4-DHPs were obtained by Hantzsch.[5] This reaction involves a one-pot condensation of an aldehyde with ethyl acetoacetate, and ammonia either in acetic acid or refluxing in alcohol for a longer time. However, the yields of 1,4-DHPs obtained by the Hantzsch method are generally low. Even though a number of modified methods[6] under improved conditions have been reported, many of them suffer from drawbacks such as unsatisfactory yields, high temperatures and long reaction times. Thus, the development of an efficient and versatile method for the preparation of Hantzsch 1,4-DHPs is an active ongoing research area and there is scope for further improvement toward milder reaction conditions and improved yields. The versatility of iodotrimethylsilane as a useful reagent in organic synthesis is well established.[7] As a continuation of our studies of TMSI,[8] we report in this communication a novel and efficient synthesis of Hantzsch 1,4-dihydropyridines by the classical Hantzsch procedure (Scheme 1) and as well as by a



Scheme 1.

Keywords: TMSI; Hantzsch 1,4-dihydropyridines; one-pot condensation; ambient temperature.

☆ IICT Communication No: 030206.

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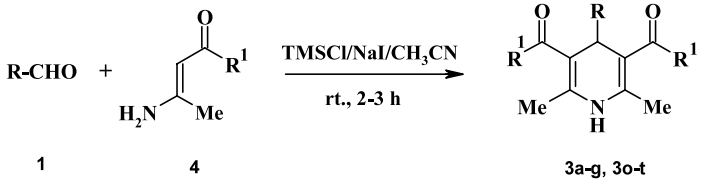
0040-4039/03/$ - see front matter
doi:10.1016/S0040-4039(03)00813-X

modified Hantzsch procedure (Scheme 2) using TMSI in CH_3CN at ambient temperature.

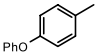
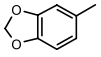
Thus, the condensation of 1 equiv. of benzaldehyde **1a** with 2 equiv. of ethyl acetoacetate **2a** and 2 equiv. of NH_4OAc in the presence of TMSI (generated in situ from TMSCl+NaI) resulted in the formation of Hantzsch 1,4-dihydropyridine **3a** (Scheme 1, method A). The reaction was complete in 6 h at room temperature and the product was isolated by usual work-up, in 80% yield, with high purity. Under similar conditions various substituted aromatic and aliphatic aldehydes carrying either electron-donating or -withdrawing substituents were converted into the expected 1,4-DHPs in good to excellent yields and the results are summarized in Table 1. All reactions were clean and efficient at room temperature and the products were obtained within 6–8 h in good yields.[9] To the best of our knowledge, this is the first report of the preparation of 1,4-DHPs at ambient temperature based on the Hantzsch procedure.

To examine the versatility of the reagent, the preparation of 1,4-DHPs was tested using a modified Hantzsch procedure. Treatment of 1 equiv. of benzaldehyde **1a** with 2 equiv. of ethyl aminocrotonate **4** in the presence



Scheme 2.

Table 1. TMSI-mediated synthesis of dihydropyridines under Hantzsch and modified Hantzsch conditions

Product[a]	R	R^1	Reaction time (h) & Yield[b] (%)	
			Method A	Method B
3a	C_6H_5	Et	6 (80)	2 (85)
3b	4-FC_6H_4	Et	8 (74)	2.5 (78)
3c	4-$MeOC_6H_4$	Et	6 (76)	2.5 (83)
3d		Et	7 (75)	2 (80)
3e	2-naphthyl	Et	6.5 (75)	2 (80)
3f	$(CH_3)_2CH$	Et	6 (76)	2 (78)
3g	C_6H_5	Me	6.5 (78)	2 (83)
3h	2-$O_2NC_6H_4$	Et	8 (73)	-
3i	4-MeC_6H_4	Et	6.5 (78)	-
3j		Et	6 (73)	-
3k	4-ClC_6H_4	Et	6 (78)	-
3l	4-HOC_6H_4	Et	7 (76)	-
3m	2-$O_2NC_6H_4$	Me	8 (73)	-
3n	2-MeC_6H_4	Me	7 (75)	-
3o		Et	-	2 (80)
3p	3,4-$Cl_2C_6H_3$	Et	-	2.5 (80)
3q	4-$O_2NC_6H_4$	Et	-	2.5 (78)
3r	3,4-$(MeO)_2C_6H_3$	Et	-	2 (82)
3s	4-$MeOC_6H_4$	Me	-	2.5 (80)
3t	4-ClC_6H_4	Me	-	2 (85)

[a] All products were characterized by IR and ^{1}H NMR spectroscopic data and their mps compared with literature mps.

[b] Isolated yields after column chromatography.

of TMSI generated in situ in CH_3CN afforded the corresponding 1,4-DHP **3a** (Scheme 2, method B) in 85% yield at room temperature. Table 1 represents the generality of the present procedure for the synthesis of various substituted 1,4-DHPs including an example prepared from an aliphatic aldehyde (Table 1, compound **3f**). All the reactions proceeded smoothly at room temperature to afford the products in good to high yields within 2–2.5 h.[9]

All the products prepared from these two routes were characterized by their spectral data and known compounds by comparison with reported data. The advantages of the present protocols are the shorter reaction times at room temperature, mild reaction conditions and due to the high reactivity of the reagent the products are obtained in high yields. In addition to this, good yields of 1,4-DHPs were obtained from *o*-substituted benzaldehydes, which is not the case in existing procedures. Another important aspect is that various functionalities such as ether, nitro, hydroxy, halide, etc., survived under the present reaction conditions. The best results were obtained using 1 equiv. of TMSCl and 1 equiv. of NaI.

In conclusion, we have demonstrated for the first time a novel synthetic protocol enabling access to Hantzsch 1,4-DHPs in good to excellent yields in short reaction times at room temperature. We believe that the present improved modification is a convenient and attractive alternative to the existing methods for the synthesis of 1,4-DHPs.

Acknowledgements

G.S.K.K.R. would like to thank the CSIR, and Ch.S.R. would like to thank the UGC, New Delhi, for the award of fellowships.

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9. Experimental:
   Synthesis of 1,4-DHPs ***3a–n***: Aldehyde **1** (5 mmol), β-keto ester **2** (10 mmol) and NH_4OAc (10 mmol) were dissolved in acetonitrile (10 mL) and stirred at room temperature. To this, TMSCl (5 mmol) was added dropwise and then NaI (5 mmol) was added in one portion and the reaction mixture was stirred at room temperature for an appropriate time (Table 1). After completion of the reaction as indicated by TLC, it was poured into ice cold water and extracted with ethyl acetate. The organic layer was washed with sodium thiosulphate and water then dried and concentrated in vacuo. The crude products were purified by column chromatography using silica gel (60–120 mesh) and eluted with ethyl acetate–hexane (3:7) to afford 1,4-DHPs in 73–80% yields.
   Synthesis of 1,4-DHPs ***3a–g***, ***3o–t***: Aldehyde **1** (5 mmol) and ethyl/methyl aminocrotonate **4** (10 mmol) were suspended in acetonitrile (10 mL). To this suspension, NaI (5 mmol) in one portion, then TMSCl (5 mmol) were added and the reaction mixture was stirred at room temperature for 2–2.5 h. After completion of the reaction as indicated by TLC, the reaction mixture was quenched with ice cold water and extracted with ethyl acetate. The organic layer was washed with sodium thiosulphate and water then dried and concentrated in vacuo and the resulting crude products were recrystallized using EtOAc: pet ether (9:1) to afford pure products **3a–g**, **3o–t** in 78–85% yields.
   NMR data for selected compounds: Entry **3e**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.95 (t, 6H, $J=8.2$ Hz), 2.29 (s, 6H), 3.92 (q, 4H, $J=8.2$ Hz), 5.55 (brs, 1H), 5.76 (s, 1H), 7.30–7.55 (m, 4H), 7.60 (d, 1H, $J=8.68$ Hz), 7.72 (d, 1H, $J=8.6$ Hz), 8.55 (d, 1H, $J=8.6$ Hz); **3f**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.75 (d, 6H, $J=7.2$ Hz), 1.30 (t, 6H, $J=8.2$ Hz), 1.55 (m, 1H), 2.30 (s, 6H), 3.92 (d, 1H, $J=7.2$ Hz), 4.15 (q, 4H, $J=8.2$ Hz), 5.60 (brs, 1H); **3h**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.18 (t, 6H, $J=8.2$ Hz), 2.30 (s, 6H), 4.0 (q, 4H, $J=8.2$ Hz), 5.60 (brs, 1H), 5.80 (s, 1H), 7.23 (m, 1H), 7.50 (m, 2H), 7.72 (d, 1H, $J=8.6$ Hz); **3k**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.20 (t, 6H, $J=8.5$ Hz), 2.30 (s, 6H), 4.10 (q, 4H, $J=8.2$ Hz), 4.90 (s, 1H), 5.75 (brs, 1H), 7.15–7.23 (m, 4H).