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Ultrasound-accelerated Synthesis of 1,4-Dihydropyridines in an Ionic Liquid

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Summary. *Hantzsch* 1,4-dihydropyridine compounds were synthesized efficiently in high yields at room temperature within short times in 1,1,3,3-*N,N,N′,N′*-tetramethylguanidinium trifluoroacetate as ionic liquid using ultrasound irradiation. The ionic liquid can be recovered conveniently and reused efficiently.

Keywords. 1,4-Dihydropyridine; *Hantzsch* reaction; Ionic liquid; Ultrasound.

Introduction

It is well known that 1,4-dihydropyridines (*DHP*s) exhibit a wide range of biological activities, acting as potent vasodilators, antihypertensives, branchodilators, antiatherosclerotics, hepatoprotective, antitumor, antimutagenic, geroprotective, and antidiabetic agents [1, 2]. *DHP*s are commercially used as calcium channel blockers for treatment of cardiovascular disease [3, 4].

1,4-Dihydropyridines are generally synthesized by the *Hantzsch* method [5], which involves cyclocondensation of an aldehyde, β-ketoester, and ammonia either in acetic acid or by refluxing in alcohols for long reaction times leading to low yields in general [6, 7]. Recently, a number of modified methods have been reported, but many of them suffer from drawbacks such as unsatisfactory yields, high temperatures, long reaction times, and tedious work-up. Thus, the reaction is carried out in two steps (the enaminoketone is used instead of β-ketoester and ammonia) [8, 9]. Therefore the development of an efficient and room temperature one-pot synthesis of *Hantzsch* 1,4-dihydropyridines seemed to be of prime importance.

In this article we demonstrate that the combination of 1,1,3,3-*N,N,N′,N′*-tetramethylguanidinium trifluoroacetate (*TMGT*) as ionic liquid and ultrasound irradia-

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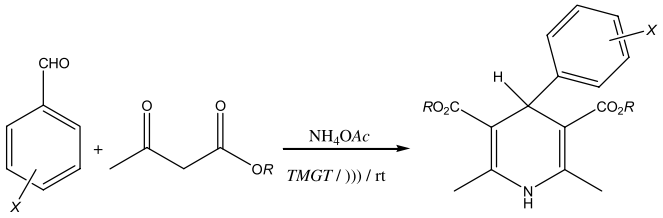

1		2		3	
	X		*R*	*X*	*R*
1a	H	**2a**	CH_3	H	CH_2CH_3
1b	4-OCH_3	**2b**	CH_2CH_3	4-OCH_3	CH_2CH_3
1c	3-OCH_3			3-OCH_3	CH_2CH_3
1d	4-CH_3			4-CH_3	CH_2CH_3
1e	2-OCH_3			2-OCH_3	CH_2CH_3
1f	3-Cl			3-Cl	CH_2CH_3
1g	3-NO_2			3-NO_2	CH_2CH_3
1h	4-NO_2			4-NO_2	CH_2CH_3
1i	4-Br			4-Br	CH_3
1j	4-NO_2			4-NO_2	CH_3

Scheme 1

tion is a rapid and efficient method for the three-component condensation synthesis of 1,4-*DHP*s at room temperature. In this approach the use of large volumes of organic solvents is avoided, work-up simplified, and reaction times are considerably decreased (Scheme 1).

Results and Discussion

The results of *TMGT* catalyzed synthesis of 1,4-*DHP*s using ultrasound irradiations are given in Table 1. Using *TMGT* as promoter for the synthesis of *Hantzsch* 1,4-dihydropyridines does not only represent a dramatic improvement at room temperature with regard to yield (84–95%) over conventional thermal heating, but the reaction times are also considerably decreased (1.45–2.30 h) compared to classical synthesis (6–8 h). After the reaction was completed, the reaction mixture is simply washed with water and the ionic liquid is isolated from the product.

To determine whether the ultrasound irradiation was an essential factor to realize the high conversions of this condensation, the same reaction was carried out in the ionic liquid without using ultrasound irradiation. As a result (Table 1) the reaction time was increased by a factor of about 4. It is important to note that in the absence of *TMGT* and without using ultrasound irradiation, the yield of the reactions decreased to 22–30% (3 h at room temperature; entry 3a, 3b, and 3h in Table 1).

To explore the scope and limitations of this reaction, we extended the reaction of β-ketoesters with various aromatic aldehydes carrying either electron releasing or electron withdrawing constituents in the *para* positions. We found that the

Table 1. One-pot synthesis of 1,4-dihydropyridines in *TMGT* under classical conditions and using ultrasound irradiation at rt

Entry	Aldehyde	β-Ketoester	Product	Yield/% (Time/h)		mp/°C Found (Reported)
				I[a]	II[b]	
1	**1a**	**2a**	**3a**	90(2) 30(3)[c]	83(7)	158–159 (158–160)[e]
2	**1b**	**2a**	**3b**	88(2) 27(3)[c]	74(6.5)	157–159 (158–160)[f]
3	**1c**	**2a**	**3c**	85(2) 88(2), 88(2.30) 87(2.30), 84(2.30)[d]	79(8)	118–120 (120)[g]
4	**1d**	**2a**	**3d**	84(2.30)	84(8.30)	135–138
5	**1e**	**2a**	**3e**	95(2.15)	78(6)	139–141 (138–143)[h]
6	**1f**	**2a**	**3f**	90(1.45)	80(6.5)	141–143 (142)[g]
7	**1g**	**2a**	**3g**	94(2)	85(7)	162–164 (163–165)[i]
8	**1h**	**2a**	**3h**	92(1.45) 22(3)[c]	84(8.5)	129–131 (128–130)[i]
9	**1i**	**2b**	**3i**	86(2.15)	83(8)	193–194 (193–194)[k]
10	**1j**	**2b**	**3j**	87(1.45)	87(7.5)	196–198 (197–198)[k]

[a] In the presence of *TMGT* and using ultrasound irradiation; [b] in the presence of *TMGT* without using ultrasound irradiation; [c] in the absence of *TMGT* without using ultrasound irradiation; [d] the same *TMGT* was used for each of the four runs; [e] Ref. [12]; [f] Ref. [13]; [g] Ref. [14]; [h] Ref. [15]; [i] Ref. [16]; [j] Ref. [17]; [k] Ref. [18]

reaction proceeded very efficiently in all cases and that the reaction time decreased for electron withdrawing substituents.

Hantzsch reactions have negative activation volumes owing to the condensation of three molecules into a single reactive intermediate and reactions with negative activation volumes are accelerated with pressure. Thus, it is well known that ultrasound irradiation [10] as well as solvophobic interactions of ionic liquids generate a microscopic internal pressure in the solvent cavity [11]. Accordingly, it is reasonable that these influences lead to accelerate three components *Hantzsch* reaction condensation.

Another advantage of the ionic liquid is that it is recyclable as reaction medium. In view of environmentally friendly methodologies, recovery and reuse of the ionic liquid is highly preferable. *TMGT* is easily separated from reaction medium by washing with water and distillation of the solvent under vacuum and it can be reused for subsequent reactions. As indicated in Table 1 (entry 3c), it showed no loss of efficiency with regard to reaction time and yield after four successive runs.

In conclusion, we present an ultrasound-accelerated synthesis of 1,4-dihydropyridines in a simple ionic liquid, *TMGT*. The significant improvements offered by this procedure are: (a) fast reaction, (b) simple operation and mild reaction conditions (room temperature), (c) high yields (84–95%), (d) cost efficiency by

recycling of the ionic liquid, and (e) green aspects avoiding hazardous organic solvents, toxic catalyst, and waste (atom efficiency).

Experimental

Melting points were measured on an Electrothermal 9100 apparatus. Elemental analyses were performed using a Heraeus CHN–O–Rapid analyzer. The results were in agreement with the calculated values. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a BRUKER DRX-300 AVANCE spectrometer at 300.13 and 75.47 MHz. NMR spectra were obtained on solutions in $CDCl_3$. All products are known compounds (except entry **3d**), which were identified by IR and ^{1}H NMR spectral data and their melting points were compared with literature reports.

2,6-Dimethyl-3,5-dicarboethoxy-4-(4-methylphenyl)-1,4-dihydropyridine (**3d**, $C_{20}H_{25}NO_4$)
A mixture of 0.259 g ethyl acetoacetate (2 mmol), 0.120 g 4-methylbenzaldehyde (1 mmol), 0.154 g ammonium acetate (2 mmol), and 0.120 g *TMGT* (0.5 mmol) was successively charged into a screw-capped vial. The mixture was irradiated in a water bath of the ultrasonic cleaner (Eyela-92303, Tokyo Rikakikai Co.) at 25–30°C for 2.30 h. Then, the reaction mixture was washed with 25 cm^3 cold H_2O. The crude product was purified by column chromatography on silica gel using *n*-heptane:ethyl acetate (7:1) as eluent to afford the pure product **3d** (0.248 g, 84%). White Solid, mp 135–138°C; ^{1}H NMR ($CDCl_3$): $\delta = 1.16$ (t, $J = 7.13$ Hz, $2CH_2\underline{CH_3}$), 2.20 (s, Ph–CH_3), 2.25 (s, Pyr–CH_3), 4.00 (q, $J = 7.15$ Hz, $2\underline{CH_2}CH_3$), 4.88 (s, Pyr–H), 5.64 (s, br, NH), 6.93–7.11 (m, Ph) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 14.28$, 19.48, 39.09, 59.73, 104.03, 127.83, 128.57, 135.51, 144.13, 144.97, 167.82 ppm; IR (KBr): $\bar{\nu} = 3350$, 2900, 1691, 1647 cm^{-1}, MS: m/z (%) = 342 ($M^+ - 1$, 10), 314 (13), 252 (21), 196 (15), 109 (60), 91 (20), 69 (20), 43 (85).

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References

[1] a) Stout DM, Meyers AI (1982) Chem Rev **82**: 223; b) Wei XY, Rulledge A, Triggle DJ (1989) J Mol Pharmacol **35**: 541; c) Bossert F, Vater W (1989) Med Res Rev **9**: 291
[2] a) Janis RA, Triggle DJ (1983) J Med Chem **25**: 775; b) Bocker RH, Guengerich FP (1986) J Med Chem **28**: 1596
[3] a) Gaudio AC, Korolkovas A, Takahata Y (1994) J Pharm Sci **83**: 1110; b) Bossert F, Meyer H, Wehinger E (1981) Angew Chem Int Ed Engl **20**: 762
[4] a) Klusa V (1995) Drugs Fut **20**: 135; b) Bretzel RG, Bollen CC, Maeser E, Federlin KF (1993) Am J Kidney Dis **21**: 53; c) Bretzel RG, Bollen CC, Maeser E, Federlin KF (1992) Drugs Fut **17**: 465; d) Boer R, Gekeler V (1995) Drugs Fut **20**: 499
[5] Hantzsch A (1882) Liebigs Ann Chem **215**: 1
[6] a) Love B, Snader KM (1965) J Org Chem **30**: 1914; b) Alajarin R, Vaquero JJ, Garcia JLN, Alvarez-Builla J (1992) Synlett 297
[7] Sausins A, Duburs G (1988) Heterocycles **27**: 269
[8] a) Gordeev MF, Patel DV, Gordon EM (1996) J Org Chem **61**: 924; b) Breitenbucher JG, Figliozzi G (2000) Tetrahedron Lett **41**: 4311; c) Ohberg L, Westman J (2001) Synlett 1296; d) Anderson AG, Berkelhammer G (1958) J Am Chem Soc **80**: 992; e) Philips AP (1949) J Am

Chem Soc **71**: 4003; f) Maquestiau A, Maeyence A, Eynde JJV (1991) Tetrahedron Lett **32**: 3839; g) Zolfigol MA, Safaiee M (2004) Synlett 827; h) Szemes F, Marchalin S, Pronayova N, Szemes F, Daich A (2003) Heterocycles **59**: 779; i) Kidwai M, Saxena S, Mohan R, Venkataramanan R (2002) J Chem Soc Perkin Trans 1, 1845; j) Tewari N, Dwivedi N, Tripathi RP (2004) Tetrahedron Lett **45**: 9011

[9] a) Yadav JS, Reddy BVS, Basak AK, Narsaiah AV (2003) Green Chem **5**: 60; b) Sabitha G, Reddy KK, Reddy CS, Yadav JS (2003) Tetrahedron Lett **44**: 4129

[10] a) Mason TJ (1997) Chem Soc Rev **26**: 443; b) Cintas P, Luche JL (1999) Green Chem **1**: 115

[11] a) Kumar A (2001) Chem Rev **1**: 101; b) Welton T (1999) Chem Rev **99**: 2071; c) Wasserscheid P, Keim W (2000) Angew Chem Int Ed **39**: 3772; d) Sheldon R (2001) Chem Commun 2399

[12] Schiff R, Puliti J (1883) Ber Atsch Chem Ges **16**: 1607

[13] Emmert D, Diefenbach E, Eck R (1927) Ber Atsch Chem Ges **60**: 2220

[14] Hinkel LE, Madel WR (1929) J Chem Soc 750

[15] Yadav JS, Reddy BVS, Reddy PT (2001) Synth Commun **31**: 425

[16] Walther WV, Raetze R (1902) J Prakt Chem **65**: 287

[17] Lepetit R (1887) Ber Atsch Chem Ges **20**: 133

[18] Cobum RA, Wierzba M, Suto MJ, Solo AJ, Triggle AM, Triggle DJ (1988) J Med Chem **31**: 2103