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Microwave-assisted synthesis of *N*,*N*-bis-(2-pyridylmethyl)amine derivatives. Useful ligands in coordination chemistry

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Abstract—Microwave-assisted synthesis of the ligands *N*,*N*-bis-(2-pyridylmethyl)amine (BMPA), *N*-(methylpropanoate)-*N*,*N*-bis-(2-pyridylmethyl)amine (MPBMPA), *N*-(propanamide)-*N*,*N*-bis-(2-pyridylmethyl)amine (PABMPA), PNBMPA (*N*-(3-propionitrile)-*N*,*N*-bis-(2-pyridylmethyl)amine), *N*-(3-aminopropyl)-*N*,*N*-bis-(2-pyridylmethyl)amine (APBMPA), and lithium *N*-(proponoate)-*N*,*N*-bis-(2-pyridylmethyl)amine (LiPBMPA) are reported. High yields and short reaction time were obtained for condensation and Michael addition.

The literature is profuse on describing metal complexes.[1] Ruthenium(II) complexes with terpyridine have been reported to catalyze the reduction of CO_2. Ruthenium(II) *N*,*N*-bis-(2-pyridylmethyl)amine (BMPA) complexes have been reported as well.[2] Mononuclear non-heme iron complexes are important in metabolic reactions and complexes with BMPA and derivatives could be used as models for activated oxygen and perform the functionalization of organic substrates, for example, hydrocarbon oxidation.[3] The reactions of polyhydroxy-organic compounds with [Fe(BMPA)Cl_3 give a product isolated which in the presence of diiron cores in metalloproteins presents enzymatic activity.[4] The *N*,*N*-bis-(2-pyridylmethyl)amine (BMPA) ligand, in particular, is a versatile chelating ligand. BMPA is a bipodal trident ligand, sometimes called BPA or DPA in the literature.[5] It has been reported that BMPA can be transformed in a tripodal tetradentate ligand when submitted to an alkylation reaction.[6] These ligands have, at least, one aliphatic and two aromatic nitrogen atoms that are able to coordinate to the metallic center. Beyond these donor atoms, the ligand PABMPA, *N*-(propanamide)-*N*,*N*-bis-(2-pyridylmethyl)amine, has the amide group that can coordinate to the metal center, while the ligand MPBMPA (*N*-(methylpropanoate)-*N*,*N*-bis-(2-pyridylmethyl)amine) has the ester group, which is unlikely to coordinate due to its weak coordination capacity. *N*-(3-aminopropyl)-*N*,*N*-bis-(2-pyridylmethyl)amine (APBMPA) also is very used.[7] Metal (BMPA) complexes of many transition metals have been vastly reported in the literature;[8,9] for example, most importantly, Cu(BMPA) complexes show a good activity in the hydrolysis of phosphate esters and DNA plasmids.[10] Very recently, two groups reported the use of BMPA conjugates with carbohydrates[11] and peptide[12] for radioimaging with ^{99m}Tc.

Microwave activation as a non-conventional energy source has become a very popular and useful technology in organic chemistry.[13] Numerous organic reactions such as acylation and alkylation reactions, aromatic and nucleophilic substitutions, condensations, cycloadditions, protection and deprotection reactions, esterifications and transesterifications, heterocyclizations, rearrangements, organometallic reactions, oxidations, and reductions assisted by microwave heating have been performed and reviewed in articles[14] and books.[15]

Our group has been expanding the use of microwave technology to other areas including oxidation, and in the present paper we present an interesting protocol to obtain ligands by microwave heating. The synthesis of some ligands, BMPA, PABMPA, MPBMPA, APBMPA,

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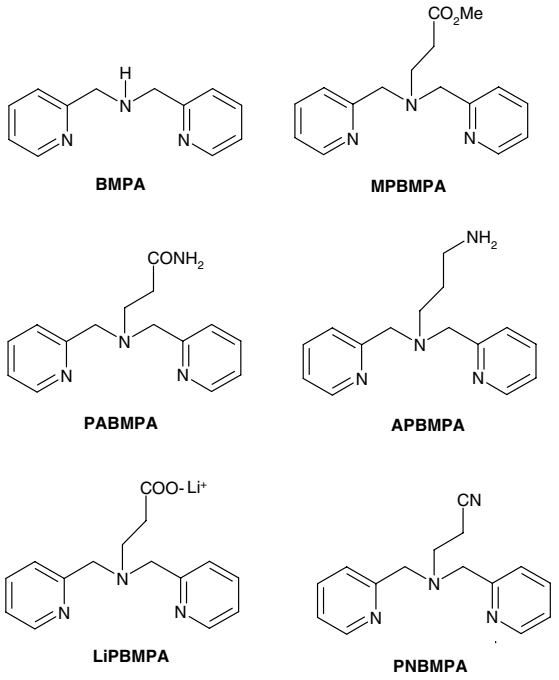


Figure 1. The ligands described in the present work.

PNBMPA, and LiPBMPA (Fig. 1) was carried out more efficiently than the traditional way, utilizing microwave irradiation in a monomode type reactor.[16]

The ligand BMPA was synthesized from 2-pyridinecarboxaldehyde and 2-pyridylmethylamine, in methanol, with irradiation of 150 W for 7 min; the desired imine was reduced using $NaBH_4$ with the same irradiation for 15 min.[17] The usual work-up afforded BMPA in a good isolated yield. The other ligands were obtained by Michael addition on BMPA with high yields (Scheme 1, Table 1).[18]

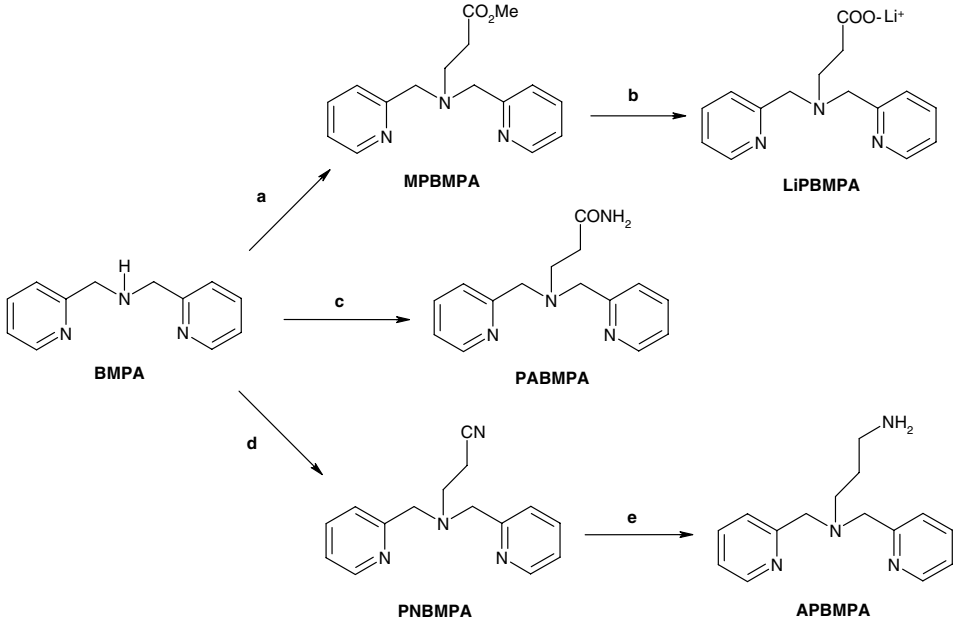
Table 1. Michael addition of the BMPA with some olefins[a]

Entry	Product	Time (min)	Yield[b] (%)
1	PABMPA	80	97
2	MPBMPA	40	95
3	PNBMPA	30	98

[a] Conditions: BMPA (5 mmol), olefin (10 mmol), and methanol (5 mL).
[b] Isolated yields.

The reaction of BMPA with acrylamide in methanol for 40 min under irradiation of 260 W furnished PABMPA. The reaction of BMPA with methylacrylate and the same irradiation reaction for 80 min yielded MPBMPA. The synthesis of APBMPA was undertaken using BMPA and acrylonitrile under irradiation for 30 min which yielded *N*-(3-propionitrile)-*N*,*N*-bis-(2-pyridylmethyl)amine (PNBMPA). This compound was reduced as described in the literature[19] affording APBMPA with a 90% yield. The known compounds were analyzed by IR, ^1H NMR, and ^{13}C NMR and compared with the literature.[3] The new ligand lithium *N*-(proponoate)-*N*,*N*-bis-(2-pyridylmethyl)amine (LiPBMPA), a salt of the MPBMPA, was also obtained. The reaction of the MPBMPA and lithium hydroxide, in methanol, under irradiation of 170 W for 20 min furnished LiPBMPA in a 95% yield. This compound was analyzed using IR, ^1H NMR, and ^{13}C NMR.[20]

The reaction of BMPA and acrylamide (Table 1, entry 1) was satisfactory yielding PABMPA with 97% after filtration of acrylamide. The eluate was stored in a freezer for few hours and then filtered and washed with hexane affording pure PABMPA. Microwave-assisted synthesis of MPBMPA (Table 1, entry 2) was faster than in ordinary thermal conditions. For example, at room temperature this reaction took one week[3] and under reflux took 10 h.[7] The purification has been done by only washing



Scheme 1. Reagents and conditions: (a) methylacrylate, MeOH, 260 W, 80 min, 95%; (b) LiOH, MeOH, 150 W, 30 min, 95%; (c) acrylamide, MeOH, 260 W, 40 min, 97%; (d) acrylonitrile, MeOH, 260 W, 30 min, 98%; (e) Ni-Ra, $NaBH_4$, 90%.

the mixture with hexane. The Michael addition of acrylonitrile on BMPA furnished PNBMPA (Table 1, entry 3) with an excellent yield in few minutes, in comparison with the literature that utilized 72 h under reflux,[19] the mixture was washed with hexane yielding 98%. The novel salt LiPBMPA was also obtained in the microwave-assisted reaction with a high yield without further purification.[20]

In summary, the main advantage of microwave-assisted production of the title ligands is the shorter reaction times and an easier work-up. The other outstanding advantage is the economy of solvent in these reactions, each equivalent of reagents was used 1 mL of methanol. All reactions were successful and it has been a full conversion in your products and simple purifications were obtained. The ligands have been used in the synthesis of different metal(complexes) in our research group.[3,21]

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16. We have used a monomode microwave CEM Discover, see more details in www.cem.com.
17. *Microwave-assisted synthesis of BMPA*: In a 10 mL pyrex-balloon, 2-pyridinecarboxaldehyde (5 mmol) and 2-pyridylmethylamine (5 mmol) in MeOH (5 mL) were irradiated at 150 W for 7 min; $NaBH_4$ (5 mmol) was added and the mixture was irradiated at 150 W for 30 min. After the usual work-up, the product was obtained in 80% yield as a brown oil.
18. *Microwave-assisted synthesis of PABMPA, MPBMPA, and PNBMPA*: In a 10 mL pyrex-ballon, BMPA (5 mmol) and olefin (15 mmol) in MeOH (5 mL) were irradiated at 260 W (time see Table 1). After the mixture was washed with hexane (4 times) and the solvent was eliminated to furnish (yields see Table 1) the compounds as orange oils.
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20. *Microwave-assisted synthesis of LiPBMPA*: In a 10 mL pyrex-ballon, MPBPA (5 mmol) and lithium hydroxide (15 mmol) in MeOH (5 mL) were irradiated at 170 W for 20 min. After the solvent was eliminated and dichloromethane was poured, the excess of lithium hydroxide was precipitated, filtered and the solvent eliminated to yield the product with 95% as a brown oil. IR cm^{-1} 3060, 1595, 1476, 1435, 1384. ^1H NMR (CD_3OD) δ 2.5 (t, 2H), 2.9 (t, 2H), 3.8 (s, 4H), 7.3 (td, 2H), 7.6 (d, 2H), 7.8 (td, 2H), 8.4 (2H); ^{13}C NMR (CD_3OD) δ 36.5, 53.0, 60.7, 123.7, 124.6, 138.7, 146.9, 160.7, 180.9.
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