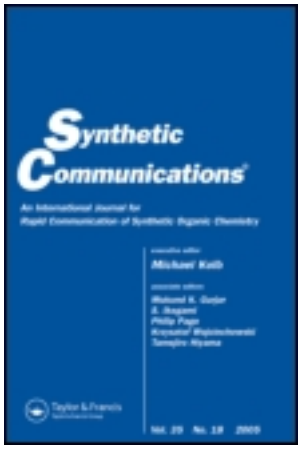

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Microwave-Assisted Synthesis of Chiral Nopinane-Annelated Pyridines by Condensation of Pinocarvone Oxime with Enamines Promoted by $FeCl_3$ and $CuCl_2$

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MICROWAVE-ASSISTED SYNTHESIS OF CHIRAL NOPINANE-ANNELATED PYRIDINES BY CONDENSATION OF PINOCARVONE OXIME WITH ENAMINES PROMOTED BY $FeCl_3$ AND $CuCl_2$

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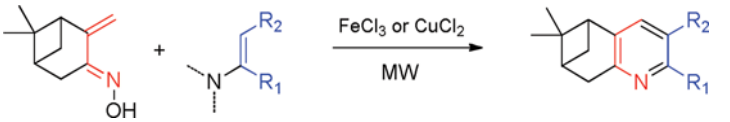
GRAPHICAL ABSTRACT



Abstract *Reaction of pinocarvone oxime with enamines and $FeCl_3$ or $CuCl_2$ resulted in annulation of nopinane carbon frame with pyridine and regioselective formation of chiral nopinane-annelated pyridines in 20–39% yields. Chemical structure of the pyridine derivatives were proved by precise NMR study.*

Keywords Emanimes; microwave; oxime; pyridines; terpenoids; transition metals

INTRODUCTION

Pyridine nucleus is one of the most important simple azaheterocycles, forming a great variety of biologically active molecules. Chiral pyridine derivatives are of special interest as ligands for coordination chemistry.[1] Natural monoterpene pinane-type hydrocarbons are among the most available primary sources of chirality for enantioselective syntheses, so pinane-type derivatives are of special interest for chiral auxiliary design, especially for syntheses of ligands used in chiral complexes of transition metals. Chiral ligands whose molecules contain both pyridine moiety and pinane carbon frame are prospective chiral auxiliaries.[2]

There are a lot of different synthetic methods for construction of pyridine derivatives, some of them being used for building chiral hybrids containing pyridine and

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pinane frames: Kröhnke pyridine synthesis,[3–5] Friedländer quinoline synthesis,[6] Michael addition of the enolate and subsequent cyclization,[7] Michael addition of the 1,3-dicarbonyl compound to α,β-unsaturated oximes, and subsequent cyclization.[8] The use of α,β-unsaturated oximes for preparation of substituted pyridines is very convenient because the substrate molecule (α,β-unsaturated oximes) contains nitrogen atom, which is transformed to the pyridine nitrogen, so there is no need to use an additional reagent as a source of nitrogen in the pyridine synthesis.

Condensation of α,β-unsaturated oximes with enamines is known,[9] but the method described was successfully applied only to quite simple pyridines and is useless for syntheses of complex molecules because of the rather drastic conditions.

Now we report a new method for designing chiral pyridine-pinane hybrides by condensation of pinocarvone oxime with enamines.

RESULTS AND DISCUSSION

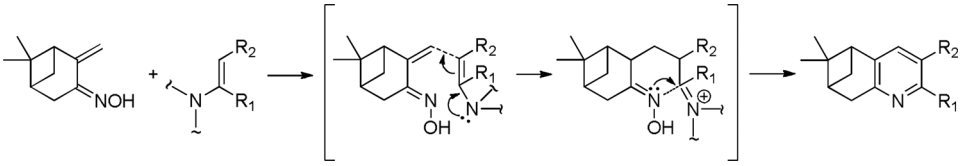
Pinocarvone oxime seems to be the most available stable nitrogen-containing derivative of the pinane series and is the most accessible pinane-type α,β-unsaturated oxime, which is easily synthesized by two-step, one-pot preparation involving nitrosochlorination–dehydrochlorination of natural occurring α-pinene.[10]

We tested condensation of pinocarvone oxime with enamines under wide range of the reaction conditions. The reaction was found to be catalyzed by a number of Lewis acids ($FeCl_3 \cdot 6H_2O$, $AlCl_3$, $BF_3 \cdot OEt_2$, $CuCl_2 \cdot 2H_2O$) and does not take place without a catalyst or in the presence of compounds such as $Al(O\text{-}i\text{-}Pr)_3$. The best results (degree of the starting material conversion, isolation yields) were obtained when $FeCl_3 \cdot 6H_2O$ was used to promote condensation. Although anhydrous $FeCl_3$ also catalyzes the reaction, $FeCl_3 \cdot 6H_2O$ provides greater yields. Different solvents can be used (benzene, toluene, xylenes, pyridine, morpholine, dimethylformamide [DMF]), but in our hands the best results were achieved when the reaction was carried out without a solvent. The condensation requires heating up to 120–130 °C, and microwave irradiation is the best choice to afford moderate yield over a period of 10–30 min, whereas ordinary heating requires a longer time to provide full conversion of the starting material, resulting in poor yields of the desired products.

The condensation technique is quite simple: a mixture of starting material (pinocarvone oxime and appropriate enamine 1:2 mol/mol) and $FeCl_3 \cdot 6H_2O$ (5–10 mol%) was heated at vigorous stirring in a sealed vessel for a certain period of time. After cooling to room temperature the mixture was treated with aqueous ammonia, and the reaction products were extracted with an organic solvent followed by column chromatography of the crude product to afford pure fused pyridines. All the pinane-pyridine derivatives synthesized are yellowish viscous oils or solids that are stable at ambient conditions.

Precise analysis of ^1H and ^{13}C NMR spectra (long-range proton–proton and proton–carbon couplings) of the substituted derivatives **9, 10, 11,** and **13** prove the following scheme of the condensation (Scheme 1), providing the C-1 enamine carbon to become α-carbon of the fused pyridine (tetrahydroquinoline) moiety.

The condensation seems to be a multistage process, with the precise role of catalyst being unclear. The catalyst ($FeCl_3$, $AlCl_3$, $BF_3 \cdot OEt_2$, $CuCl_2$) is capable of forming complexes both with substrate (α,β-unsaturated oxime) and reagents (emanine) as



Scheme 1. General reaction scheme.

well as with all the intermediates having donor heteroatomic functions. Probably the catalyst activates the substrate by complexation, because in absence of an enamine, self-condensation of α,β-unsaturated oxime occurs in the presence of $FeCl_3$, resulted in a tar-like product.

The yields of the desired products are not high (Scheme 2), probably due to (a) limited stability of the starting material under the reaction conditions and (b) the fused pyridines formed are not inert under the reaction conditions and can act as substrates for further condensation. In certain cases the next step condensation product can be isolated, as it was shown for the pair oxime **1**–enamine **14**. Thus, when the most active catalyst was used ($FeCl_3 \cdot 6H_2O$), double condensation C_2-symmetric product **15** was isolated, whereas less active catalyst ($CuCl_2 \cdot 2H_2O$) provided isolation of the primary condensation product **16**.

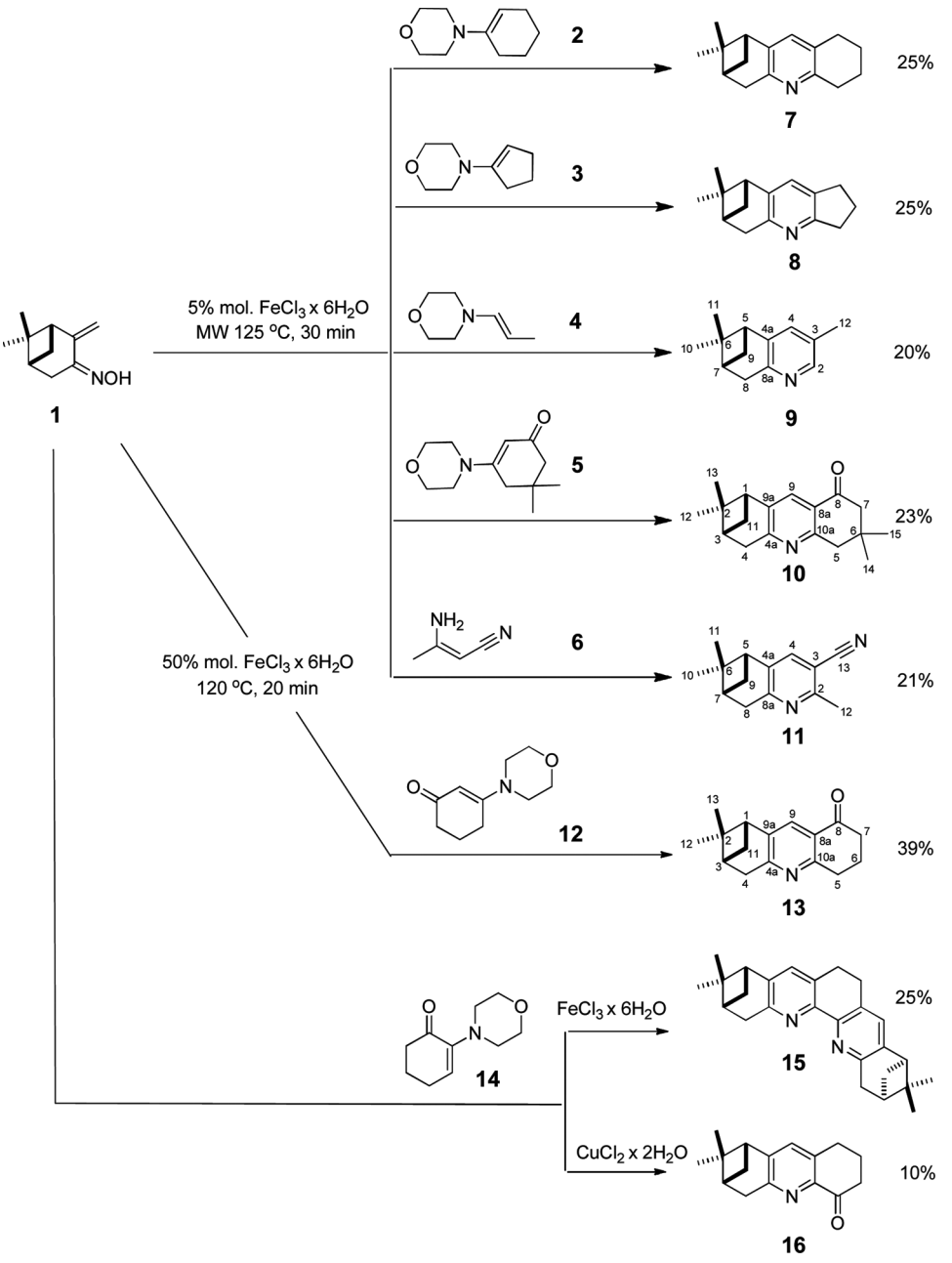
In spite of moderate yields, the condensation seems to be a short and very convenient way to a variety of pinane-pyridine hybrids including previously published molecules. Thus, compounds **7** and **8** were prepared earlier by three-step syntheses from pinocarvone oxime,[11] whereas compounds **15** and **16** were synthesized by four- and six-step procedures correspondingly from pinocarvone.[12]

EXPERIMENTAL

All the solvents used were freshly distilled. (+)-Pinocarvone (*E*)-oxime with mp 124 °C (from light petroleum) (lit.[13] mp 132–134 °C from hexane for a sample with unknown optical purity) and $[\alpha]_D^{23} + 14$ (*c* 0.85, $CHCl_3$) were prepared according to nitrosochlorination–dehydrochlorination[13,14] by addition of a solution of NOCl in CH_2Cl_2 to (−)-α-pinene (W290203, Kosher) followed by treatment with Et_3N.[10] Enamines **2**,[15] **3**,[15] **5**,[16] **12**,[16] and **14**[17] were prepared according to the published method by heating the corresponding ketones with morpholine in benzene under azeotropic distillation. Enamine **4** was prepared from propanal, morpholine, and anhydrous K_2CO_3 at cooling as described in Ref.[18] 3-Aminocrotononitrile (diacetonitrile) **6** was prepared by treatment of acetonitrile with Na.[19]

Microwave-assisted syntheses were carried out in a single-mode microwave reactor Discover™ System S-Class (CEM corp., USA) using a special 35-ml reaction vessel.

Merck silica gel 60 (0.063–0.100 mm) was used for preparative column chromatography. Analytical thin-layer chromatography (TLC) was carried out on a ready-to-use plates (SiO_2 on Al foil). Visualization of components was achieved by sprinkling the plates with visualization solutions followed by heating to 100–150 °C. The visualization solutions were (a) $FeCl_3 \cdot 6H_2O$ (10 g) + 95% aq. EtOH (100 mL), (b)



Scheme 2. Synthesis of chiral nopinane-annelated pyridines. (The numbering scheme is given for NMR interpretation.)

ninhydrin (0.5 g) + glacial AcOH (3 mL) + 95% aq. EtOH (100 mL), and (c) Dragendorff's reagent [mixture of a solution of $BiONO_3$ (0.85 g) + glacial AcOH (10 mL) + of H_2O (40 mL) and a solution of KI (8.0 g) + H_2O (20 mL)].

NMR spectra were recorded at 25–28 °C for solutions (*c* 20–40 mg/mL) on a Bruker DRX-500 spectrometer (500.13 MHz for ^{1}H, 125.75 MHz for ^{13}C) locked to the deuterium resonance of the solvent. The chemical shifts were calculated relative to the solvent signals ($CDCl_3$) used as the internal standard: δ_C 76.90 ppm and δ_H 7.24 ppm. Signal assignment was made using *J* modulated ^{13}C NMR spectra (proton-noise-decoupling, the opposite phases for the signals of the atoms with the odd and even numbers of the attached protons, tuning to the constant $J = 135$ Hz) and 2D NMR spectra: (1) homonuclear $^{1}H-^{1}H$ correlation, (2) heteronuclear $^{13}C-^{1}H$ correlation at the direct spin-spin coupling constants ($J = 135$ Hz), and (3) heteronuclear $^{13}C-^{1}H$ correlation at the long-range spin-spin coupling constants ($J = 10$ Hz). Carbon–proton spin-spin coupling constants were taken from proton-coupled ^{13}C NMR spectra.

Infrared (IR) spectra were recorded on a Bruker Tensor 27 spectrophotometer for solutions in KBr (*c* 0.25%). Ultraviolet (UV) spectra were recorded on an Agilent 8453 instrument. Optical rotation was measured with a PolAAr 3005 polarimeter at 589 nm and are expressed in $deg \cdot cm^3 \cdot g^{-1} \cdot dm^{-1}$ and *c* is expressed in $g/100\,cm^3$. Melting points were determined by differential scanning calorimetry using a Netzsch STA 409 instrument. Mass spectra were obtained on a Termo electron DFS mass spectrometer (electron impact ionization, EI, 70 eV).

General Procedure

Mixture of (+)-pinocarvone oxime **1** (165 mg, 1 mmol), enamine **2**–**6** (2 mmol), and $FeCl_3 \cdot 6H_2O$ (20 mg, 0.07 mmol) was stirred at 130 °C under microwave irradiation for 25 min. The starting power was set to 80 W and it was automatically adjusted to maintain the preselected temperature 130 °C. The mixture was cooled to room temperature, diluted with CH_2Cl_2 (40 mL), and poured into saturated aqueous NH_3 (20 mL). The reaction products were extracted with CH_2Cl_2 (2×30 mL). The combined organic extract was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to leave the crude product, which was then purified by column chromatography (SiO_2, light petroleum–EtOAc, 40:1→5:1) to give corresponding substituted pyridines **7** (25% yield), **8** (25%), **9** (20%), **10** (23%), or **11** (21%).

Preparation of (1*R*,3*R*)-2,2-Dimethyl-1,2,3,4,6,7-hexahydro-1,3-methanoacridin-8(5*H*)-one (13)

Mixture of (+)-pinocarvone oxime **1** (330 mg, 2 mmol), 3-morpholino cyclohex-2-enone **12** (362 mg, 2 mmol), and $FeCl_3 \cdot 6H_2O$ (270 mg, 1 mmol) was stirred 20 min at 120 °C. The mixture was cooled to room temperature and diluted with CH_2Cl_2 (40 mL). Reaction mixture was poured into saturated aqueous NH_3 solution. The reaction products were extracted with CH_2Cl_2 (2×30 mL). The combined organic extract was dried over Na_2SO_4, filtered, and concentrated at reduced pressure to leave the crude product, which was then purified by column chromatography (SiO_2, petroleum ether–EtOAc, 10:1→5:1) to give the title substituted pyridine **13** in 39% yield.

Preparation of (2*R*,4*R*,9*R*,11*R*)-3,3,10,10-Tetramethyl-1,2,3,4,6,7,9,10,11,12-decahydro-2,4,9,11-dimethanodibenzo[*b,j*][1,10]phenanthroline (15)

Mixture of (+)-pinocarvone oxime **1** (330 mg, 2 mmol), 2-morpholino cyclohex-2-enone **14** (362 mg, 2 mmol), and $FeCl_3 \cdot 6H_2O$ (300 mg, 1.1 mmol) was stirred at 120 °C until the mixture solidified (ca. 15 min). The mixture was cooled to room temperature, treated with CH_2Cl_2 (40 mL), and poured with vigorous stirring into a solution of tartaric acid (3 g) in saturated aqueous NH_3 (40 mL). The mixture was 1 h at room temperature in a closed flask, the organic phase was separated, and the aqueous solution was extracted with CH_2Cl_2 (2×30 mL). The combined organic extract was dried over Na_2SO_4, filtered, and concentrated at reduced pressure to leave the crude product, which was then purified by column chromatography (SiO_2, petroleum ether–EtOAc, 10:1→5:1) to give the title substituted dihydrophenantroline **15** in 25% yield.

Preparation of (1*R*,3*R*)-2,2-Dimethyl-1,2,3,4,7,8-hexahydro-1,3-methanoacridin-5(6*H*)-one (16)

A mixture of (+)-pinocarvone oxime **1** (330 mg, 2 mmol), 2-morpholino cyclohex-2-enone **14** (362 mg, 2 mmol), and $CuCl_2 \cdot 2H_2O$ (171 mg, 1 mmol) was stirred at 120 °C for 20 min. The mixture was cooled to room temperature, treated with CH_2Cl_2 (40 mL), and poured with vigorous stirring into saturated aqueous NH_3 (20 mL). The organic phase was separated, and the aqueous solution was extracted with CH_2Cl_2 (2×30 mL). The combined organic extract was dried over Na_2SO_4, filtered, and concentrated at reduced pressure to leave the crude product, which was then purified by column chromatography (SiO_2, petroleum ether–EtOAc, 40:1→5:1) to give the title substituted pyridine **16** in 10% yield.

CONCLUSION

In conclusion, a new method for syntheses of pinane-fused pyridine derivatives was developed involving easily available pinocarvone oxime as starting material in the condensation reaction under transition-metal ion catalysis with microwave promotion. The method seems to be reasonable choice as compared to known methods because of its simplicity and the possibility of one-step preparation of certain fused pyridines.

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SUPPLEMENTAL MATERIAL

Supplemental data for this article can be accessed on the publisher's website.

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