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Synthesis of chiral nopinane annelated 3-methyl-1-aryl-1*H*-pyrazolo[3,4-*b*]pyridines by condensation of pinocarvone oxime with 1-aryl-1*H*-pyrazol-5-amines

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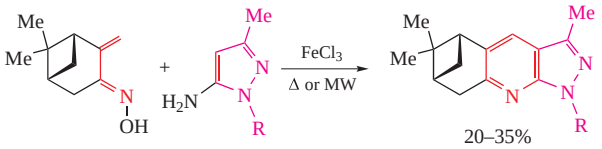
Chiral 1*H*-pyrazolo[3,4-*b*]pyridines fused with nopinane frame were obtained by $FeCl_3$-catalyzed assembling of pinocarvone oxime and 1-aryl-1*H*-pyrazol-5-amines. Chemical structures of new compounds were solved by NMR spectroscopy and confirmed by quantum chemical calculations and X-ray crystallography.

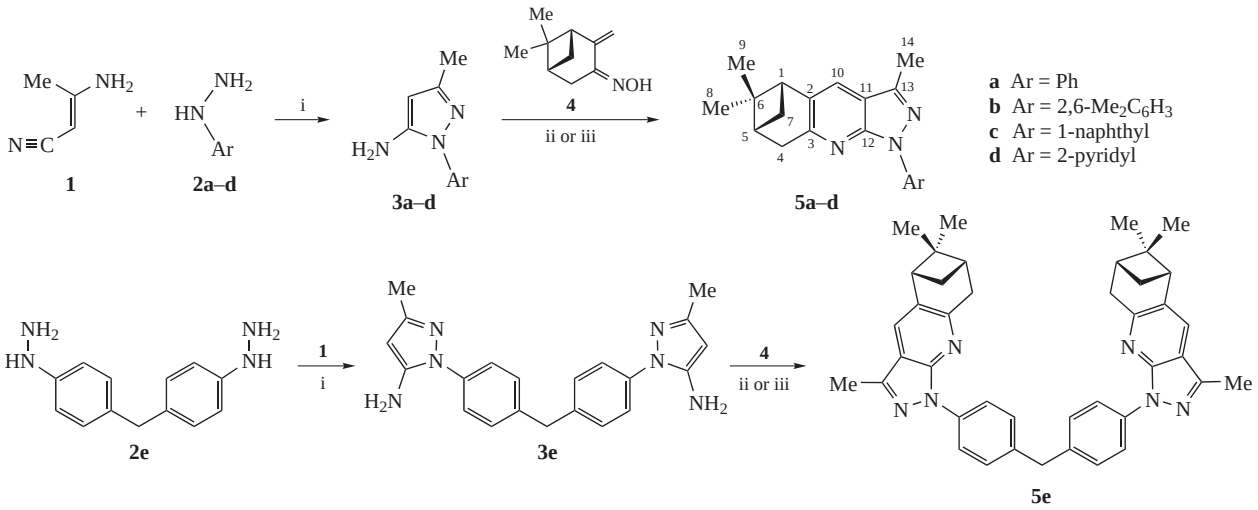


Hybrid molecules containing fragments of pinane and pyridine are of great interest as chiral polydentate ligands and starting compounds in the synthesis of chiral polyfunctional compounds.[1,2] Pyrazolo[3,4-*b*]pyridines are used for the preparation of various photoluminescent molecules[3–6] including those useful for fluorescence imaging of living cells,[7] for mercury detection with fluorescent sensors,[8] for mechanistic study of association with lysozyme[9] and bovin serum albumin.[10] Pyrazolo[3,4-*b*]pyridines exhibit a wide range of biological activity[11–13] including anxiolytic-like activity[14] and are inhibitors of p38α MAP kinase,[15] adenosine receptors,[16] glycogen synthase kinase-3,[17] kinase B-RafV600E.[18] Therefore, it is of interest to synthesize new representatives of pyrazolo[3,4-*b*]pyridines.

Annelated nopinane derivatives can be obtained by condensation of pinocarvone oxime with β-keto esters[19] or with enamines derived from carbonyl or 1,2-dicarbonyl compounds.[20,21] Reaction of α,β-unsaturated carbonyl compounds with 5-aminopyrazoles is the main method for the synthesis of pyrazolo[3,4-*b*]pyridines.[22] Since 5-aminopyrazoles can be considered as heterocyclic analogues of enamines, we decided to test them in condensation with pinocarvone oxime to access new fused heterocyclic systems. Herein, we report on the syntheses of new pyrazolo[3,4-*b*]pyridines annelated with nopinane frame (Scheme 1).

Substituted aminopyrazoles **3a–e** were prepared by condensation of the corresponding arylhydrazines **2a–e** with a *ca.* 1:1 mixture of *E*- and *Z*-isomers of 3-aminobut-2-enenitrile **1**[23,24] (see Scheme 1). Compounds **3a**[25] and **3d**[26] are the known ones, while pyrazoles **3b**, **3c**, and **3e** are new. Various aminopyrazoles can serve as precursors for fused pyridines,[22] however reaction of 1-aryl-1*H*-pyrazol-5-amines with α,β-unsaturated oximes has not been studied yet.

Solvent-free reaction of pinocarvone oxime **4** [prepared by nitrosochlorination–dehydrochlorination of (–)-α-pinene[27]] with 1-aryl-1*H*-pyrazol-5-amines **3a–e** and $FeCl_3 \cdot 6H_2O$ at 120 °C afforded the corresponding fused 3-methyl-1-aryl-1*H*-pyrazolo-[3,4-*b*]pyridines **5a–e** in moderate (20–35%) isolated yields (see



Scheme 1 *Reagents and conditions:* i, Pr^{i}OH, HCl aq., reflux, 2 h; ii, $FeCl_3 \cdot 6H_2O$, MeCN, 20 °C, 30 min, then 120 °C, 1 h; iii, MW, 180 °C, 1 h.

Scheme 1, the numbering of the pinane moiety corresponds to the numbering pattern of the pinane frame[28]).

Microwave irradiation is widely used to promote syntheses of fused pyrazolo[3,4-*b*]pyridines.[29–32] Hence, we decided to apply microwave irradiation to the reaction between compounds **4** and **3a**–**e**. Monitoring the reaction mixture proved that destruction of pinocarvone oxime **4** was faster than consumption of aminopyrazoles **3a**–**e**. At the same time, excess of pinocarvone oxime **4** does not affect the yields of products **5a**–**e** (no significant difference between 2- or 4-fold excess of pinocarvone oxime was found). Additives of water scavengers (anhydrous sodium sulfate, silica gel, molecular sieves) did not improve the yields, moreover, they were found to speed up resinification of the reaction mixtures, probably because of local overheating due to additional heterogeneity.[33,34] Under the microwave irradiation, addition of $FeCl_3 \cdot 6H_2O$ or addition of an inert diluent (toluene, xylene) also did not increase the yields. In total, for the solvent-free microwave syntheses of 3-methyl-1-aryl-1*H*-pyrazolo[3,4-*b*]-pyridines **5a**–**e**, the temperature of ~180 °C was a reasonable compromise: at lower temperatures the reactions were slow, whereas at higher temperatures fast destruction of the reactants occurred. Moderate isolated yields are probably caused by formation of stable complexes between products **5a**–**e** and Fe-salts, which cannot be destroyed during the isolation.

Structures of nopinane annelated derivatives **5a**–**e** were proved by NMR spectra based on typical chemical shifts and spin–spin couplings in nopinane annelated pyridines.[19–21] Precise analysis of 2D NMR spectra of the compounds synthesized allowed us to conclude that compounds **5a**–**e** belong to the same structural and configuration series. However, calculated (empirical additive schemes) ^{13}C chemical shifts in compounds **5a**–**e** (Table S1, Online Supplementary Materials) are in poor agreement with the experimental ones. The same was observed for the starting 1-aryl-1*H*-pyrazol-5-amines **3a**–**e**. Therefore, we carried out accurate NMR shift calculations for *N*-(pyridin-2-yl) derivatives **3d** and **5d** to check whether the proposed structures were correct.

Geometry optimization and NMR chemical shifts at the DFT level were obtained using ORCA program system[35] by utilizing Gauge Including Atomic Orbitals (GIAOs, London orbitals) with the hybrid exchange-correlation functional PBE0 and basis set aug-cc-pVDZ, which was found to be an appropriate compromise in calculation of ^{13}C chemical shifts for aromatic compounds.[36] Solvent influence was taken into consideration using the Polarizable Continuum Model (PCM).[37] Chemical shifts were recomputed relative to $SiMe_4$, whose chemical shifts were calculated by the same method. Spin–spin couplings were calculated by Dalton[38] using DFT (PBE0/aug-cc-pVDZ). The calculated chemical shifts for compounds **3d** and **5d** with satisfactory mean absolute errors (*mae*) of 1.32 and 1.42 ppm, respectively, are given in Table S2 and Table S3 (see Online Supplementary Materials). Calculated spin–spin couplings of the carbon atoms in compound **5d** are in acceptable agreement with experimental values (Table S4) supporting the presence of 1*H*-pyrazolo[3,4-*b*]pyridine moiety in the molecules.

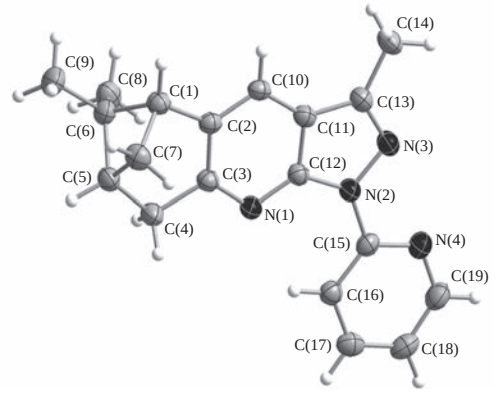


Figure 1 Thermal ellipsoid plot of **5d** in the crystal structure showing 50% probability ellipsoids.

Crystallization of pyridine derivative **5d** from light petroleum brought about well-shaped crystals suitable for single crystal X-ray diffractometry. Absorption corrections were applied with the use of the SADABS program in non-centrosymmetric diffraction class 2.[39] The crystal structures were solved by direct methods and refined by full-matrix least squares techniques with the use of the SHELXTL package[40] and OLEX2 GUI.[41] Atomic thermal displacement parameters for non-hydrogen atoms were refined anisotropically. According to single crystal X-ray investigation, molecule of the pyridine derivative **5d** in the crystal structure (Figure 1)† has both bond lengths and bond angles of typical values. Careful analysis of the packing by CrystalExplorer v.17.5[42] supported by Tonto v.17.04[43] using promolecular Hirshfeld analysis and CE-HF/3-21G interaction energy models[44] allowed us to identify some specific π–π and ^{Ar}H–π intermolecular interactions in the crystal structure (see Online Supplementary Materials).

Thus, all the compounds **5a**–**e**, prepared from pinocavone oxime **4** and 1-aryl-1*H*-pyrazol-5-amines **3a**–**e**, are really nopinone annelated 3-methyl-1-aryl-1*H*-pyrazolo[3,4-*b*]pyridines and belong to the new family of chiral heterocyclic compounds with the 3,6,6-trimethyl-5,6,7,8-tetrahydro-1*H*-5,7-methanopyrazolo[3,4-*b*]-quinoline scaffold. All the fused 1*H*-pyrazolo[3,4-*b*]pyridines synthesized are white or yellowish solids or viscous oils which are stable at room teperature on the open air for months. We anticipate of using them as ligands, fluorescent labels and biologically active substance.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2018.11.006.

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† *Crystal data for* **5d**: $C_{19}H_{20}N_4$, M = 304.39, monoclinic, space group $P12_11$ at T = 200 K, a = 6.4706(6), b = 11.7781(11) and c = 10.4010(9) Å, β = 98.524(3)°, Z = 2, Z' = 1, V = 783.92(12) Å^3, d_{calc} = 1.290 g cm^{-3}, $\mu(CuK\alpha)_{calc}$ = 0.616 mm^{-1}, 8.596° < 2θ < 135.968° for data collection; index ranges $-7 \leqslant h \leqslant 7$, $-14 \leqslant k \leqslant 13$, $-12 \leqslant l \leqslant 12$; 10835 reflections collected, 2795 reflections independent, R_{int} = 0.0230, R_σ = 0.0232. Data/restraints/parameters 2795/1/212. GOOF on F^2 1.032; final R indexes for $I \geqslant 2\sigma(I)$: R_1 = 0.0256, wR_2 = 0.0645, for all data: R_1 = 0.0257, wR_2 = = 0.0646, largest diff. peak/hole: 0.14/–0.13 e Å^{-3}. Flack parameter –0.06(9).

CCDC 1584003 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

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