Efficient Synthesis of Hantzsch Esters and Polyhydroquinoline Derivatives in Aqueous Micelles

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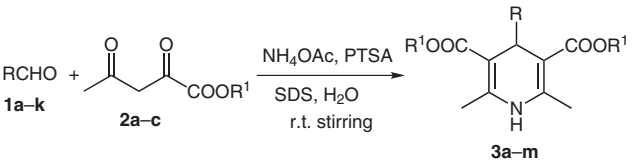
Abstract: Hantzsch 1,4-dihydropyridine and polyhydroquinoline derivatives were synthesized in excellent yields in aqueous micelles. The reaction is catalyzed by PTSA and strongly accelerated by ultrasonic irradiation.

Key words: Hantzsch esters, polyhydroquinoline derivatives, aqueous micelles, PTSA



Scheme 1

Hantzsch 1,4-dihydropyridines (1,4-DHP) and their derivatives are an important class of bioactive molecules in the pharmaceutical field.[1] These compounds are well known as calcium channel modulators and have emerged as one of the most important classes of drugs for the treatment of hypertension.[2] 1,4-Dihydropyridine derivatives possess a variety of biological activities such as vasodilator, branchodilator, antitumor, hepatoprotactive, and geroprotactive activity.[3]

Despite the potential importance of 1,4-dihydropyridyl compounds from a pharmaceutical, industrial, and synthetic point of view,[4] comparatively few methods for their preparation have been reported. The classical method for the synthesis of 1,4-dihydropyridines is the one-pot condensation of aldehydes with ethyl acetoacetate and ammonia either in acetic acid or by refluxing in alcohol.[5] The classical method, however, has several drawbacks such as harsh reaction conditions, long reaction times, and generally low yields of products. Thus, improved synthetic procedures for the synthesis of Hantzsch esters[6] and polyhydroquinoline derivatives[7] are in constant demand.

As a part of our continual efforts towards the development of efficient synthetic procedures for multicomponent reactions, we turned our attention towards the synthesis of 1,4-dihydropyridines and polyhydroquinoline derivatives. We report herein a practical synthesis of 1,4-dihydropyridines and polyhydroquinoline derivatives in aqueous micelles catalyzed by PTSA under ultrasonic irradiation.

In order to optimize the reaction conditions for 1,4-dihydropyridines, we took the reaction of benzaldehyde, ethyl acetoacetate, and ammonium acetate as a model (Scheme 1).

Our initial attempts to condense benzaldehyde, ethyl acetoacetate, and ammonium acetate using PTSA in aqueous micelles (SDS, 0.1 M) yielded **3a** (65%) in four hours. The same reaction without PTSA yielded **3a** in 35% yield. Thus the catalytic efficiency of PTSA was definitely identified. Using methane sulfonic acid instead of PTSA we isolated **3a** in 63% yield. In another experiment, camphor-10-sulfonic acid was used and **3a** was isolated in 62% yield. In order to see the effect of temperature, we refluxed the reaction mixture for three hours but there was no significant improvement in the yield of the product. It was observed that in neat water (absence of SDS) the reaction gave poor yields.

When the reaction mixture was irradiated with ultrasound, almost quantitative conversion was observed (TLC) within one hour and **3a** was isolated in 96% yield. We also carried out the reaction in various solvents. The ultrasonic irradiation in aqueous micelles gave better yields than in solvents such as methanol, ethanol, or THF (Table 1).

Table 1 Optimization of Reaction Conditions for 1,4-Dihydropyridines[a]

Entry	Catalyst	Solvent	Time (h)	Yield (%)[b]
1	None	H_2O	12	16
2	PTSA	H_2O	6	28
3	PTSA	SDS (aq)	4	65
4	MSA	SDS (aq)	4	63
5	CSA	SDS (aq)	4	62
6	PTSA[c]	SDS (aq)	1	96
7	PTSA[c]	THF	1	62
7	PTSA[c]	MeOH	1	74
8	PTSA[c]	EtOH	1	78

[a] Reaction conditions: benzaldehyde (1 mmol), ethyl acetoacetate (2 mmol), NH_4OAc (1 mmol), catalyst (10 mol%).
[b] Isolated yield.
[c] Ultrasonic irradiation.

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Table 2 Ultrasound-Accelerated Synthesis of 1,4-Dihydropyridines[a]

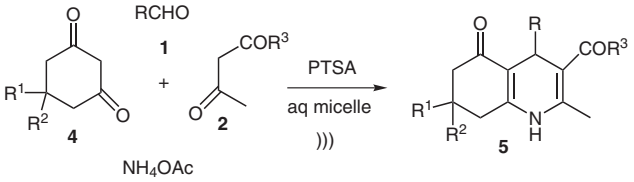
Entry	R	R^1	Product	Yield (%)[b]
1	H	Me	**3a**	97
2	H	Et	**3b**	95
3	H	*t*-Bu	**3c**	96
4	Me	Et	**3d**	95
5	Ph	Et	**3e**	96
6	2-HOC_6H_4	Et	**3f**	91
7	2-$O_2NC_6H_4$	Et	**3g**	93
8	4-MeC_6H_4	Et	**3h**	94
9	3-$O_2NC_6H_4$	Et	**3i**	93
10	Me	Me	**3j**	90
11	2-$O_2NC_6H_4$	Me	**3k**	92
12	4-$MeO_2CC_6H_4$	Me	**3l**	91
13	4-Pyridyl	Me	**3m**	90

[a] Reaction conditions: aldehyde (1 mmol), acetoacetate ester (2 mmol), NH_4OAc (1 mmol), PTSA (10 mol%), ultrasound, 1 h.
[b] Isolated yield.

Using the optimized reaction conditions,[8] we synthesized a series of 1,4-dihydropyridine derivatives under ultrasonic irradiation (Table 2). 4-Aryl-1,4-dihydropyridines were synthesized in excellent yields with a number of electron-rich as well as electron-deficient aromatic aldehydes. A heterocyclic aldehyde (entry 13, Table 2) also resulted to good conversion into 1,4-dihydropyridines. Aliphatic aldehydes such as formaldehyde and acetaldehyde can also be used for the synthesis of 1,4-dihydropyridines with similar success.

After successfully synthesizing a series of Hantzsch esters in excellent yields under ultrasonic irradiation, we turned our attention towards the synthesis of polyhydroquinoline derivatives via unsymmetrical Hantzsch reaction under ultrasonic irradiation conditions (Scheme 2).

We carried out the four-component coupling reaction of a cyclic 1,3-diketone, an aldehyde, an acetoacetatic ester, and ammonium acetate in aqueous micelles. The reaction was catalyzed by PTSA and was sonicated for 1–3 hours.



Scheme 2

Table 3 Ultrasound-Accelerated Synthesis of Polyhydroquinoline Derivatives[a]

Entry	R	R^1	R^2	R^3	Time (h)	Product	Yield (%)[b]
1	Ph	H	H	OEt	1.5	**5a**	92
2	4-ClC_6H_4	H	H	OEt	1.5	**5b**	91
3	4-MeC_6H_4	H	H	OEt	1.5	**5c**	93
4	4-$MeOC_6H_4$	H	H	OEt	1.5	**5d**	90
5	Ph	Me	Me	OEt	1.5	**5e**	89
6	3-$O_2NC_6H_4$	Me	Me	OEt	1.5	**5f**	93
7	4-HOC_6H_4	Me	Me	OEt	1.5	**5g**	91
8	3-$MeOC_6H_4$	Me	Me	OEt	1.5	**5h**	90
9	1-Naphthyl	Me	Me	OEt	1.5	**5i**	92
10	4-$O_2NC_6H_4$	Me	Me	OEt	1.5	**5k**	92
11	4-HO-3-$MeOC_6H_3$	Me	Me	OEt	1.5	**5l**	90
12	4-$MeOC_6H_3CH{=}CH$	Me	Me	OMe	1.5	**5m**	93
13	4-MeC_6H_4	Me	Me	OMe	1.5	**5n**	91
14	4-EtO-3-HOC_6H_3	Me	Me	O*t*-Bu	1.5	**5o**	88
15	4-HOC_6H_4	Me	Me	O*t*-Bu	1.5	**5p**	89
16	3-$MeOC_6H_4$	Me	Me	Me	3	**5q**	75
17	4-$Me_2NC_6H_4$	Me	Me	Me	3	**5r**	72

[a] Reaction conditions: aldehyde (1 mmol), acetoacetic ester/acetyl acetone (1 mmol), cyclic β-diketone (1 mmol), NH_4OAc (1 mmol), PTSA (10 mol%), ultrasound.
[b] Isolated yield.

Using the optimized reaction conditions,[9] we synthesized a number of polyhydroquinoline derivatives and the results are shown in Table 3.

The results of Table 3 clearly indicate the feasibility of four-component unsymmetrical Hantzsch reaction in aqueous micelles. The products were synthesized in excellent yield under ultrasonic irradiation. The method has the ability to tolerate a variety of functional groups such as hydroxy, chloro, nitro, methoxy, and unsaturation. We observed that in the case of acetylacetone the reaction took a longer time to complete and the isolated yields were somewhat lower than corresponding acetoacetic ester.

In conclusion, we have developed an efficient and versatile method for the synthesis of symmetrical and unsymmetrical Hantzsch esters. The reaction is catalyzed by PTSA and has been carried out under ultrasonic irradiation at room temperature. The process has several advantages from economical and environmental points of view such as short reaction time, high yields, and mild reaction conditions.

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(8) **Typical Experimental Procedure for the Synthesis of 1,4-Dihydropyridine Derivatives**
In a 25 mL round-bottomed flask, benzaldehyde (1 mmol), ethyl acetoacetate (2 mmol), NH_4OAc (1 mmol), and PTSA (0.1 mmol) was added. To this an aqueous solution of SDS (3 mL, 0.1 M) was added. The reaction mixture was immersed in an ultrasonic bath and irradiated for 1 h. Then, the reaction mixture was diluted with brine and extracted with EtOAc. The organic layer was dried over anhyd Na_2SO_4 and concentrated to give a crude product. The pure product was obtained by crystallization of the crude material from MeOH; mp 158 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.21 (t, *J* = 7.7 Hz, 6 H), 2.29 (s, 6 H), 4.08 (q, *J* = 7.7 Hz, 4 H), 4.98 (s, 1 H), 6.00 (s, 1 H), 7.01–7.26 (m, 5 H). IR (KBr): 3322, 1676, 1633 cm^{-1}. MS: *m/z* = 330 $[M + H]^+$. Anal. Calcd for $C_{19}H_{23}NO_4$: C, 69.28, H, 7.04, N, 4.25. Found: C, 69.12, H, 6.98, N, 4.14.

(9) **Typical Experimental Procedure for the Synthesis of Polyhydroquinoline Derivatives**
In a 25 mL round-bottomed flask, dimedone (1 mmol), benzaldehyde (1 mmol), ethyl acetoacetate (1 mmol), NH_4OAc (1 mmol), and PTSA (0.1 mmol) was added. To this an aqueous solution of SDS (3 mL, 0.1 M) was added. The reaction mixture was immersed in an ultrasonic bath and irradiated until reaction was complete (TLC monitoring, 1–3 h). The reaction mixture was diluted with brine and extracted with EtOAc. The organic layer was dried over anhyd Na_2SO_4 and concentrated to give a crude product. The pure product was obtained by crystallization from MeOH; mp 203–204 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.94 (s, 3 H), 1.07 (s, 3 H), 1.21 (t, *J* = 7.1 Hz, 3 H), 2.13–2.29 (m, 4 H), 2.35 (s, 3 H), 4.06 (q, *J* = 7.1 Hz, 2 H), 5.07 (s, 1 H), 6.64 (s, 1 H), 7.08–7.13 (m, 1 H), 7.18–7.23 (m, 2 H), 7.28–7.33 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.92, 17.96, 25.84, 28.15, 31.38, 35.33, 39.65, 49.50, 58.52, 104.72, 110.70, 124.74, 126.59, 126.72, 142.41, 145.82, 147.47, 166.24, 194.43. IR (KBr): 3287, 3078, 2963, 1697, 1611 cm^{-1}. MS: *m/z* = 340 $[M + H]^+$. Anal. Calcd for $C_{21}H_{25}NO_3$: C, 74.31, H, 7.42, N, 4.13. Found: C, 74.27, H, 7.39, N, 4.08.