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SECTION 9. Chemistry and chemical technology.

SYNTHESIS OF A NEW CAMPHOR-DERIVED CHIRAL ORGANIC PHOSPHORIC ACID CATALYST AND ITS APPLICATION IN THE HANTZSCH REACTION

Abstract: A new chiral, camphor-derived organic phosphoric acid catalyst, 2-endo-3-endo-dimethylbornane-2,3-diyl phosphate, was synthesized and was successfully used as organocatalyst in the synthesis of optical active 3-ethyl 5-methyl 6-methyl-4-(4-nitrophenyl)-2-(trifluoromethyl)-1,4-dihydropyridine-3,5-dicarboxylate (3), and methyl 2,2,7-trimethyl-5-(4-nitrophenyl)-4-oxo-5,8-dihydro-4H-[1,3]dioxino[4,5-b]pyridine-6-carboxylate (4).

Key words: Hantzsch reaction, dihydropyridine, chiral organocatalysts.

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Introduction

Asymmetric Hantzsch reaction is a useful multicomponent organic reaction that yields optically active 1,4-dihydropyridines, wherein chiral organic catalysts are found to be particularly effective[1]. The main goal in this reaction is to develop catalysts which can effect both chemical and optical yield of the reactions.

Currently there are a number of studies on Hantzsch reaction, many of which are directed at achiral products and mechanistical investigations[2]. Few studies, however, are focused on asymmetric variants of this reaction. There are many derivatives of the Hantzsch products (1,4-dihydropyridines) which found use as drugs in medicine[3-7]. Therefore, the synthesis of optically active dihydropyridines is in demand.

Asymmetric Hantzsch reactions are catalyzed generally by phosphoric acids derived from

TADDOL or BINOL in the literature[8-10]. Evans and Gestwicki made use of this type of catalysts successfully to achieve asymmetric four-component Hantzsch reaction with high enantioselectivities[11]. In this paper, we describe the facile synthesis of a new organic phosphoric acid catalyst and its application in asymmetric Hantzsch reaction.

The synthetic route we followed for the synthesis of chiral organic catalyst 2-endo-3-endo-dimethylbornane-2,3-diyl phosphate is shown in scheme 1. We took optically active (1R)-camphorquinone and reacted it with two equivalent of methyl lithium, subsequent quenching of which with phosphoryl chloride gave chiral phosphoryl chloride **1**. This chiral phosphoryl chloride **1** was hydrolysed next to give chiral phosphoric acid **2**.



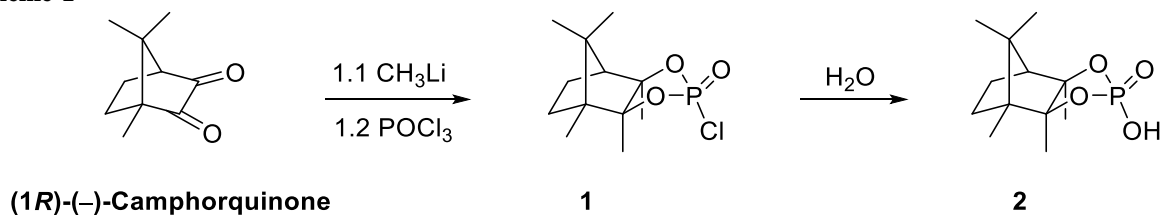
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Scheme-1



Having successfully synthesized our chiral phosphoric acid, we evaluated its activities in the three-component asymmetric Hantzsch reaction to obtain optically active 3-ethyl 5-methyl 6-methyl-4-(4-nitrophenyl)-2-(trifluoromethyl)-1,4-

dihydropyridine-3,5-dicarboxylate (**3**), and methyl 2,2,7-trimethyl-5-(4-nitrophenyl)-4-oxo-5,8-dihydro-4H-[1,3]dioxino[4,5-b]pyridine-6-carboxylate (**4**). The results are summarized in Scheme-2

Scheme-2

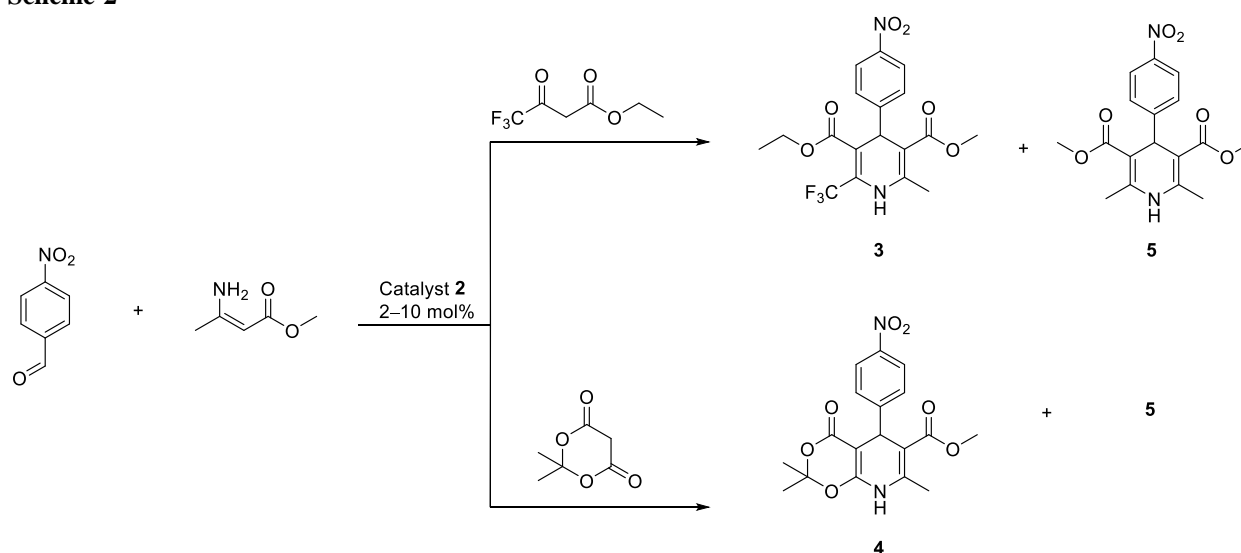


Table 1

Entry	Solvent	Catalyst (mol%)	Yield (%)		ee (%)	
			product (3)	product (4)	product (3)	product (4)
1	toluene	2	88	84	29	36
2	toluene	5	87	84	38	44
3	toluene	10	88	85	41	46
4	ethanol	2	84	82	22	28
5	ethanol	5	83	81	26	34
6	ethanol	10	83	82	31	37
7	acetonitrile	2	90	86	33	41
8	acetonitrile	5	89	87	40	46
9	acetonitrile	10	89	86	42	49

For the synthesis of Hantzsch dihydropyridines (**3** and **4**), we reacted ethyl 4,4,4-trifluoro-3-oxobutanoate and Meldrum's acid with methyl 3-aminocrotonate and 4-nitrobenzaldehyde in the presence of various amounts of catalyst **2**. We tested toluene, ethanol and acetonitrile as the solvents with 2, 5, and 10 mol% catalyst loadings. Acetonitrile was

the best among all, yielding the highest chemical yield and enantioselectivities. In all our efforts we observed formation of the side product **5**, but with trace amounts. At this point, we should note that most previous literature targeting Hantzsch dihydropyridine synthesis yielded a number of side

products that complicated purification and lowered practicality.

Antimicrobial properties of **3** and **4** was investigated comparatively with that of alcohol, furasilin, nitrofungin. We tested golden staphylococci (*St. aureus*), coliforms (*E. coli*), blue-green pus bacillus (*Ps. Aeruginosa*), Candida species mushrooms (*Cand. Albicans*). Synthesized drug candidates have acted in different ways to different microorganisms. Tested compounds killed golden staphylococci (*St. aureus*), coliforms (*E. coli*), blue-green pus bacillus (*Ps. Aeruginosa*) 1:400, 10, 1:800 ratio but Candida 10, 1:400 ratio during 20 min. The study shows that these drugs can be used as antifungal and antibacterial substances.

In conclusion, we have described a practical, facile synthesis of a novel chiral, camphor-derived phosphoric acid catalyst (**2**) which we found useful in affecting asymmetric Hantzsch dihydropyridine synthesis. Both dihydropyridine products showed remarkable antibacterial properties. Our works along these lines are in progress.

Experimental

Melting points are uncorrected and were recorded on SMP 30 apparatus. ¹H NMR and ¹³C NMR spectra were recorded on a 400 spectrophotometer using in DMSO-*d*₆, or CDCl₃ as the solvent. Chemical shifts values are reported in ppm taking tetramethylsilane as the internal standard and J values are given in hertz. The types of signals are indicated by the following letters: s=singlet, d=doublet, t=triplet, m=multiplet. Polarimetric measurements were made by AUTOPOL III automatic polarimeter and reported as follows: $[\alpha]_D^T$ (c in g per 100 ml, solvent). Enantiomeric excess (ee) values of chiral adducts were measured by an HPLC system using a AS-H chiral column (0.46 cm × 25 cm) and AD-H chiral column (0.46 cm × 25 cm). Flash column chromatography (FCC) was performed by using glass columns with flash grade silica gel (70-230 mesh). Reactions were monitored by thin-layer chromatography (TLC) using precoated silica gel plates, visualized by UV light. All organic extracts were dehydrated over oven-dried MgSO₄.

2-endo-3-endo-Dimethylbornane-2,3-diyl chlorophosphate(1)

A solution of (1*R*)-camphorquinone (2 g, 12 mmol) in dry THF (40 ml) under dry N₂, was stirred at -78 °C and to this added methyllithium in diethyl ether (23 mL; 1.6M) dropwise over a period of 20 min. The mixture was stirred at -78 °C for 1 h and then allowed to warm to ambient temperature. Then, the mixture was cooled again to -78 °C and 1.37 ml POCl₃ was added and the mixture was stirred for 3 h at this temperature, which was later allowed to warm to ambient temperature. The reaction mixture

was washed with saturated NaCl (50 ml) and then water (50 ml). Evaporation of the solvent gave an oil which was purified by chromatography eluting with ethyl acetate and hexane (5:1, MerckSilica Gel 60 F₂₅₄, 0,070-0.230 mm). This gave compound 2-endo-3-endo-dimethylbornane-2,3-diyl chlorophosphate (2.9g, 87%); $[\alpha]_D^T = -5.6$ (c 2.5, DCM); m.p.=120.

¹H NMR (CDCl₃-*d*₁, δ, ppm): 0.81 (s, 3H, CH₃), 0.83 (s, 3H, CH₃), 1.14 (s, 3H, CH₃), 1.25 (s, 3H, CH₃), 1.26 (s, 3H, CH₃), 1.28-1.34 (m, *J*=5.2 Hz, 4H, 2CH₂), 1.59 (t, *J*=7.1 Hz, 1H, CH).

¹³C NMR (100MHz, CDCl₃-*d*₁): 82.32, 80.53, 56.81, 53.23, 48.27, 30.85, 24.28, 23.29, 23.19, 22.78, 21.45, 9.89

2-endo-3-endo-Dimethylbornane-2,3-diyl phosphate(2)

A mixture 0.53g (1.9 mmol) of 2-endo-3-endo-dimethylbornane-2,3-diyl chlorophosphate, 19 ml distilled water and 19 ml THF was heated under reflux for 24 h. The progress of reaction was monitored by TLC. After the completion of reaction, the combined organic extracts were washed, dried and evaporated to give white crystal compound (0.49g, 94%); $[\alpha]_D^T = -4.98$ (c 2.5, DCM); m.p.=148.

¹H NMR (CDCl₃-*d*₁, δ, ppm): 0.87 (s, 3H, CH₃), 0.88 (s, 3H, CH₃), 1.27 (s, 3H, CH₃), 1.33 (s, 3H, CH₃), 1.43 (s, 3H, CH₃), 0.98-1.19 (m, *J*=5.4 Hz, 4H, 2CH₂), 1.61 (t, *J*=7.3 Hz, 1H, CH).

¹³C NMR (100MHz, CDCl₃-*d*₁): 94.46, 92.43, 54.23, 52.19, 47.91, 29.96, 24.04, 22.53, 21.70, 20.73, 18.93, 9.42

3-Ethyl 5-methyl 6-methyl-4-(4-nitrophenyl)-2-(trifluoromethyl)-1,4-dihydropyridine-3,5-dicarboxylate (3):

Methyl 3-aminocrotonate (0.115 g, 1 mmol), trifluoroacetate ester (0.146g, 1 mmol), *p*-nitrobenzaldehyde (0.151 g, 1 mmol), 0.002 equiv (2mmol%) catalyst (2-endo-3-endo-dimethylbornane-2,3-diyl phosphate) and toluene (1 ml) were charged in a round bottom flask. Then the reaction mixture was stirred at room temperature for 4 hours. The progress of reaction was monitored by TLC. After the completion of reaction, the product of reaction purified by chromatography eluting with ethyl acetate and hexane (1:6, MerckSilica Gel 60 F₂₅₄, 0,070-0.230 mm). This gave compound 3-ethyl 5-methyl 6-methyl-4-(4-nitrophenyl)-2-(trifluoromethyl)-1,4-dihydropyridine-3,5-dicarboxylate (3) (0.36g, 88%); ee=29 %; m.p.=238.

¹H NMR (CDCl₃-*d*₁, δ, ppm): 0.87(t, *J*=5.6, 3H, CH₃); 2.27 (s, 3H, CH₃); 3.21 (s, 3H, OCH₃); 4.15 (q, *J*=6.9, 2H, CH₂); 4.71 (s, H, CH); 5.06 (s, 1H, NH); 7.27-7.92 (dd, *J*=8.6, *J*=8.6, 4H, Ar).

¹³C NMR (100MHz, CDCl₃-*d*₁): 173.02, 166.98, 150.11, 147.48, 146.42, 143.57, 128.27, 123.75, 122.70, 102.75, 100.12, 50.54, 49.27, 42.20, 20.05, 16.41

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Methyl 2,2,7-trimethyl-5-(4-nitrophenyl)-4-oxo-5,8-dihydro-4H-[1,3]dioxino[4,5-b]pyridine-6-carboxylate (4): Methyl 3-aminocrotonate (0.115 g, 1 mmol), Meldrum's acid (0.114 g, 1 mmol), p-nitrobenzaldehyde (0.151 g, 1 mmol), 0.002 equiv (2mmol%) catalyst (2-endo-3-endo-dimethylbornane-2,3-diyl phosphate) and toluene (1 ml) were charged in a round bottom flask. Then the reaction mixture was stirred at room temperature for 3 hours. The progress of reaction was monitored by TLC. After the completion of reaction, the product of reaction purified by chromatography eluting with ethyl acetate and hexane (1:6, MerckSilica Gel 60 F₂₅₄, 0,070-0.230 mm). This gave compound 3-ethyl 5-methyl 6-methyl-4-(4-nitrophenyl)-2-(trifluoromethyl)-1,4-dihydropyridin-3,5-dicarboxylate (3) (0.31g, 84%); ee=36 %; m.p=246.

¹HNMR (CDCl₃-d₁, δ, ppm): 1.57-1.60(s, 6H, 2CH₃); 2.29 (s, 3H, CH₃); 3.57 (s, 3H, OCH₃); 5.03 (s, H, CH); 8.78 (s, 1H, NH); 7.29-8.01 (dd, J=8.7, J=8.7 4H, Ar).

¹³C NMR (100MHz, CDCl₃-d₁): 171.04, 167.14, 161.86, 150.85, 148.23, 145.61, 128.66, 123.32, 112.39, 106.08, 66.88, 51.61, 39.63, 28.62, 28.33, 19.37.

Dimethyl 2,6-dimethyl-4-(4-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate(5)

This compound is the side product of the reactions given in table 2. (0.13-0.14g, 4%).

¹HNMR (CDCl₃-d₁, δ, ppm): 2.29 (s, 6H, 2CH₃); 3.57 (s, 3H, CH₃); 5.03 (s, H, CH); 5.83 (s, 1H, NH); 7.35-8.02 (dd, j=8.7; 8.7, 4H, Ar). ¹³C NMR(100MHz, CDCl₃-d₁): 166.57, 153.16, 145.33, 143.38, 127.12, 122.50, 101.95, 50.00, 38.91, 18.60.

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