SOI: 1.1/TAS DOI: 10.15863/TAS

International Scientific Journal
Theoretical & Applied Science

p-ISSN: 2308-4944 (print) **e-ISSN:** 2409-0085 (online)

Year: 2018 **Issue:** 06 **Volume:** 62

Published: 25.06.2018 **http://T-Science.org**

SECTION 9. Chemistry and chemical technology.

Abel Magerramov
Academician, rector,
Baku State University

Idris Ahmedov
Ph.D Professor of Chemistry,
Baku State University

Malahat Kurbanova
Ph.D, Professor of Chemistry,
Baku State University

Elnur Huseyinov
Ph.D, The scientific researcher,
Baku State University
elnur.huseynov85@gmail.com

SYNTHESİS OF A NEW CAMPHOR-DERİVED CHİRAL ORGANİC PHOSPHORİC ACİD CATALYST AND İTS APPLİCATİON İN THE HANTZSCH REACTİON

***Abstract**: A new chiral, camphor-derived organic phosphoric acid catalyst, 2-endo-3-endo-dimethylbornane-2,3-diyl phosphate, was synthesized and was succesfully 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.*

***Language**: English*

***Citation**: Magerramov A, Ahmedov I, Gurbanova M, Huseyinov E (2018) SYNTHESİS OF A NEW CAMPHOR-DERİVED CHİRAL ORGANİC PHOSPHORİC ACİD CATALYST AND İTS APPLİCATİON İN THE HANTZSCH REACTİON. ISJ Theoretical & Applied Science, 06 (62): 48-51.*

***Soi**: http://s-o-i.org/1.1/TAS-06-62-11 **Doi**: crossref https://dx.doi.org/10.15863/TAS.2018.06.62.11*

Introduction

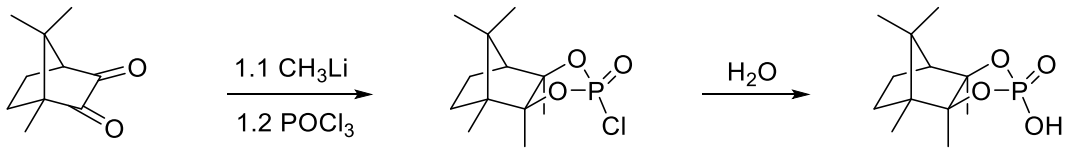
Asymmetric Hantzsch reaction is a useful multicomponent organic reaction that yields optically active 1,4-dihydropyridines , wherein chiral organic catalysts are found to be particularly effective[1]. The main goal in this reaction is to develop catalysts which can effect both chemical and optical yield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

Scheme-1



(1*R*)-(–)-Camphorquinone **1** **2**

Having succesfully 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

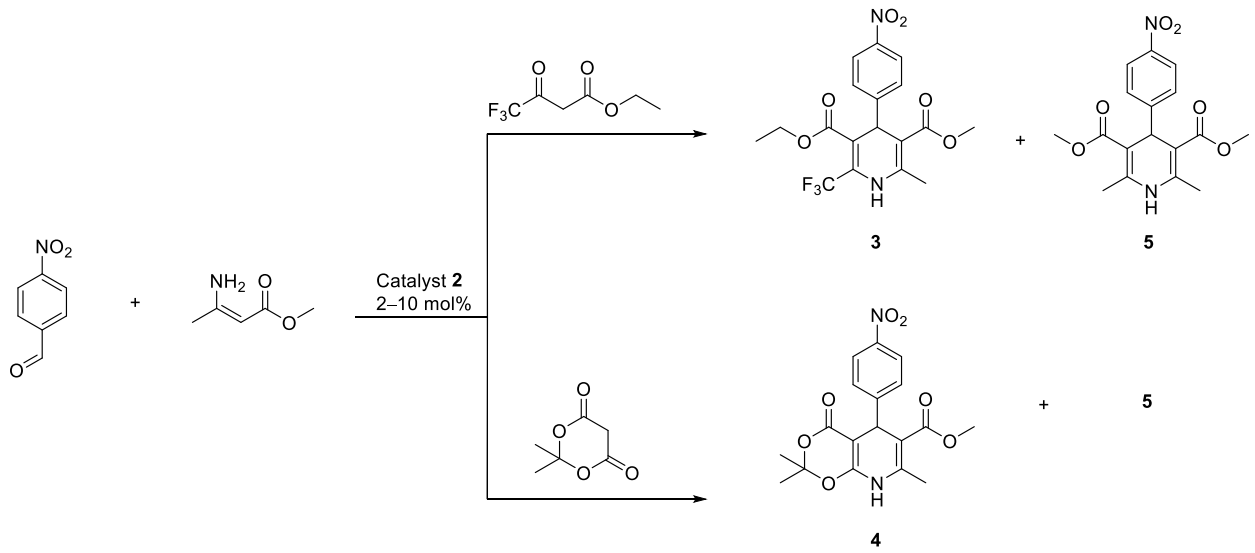


Table 1

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 targetting 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. Aeruginoza*), 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. Aeruginoza*) 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, campor-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. ^{1}H NMR and ^{13}C NMR spectra ware recorded on a 400 spectrophotometr using in DMSO-*d6*, or $CDCl_3$ as the solvent. Chemical shifts values are reported in ppm taking tetramethylsilane as the internal standart 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 polarimetr 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 chromotography (FCC) was performed by using glass columns with flash grade silica gel (70-230 mesh). Reactions were monitored by thin-layer chromotography (TLC) using precoated silica gel plates, visualized by UV light. All organic extracts were dehydrated over oven-dried $MgSO_4$.

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 N_2, 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 °Cfor 1 h and then allowed to warm to ambient temperature. Then, the mixture was cooled again to –78 °C and 1.37 ml $POCl_3$ was added and the mixture was stirred for 3 h at this temparature, which was later allowed to warm to ambient temperature. The reaction mixture waswashed 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 F_{254}, 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.

^{1}HNMR ($CDCl_3$-d_1, δ, ppm):0.81 (s, 3H, CH_3), 0.83 (s, 3H, CH_3), 1.14 (s, 3H, CH_3), 1.25 (s, 3H, CH_3),1.26 (s, 3H, CH_3), 1.28-1.34 (m, *J*=5.2 Hz , 4H, $2CH_2$), 1.59 (t, *J*=7.1 Hz,1H, CH).

^{13}C NMR (100MHz, $CDCl_3$-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 distillated 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.

^{1}HNMR ($CDCl_3$-d_1, δ, ppm):0.87 (s, 3H, CH_3), 0.88 (s, 3H, CH_3), 1.27 (s, 3H, CH_3), 1.33 (s, 3H, CH_3),1.43 (s, 3H, CH_3), 0.98-1.19 (m, *J*=5.4 Hz , 4H, $2CH_2$), 1.61 (t, *J*=7.3 Hz,1H, CH).

^{13}C NMR (100MHz, $CDCl_3$-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 F_{254}, 0,070-0.230 mm). This gave compound 3-etyl 5-metyl 6-metyl-4-(4-nitrophenyl)-2-(triflüorometyl)-1,4-dihiydropiridin-3,5-dicarboksilat (3) (0.36g, 88%); ee=29 %; m.p=238.

^{1}HNMR ($CDCl_3$-d_1, δ, ppm): 0.87(t, *J* =5.6, 3H, CH_3); 2.27 (s, 3H, CH_3); 3.21 (s, 3H, OCH_3); 4.15 (q,*J*=6.9, 2H,CH_2); 4.71 (s, H, CH); 5.06 (s, 1H, NH); 7.27-7.92 (dd, *J*=8.6, *J*=8.6, 4H, Ar).

^{13}C NMR (100MHz, $CDCl_3$-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

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 F_{254}, 0,070-0.230 mm). This gave compound 3-etyl 5-metyl 6-metyl-4-(4-nitrophenyl)-2-(triflüorometyl)-1,4-dihiydropiridin-3,5-dicarboksilat (3) (0.31g, 84%); ee=36 %; m.p=246.

^{1}HNMR ($CDCl_3$-d_1, δ, ppm): 1.57-1.60(s, 6H, $2CH_3$); 2.29 (s, 3H, CH_3); 3.57 (s, 3H, OCH_3); 5.03 (s, H, CH); 8.78 (s, 1H, NH); 7.29-8.01 (dd, *J* =8.7, *J* =8.7 4H, Ar).

^{13}C NMR (100MHz, $CDCl_3$-d_1): 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%) .

^{1}HNMR ($CDCl_3$-d_1, δ, ppm): 2.29 (s, 6H, $2CH_3$); 3.57 (s, 3H, CH_3); 5,03 (s, H, CH); 5.83 (s, 1H, NH); 7.35-8.02 (dd, j=8.7; 8.7, 4H, Ar). ^{13}C NMR(100MHz, $CDCl_3$-d_1): 166.57, 153.16, 145.33, 143.38, 127.12, 122.50, 101.95, 50.00, 38.91, 18.60.

Acknowledgements

This work was supported by the Science Development Foundation under the President of the Republic of Azerbaijan – **Grant №EİF-Mob-2-2013-4(10)-13/11/4**

References:

1. Magerramov A.M., Guseynov E.Z., Kyrbanova M.M., Akhmedov I.M., Tan'eli.Dzh. (2016) Modifitsirovannaya reaktsiya Gancha v prisutsviikhiral'nykh organicheskikh katalizatorov // Zhurnal Organicheskoy khimii, 2016, T, 52, c. 713–717.
2. Mielcarek J., Grobelny P., Szamburska O. (2005) The effect of beta-carotene on the photostability of nisoldipine // Methods Find ExpClinPharmacol, 2005, V, 27 (3), p. 167–171.
3. Pattan S.R., Parate A.N., Sirisha K., Achaiah G. and Reddy V.M. (2007) Chemical and Pharmacological significance of 1,4-dihydropyridines- A Review // Indian Drugs, 2007, V, 44(2), p. 73-90.
4. Löhn M., Muzzulini U., Essin K. et al. (2002) Cilnidipine is a novel slow-acting blocker of vascular L-type calcium channels that does not target protein kinase C // J. Hypertens,2002, V, 20 (5), p. 885–93.
5. Bretzelb R.G., Bollen C.C., Maester E., Federlin K.F. (1992) An Efficient Synthesis of Polyhydroquinoline derivatives // Drugs Future, 1992, V, 17, p. 465-468.
6. Briukhanov V.M., Zverev-laf Elkin V.I. (1994) The effect of calcium antagonists on the development of inflammatory edema in rats // ExpClinPharmacol, 1994, V, 57, p. 47-49.
7. Barrios V., Escobar C., Navarro A., Barrios L., Navarro-Cid J., Calderón A. (2006) Lercanidipine is an effective and well tolerated antihypertensive drug regardless the cardiovascular risk profile: The LAURA study// International journal of clinical practice, 2006, V, 60 (11), p. 1364–70.
8. Brian J. B., Richard E., Mary F. M., Khalid R. , Malcolm S. (1995) Synthesis of camphor based chiral crown ethers and their interactions with amino acid derivatives // J.Chem. Soc. Perkin trans, 1995, V, 2, p. 1909-14.
9. Arnaund V and Andre B.C. (2006) Enantioselective Cyclopropanation with TADDOL-Derived Phosphate Ligands // Adv.Synth.Catal, 2006, V, 348, p. 2363-2370.
10. Dieter S., Albert K.B., Hans-Ulrich B., Arkadius P., Christof S., Ralf W and Bernd W.S. (2012) Preparation and Characterization of New C2-and C1- Symmetric Nitrogen, Oxygen, Phosphorus, and Sulfur Derivatives and Analogs of TANDOL // Helvetica Chimica Acta, 2012, V, 95, p.1303-1324.
11. Christopher G., Evans and Jason E. Gestwicki. (2009) Enantioselective Organocatalytic Hantzsch Synthesis of Polyhydroquinolines // Org. Lett, 2009, V, 11 (14), p. 2957-2959.