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Microwave-assisted synthesis of azepines *via* nucleophilic aromatic substitution

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Abstract: A novel and efficient route has been developed to afford dipyridoazepine derivatives from primary amines and 3,3′-(*Z*)-ethene-1,2-diylbis(4-chloropyridine). The procedure based on a double nucleophilic aromatic substitution provides a valuable synthetic tool for the synthesis of dipyridoazepines. The reaction proceeds without catalyst, under microwave irradiation conditions.

Keywords: azepines; heterocycles; nucleophilic aromatic substitution; transition metal-free conditions; microwave irradiation.

INTRODUCTION

Iminostilbene (5*H*-dibenz[*b*,*f*]azepine, **1**) is tricyclic heterocycle (Fig. 1). Derivatives of this scaffold have been reported to exhibit various biological activities, including antioxidant[1] and anticancer activity.[2] 5*H*-Dibenz[*b*,*f*]azepine is important structural element for the registered anticonvulsant drug carbamazepine (**2**)[3] and the tricyclic antidepressant (TCA) opipramol (**3**).[4] Strong interest in the synthesis of 5*H*-dibenz[*b*,*f*]azepine derivatives still exists as well as their applications in medicinal chemistry.[5] Methods based on the double *N*-arylation reaction of primary amines are of great significance since they provide a route to a variety of *N*-substituted iminostilbenes.[6]

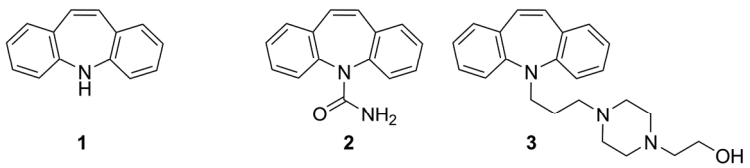

Fig. 1. Iminostilbene and tricyclic 5*H*-dibenz[*b*,*f*]azepine drugs.

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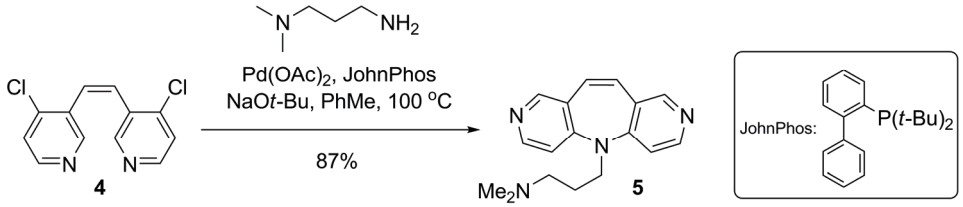
Recently, an efficient synthetic procedure for the synthesis of 5*H*-dipyrido-[4,3-*b*:3′,4′-*f*]azepine compounds *via* a double palladium-catalyzed amination–cyclization reaction (Scheme 1) was disclosed.[7] The synthesized compounds were found to exhibit interesting *in vitro* antibacterial activities.[8]



Scheme 1. Pd-catalyzed synthesis of 5*H*-dipyrido[4,3-*b*:3′,4′-*f*]azepine compounds.

The electron-deficient nature of γ-halopyridines enables the reaction with different nucleophiles in a nucleophilic aromatic substitution reaction (S_NAr) *via* an addition–elimination mechanism. The displacement of chloride from 4-chloro-pyridine by primary amines has been well studied and shown to be an efficient approach for the synthesis of 4-(alkylamino)pyridine derivatives. However, high temperatures and prolonged reaction times are usually required.[9]

In continuation of ongoing studies of biologically active tricyclic hetero-cycles,[7,8,10] herein the synthesis of 5*H*-dipyrido[4,3-*b*:3′,4′-*f*]azepines using the double S_NAr reaction of 3,3′-(*Z*)-ethene-1,2-diylbis(4-chloropyridine) with pri-mary aliphatic amines under microwave irradiation is reported.

EXPERIMENTAL

Instrumentation

Microwave reactions were performed in a Biotage Initiator 2.5 microwave reactor. The IR spectra were recorded on a Perkin–Elmer FTIR 1725X spectrophotometer. The NMR spectra were recorded on a Bruker Ultrashield Avance III spectrometer (500 MHz) using TMS as the internal standard. The chemical shifts are expressed in ppm (δ) values and coupling constants (J) in Hz. The ESI–MS (HRMS) spectra were acquired on an Agilent Technologies 1200 Series instrument equipped with a Zorbax Eclipse Plus C18 column and a DAD detector in combination with a 6210 time-of-flight LC/MS instrument operated in the positive ion mode. The samples were dissolved in MeOH. Thin-layer chromatography was performed on pre-coated Merck silica gel 60 F254 and Merck RP-18 F254 plates. The solution MeOH (NH_3) stands for a combination MeOH/NH_3 (aq.) in 9:1 volume ratio.

Chemistry

General procedure for azepine synthesis. A reaction tube, containing a stirring bar, was charged with 3,3′-(*Z*)-ethene-1,2-diylbis(4-chloropyridine), *N*-methylpyrrolidone (NMP) and amine (10 equiv.), and capped. After pre-stirring at room temperature for 2 min, the reaction mixture was heated to 150 °C and stirred at same temperature for 3 h under microwave conditions. The products were purified by preparative column chromatography: SiO_2, CH_2Cl_2/MeOH(NH_3) = 9:1.

N,N-*Dimethyl-5*H-*dipyrido[4,3*-b:*3′,4′*-f*]azepine-5-propanamine (**5**)*.[7] Following the general procedure, a mixture of 3,3′-(*Z*)-ethene-1,2-diylbis(4-chloropyridine) (20 mg, 0.080 mmol), *N*,*N*-dimethylpropane-1,3-diamine (100 μL, 0.80 mmol), and *N*-methyl-2-pyrrolidone (0.5 mL) was stirred at 150 °C for 24 h or for 3 h under microwave conditions. Yield: 14 mg, 61 %.

*5-[3-(Morpholin-4-yl)propyl]-5*H-*dipyrido[4,3*-b:*3′,4′*-f*]azepine (**6**)*.[7] Following the general procedure, a mixture of 3,3′-(*Z*)-ethene-1,2-diylbis(4-chloropyridine) (20 mg, 0.080 mmol), *N*-(3-aminopropyl)morpholine (90 μL, 0.80 mmol), and *N*-methyl-2-pyrrolidone (0.5 mL) was stirred at 150 °C for 24 h or for 3 h under microwave conditions. Yield: 16 mg, 62 %.

N,N-*Dimethyl-5*H-*dipyrido[4,3*-b:*3′,4′*-f*]azepine-5-ethanamine (**7**)*. Following the general procedure, a mixture of 3,3′-(*Z*)-ethene-1,2-diylbis(4-chloropyridine) (20 mg, 0.080 mmol), *N*,*N*-dimethylethane-1,2-diamine (75 μL, 0.80 mmol), and *N*-methyl-2-pyrrolidone (0.5 mL) was stirred at 150 °C for 24 h or for 3 h under microwave conditions. Yield: 12 mg, 56 %.

*5*H-*Dipyrido[4,3*-b:*3′,4′*-f*]azepine-5-propanol (**8**)*. Following the general procedure, a mixture of 3,3′-(*Z*)-ethene-1,2-diylbis(4-chloropyridine) (20 mg, 0.080 mmol), 3-(dimethylamino)propan-1-ol (60 μL, 0.80 mmol), and *N*-methyl-2-pyrrolidone (0.5 mL) was stirred at 150 °C for 24 h or for 3 h under microwave conditions. Yield: 9 mg, 45 %.

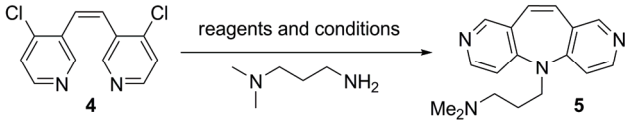
The characterization data for compounds **5**–**8** are given in the Supplementary material to this paper.

RESULTS AND DISCUSSION

Chemistry

The previously reported method[7] for the synthesis of *N*,*N*-dimethyl-*5H*--dipyrido[4,3-*b*:3′,4′-*f*]azepine-5-propanamine (**5**) (Scheme 1, Table I, entry 1) is simple and efficient. Nevertheless, the use of palladium as a catalyst makes it an expensive procedure. In order to simplify and to re-examine the reaction mechanism, an experiment was performed that focused on Pd-free conditions. In the absence of $Pd(OAc)_2$, ligand and base, the reaction of stilbene **4** and *N*,*N*--dimethylpropane-1,3-diamine in PhMe did not occur at 100 °C (Table I, entry 2), which strongly supported the earlier conclusion[7] that palladium really is needed for the formation of the product. Next, an attempt was made to optimize the reaction of stilbene **4** with *N*,*N*-dimethylpropane-1,3-diamine under S_NAr reaction conditions in order to define the reaction parameters that could possibly result in comparable yield to that given by the Pd-catalyzed method. Since the S_NAr reaction of 4-chloropyridine and primary amines is often performed at elevated temperatures, toluene was replaced with *N*-methylpyrrolidone (NMP), a solvent with a higher boiling point. When the reaction temperature was elevated to 150 °C, the azepine **5** was obtained in moderate yield (Table I, entry 4). The same reaction in NMP at 100 °C did not occur thus confirming that elevated temperatures are necessary for the formation of the desired product (Table I, entry 3). Finally, microwave irradiation was applied in order to shorten the reaction time. Performing the reaction in a microwave reactor for 3 h at 150 °C, resulted in azepine **5** in 61 % yield (Table I, entry 5).

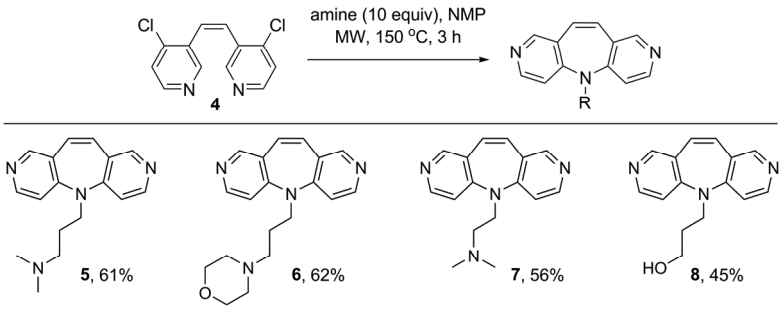
Table I. Synthesis of **5** under various conditions



Entry	Solvent	*t* / °C	Pd-catalyzed	MW	Time, h	Yield, %
1[a]	PhMe	100	+	–	24	87
2[b]	PhMe	100	–	–	24	0
3[b]	NMP	100	–	–	24	0
4[b]	NMP	150	–	–	24	58
5[b]	NMP	150	–	+	3	61

[a]$Pd(OAc)_2$ (5 mol %), JohnPhos (10 mol %), amine (3 equiv), NaO*t*-Bu (2.8 equiv); [b]10 equiv. of amine

The same reaction conditions were then applied for the synthesis of one known and two new azepine derivatives (**6**–**8**, respectively; Scheme 2).



Scheme 2. Synthesis of azepine derivatives.

CONCLUSIONS

In conclusion, the first microwave-assisted synthetic procedure for the formation of 5*H*-dipyrido[4,3-*b*:3′,4′-*f*]azepines based on the double S_NAr reaction of 3,3′-(*Z*)-ethene-1,2-diylbis(4-chloropyridine) with primary aliphatic amines has been reported. This novel methodology was successfully applied for the synthesis of new azepine derivatives. Although the yields were lower than in the previously reported Pd-catalyzed method, this procedure has the great advantage of being transition metal-free, and the time of the reaction was significantly shortened by microwave heating. The next step in the development of methodology will be the replacement of NMP with less toxic solvent, towards a green procedure for the synthesis of azepines.

SUPPLEMENTARY MATERIAL

The characterization data for compounds **5**–**8** are available electronically electronically at the pages of journal website: http://www.shd.org.rs/JSCS/, or from the corresponding author on request.

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ИЗВОД

СИНТЕЗА АЗЕПИНА НУКЛЕОФИЛНОМ АРОМАТИЧНОМ СУПСТИТУЦИЈОМ У МИКРОТАЛАСНИМ РЕАКЦИОНИМ УСЛОВИМА

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Развијена је нова метода за синтезу дипиридоазепинских једињења. Азепински прстен формиран је реакцијом двоструке нуклеофилне ароматичне супституције, реакцијом примарног амина и одговарајућег стилбена. Предност нове методе, у односу на раније описане синтезе азепина, јесте ефикасна синтеза без присуства катализатора на бази прелазних метала. Додатно, реакционо време значајно је смањено применом микроталасних реакционих услова.

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