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2,3-Disubstituted imidazo[1,2-a]pyridines from 2-aminopyridines and acetophenones. Catalyst's efficiency and solid state NMR study.

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Dedicated to Acad. Dimiter Ivanov on the occasion of his 120th birth anniversary

Various sulfonic and carboxylic acids were tested as catalyst in a direct acid catalyzed conversion of 2-aminopyridines and acetophenones into 2,3-disubstituted imidazo[1,2-a]pyridines in order to improve the reaction yield. The most effective catalyst, isoquinoline-5-sulfonic acid, was applied in the reaction between substituted aminopyridines and acetophenones. The efficiency of the catalysts and their influence on the products distribution is discussed. Several chiral acids were also used but no stereoselectivity was induced. NMR study shows existence of two different species in the solid state, differentiation between them was not possible based on the available experimental and theoretical considerations.

Key words: imidazo[1,2-a]pyridines, 2-aryl-3-(1-arylethyl) substituted, 2-aryl-3-(1-arylethenyl) substituted, catalysts, solid state NMR

INTRODUCTION

Imidazo[1,2-a]pyridines are fused nitrogen-bridged heterocyclic compounds exhibiting a broad spectrum of biological activities [1-5]; antimicrobial, anti-inflammatory, antiviral, cytotoxicity, sedative, and many others. These properties are critically dependent on the presence and nature of substituents at positions 2 and 3 of the imidazole ring [6-8], which is demonstrated by the immense efficiency of some formulations on the market like zolpidem, necopidem, saripidem, alpidem, zolimidine, olprinone [9].

The observed pharmacological activities stimulated the development of numerous methods for the preparation of compounds possessing imidazo[1,2-a]pyridine scaffold [10-14]. 2,3-Disubstituted products are most commonly obtained by multicomponent reactions of 2-aminopyridines with aldehydes and alkynes, nitriles, isocyanides, thiocyanates [15-21], including catalytic variants. In the latter, Lewis acids like Zn(II) [22], Cu(II) [23,24], Cu(II)/Fe(III) [25], Fe(III) [26], In(III) [27] salts are found to be highly efficient catalysts. Contrary to aldehydes, ketones are poorly examined, mainly in direct reaction with 2-aminopyridine in a bromine containing ionic liquid [28] or in iodine [29,30] or iodobenzene [31] catalysed conversions.

Recently, we reported on the direct acid catalyzed conversion of 2-aminopyridines and acetophenones into 2,3-disubstituted imidazo[1,2-a]-pyridines [32,33]. Two products were obtained as easy separable mixtures, 2-aryl-3-(1-arylethyl) and 2-aryl-3-(1-arylethenyl)imidazo[1,2-a]pyridines. However, the reaction was not complete; the products were isolated in moderate to high total yields. The aim of the current work is to improve the conversion by finding out more efficient catalysts. Additionally, since the main product is obtained as a racemic mixture, attempts to conduct the reaction stereoselectively have been undertaken. Moreover, solid state NMR spectra of racemic 2-phenyl-3-(1-phenylethyl)imidazo[1,2-a]pyridine reveal two different forms, pointing out to a possible alternative explicit method for enantiomeric purity estimation.

EXPERIMENTAL

Materials, Methods and Apparatus

All reagents were purchased from Aldrich, Merck and Fluka and were used without any further purification. Merck Silica gel 60 (0.040-0.063 mm) was used for flash chromatography purification of the products. The high performance liquid chroma-

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tography (HPLC) enantioseparations were performed on an Agilent 1100 System fitted with diode array detector and manual injector with a 20 μl injection loop. A stainless-steel Nucleosil Chiral-2 column (Macherey-Nagel GmbH & Co. KG, Düren, Germany) was used; 250x4 mm, particle size 5 μm, pore size 100 Å, chiral selector *N*-(3,5-dinitro-benzoyl)-*D*-phenylglycine. The HPLC grade solvents were purchased from Sigma-Aldrich and LabScan.

Synthetic Procedure

All reactions were carried out in constant conditions by following a published protocol [32,33]. Shortly, a mixture of 2-aminopyridine (1 mmol), acetophenone (5 mmol), and catalyst (10 mol %) was refluxed for 1 h; acetophenone 202°C, 4-methylacetophenone 226°C, 4-chloroacetophenone 232°C. The products were purified by flash chromatography on silica gel by using mobile phase with a gradient of polarity from CH_2Cl_2 to acetone:CH_2Cl_2 5:95. The results are summarized on Tables 1 and 2. The characterization of the compounds is published in ref. 32 and 33.

HPLC Analyses

Resolution of **3a** enantiomers by HPLC was performed at 25°C by using hexane/*i*-PrOH 80:20 as eluent: the flow rate was varied and similar separations were achieved: flow rate 0.7 ml/min, retention times: t_R-1 12.18 min, t_R-2 12.84 min; flow rate 1 ml/min, retention times: t_R-1 10.75 min, t_R-2 11.38 min.

NMR Spectra

The NMR spectra were recorded on a Bruker Avance II+ SB 600 spectrometer (Rheinstetten, Germany) at room temperature using standard Bruker library pulse programs [34]. ^{13}C and ^{15}N NMR spectra were recorded at 150.91 and 60.81 MHz. The liquid state ^{15}N chemical shifts were extracted from the heteronuclear multiple bond (long range) correlation and quoted as δ-values in ppm using the unified Ξ scale [35]. For the spectra in solid state α-glycine (43.5 ppm for ^{13}C and 33.4 ppm for ^{15}N) has been employed as external reference [36].

Solid state ^{13}C and ^{15}N NMR spectra were recorded on a 4 mm double resonance CPMAS probehead. The sample was ground softly with a mortar and pestle and then packed tightly in a 4-mm zirconium oxide rotor. The magic angle was adjusted using the ^{79}Br resonance of KBr. Samples were spun at 6.0 kHz for all experiments. Typical radio-frequency (RF) field strengths were 30-65 kHz for ^{13}C and ^{15}N. The Hartmann–Hahn polarization transfer was optimized to a contact time of 2 ms for ^{13}C and 4 ms for ^{15}N with a linear ramp starting at 50%. ^{13}C NMR spectra were obtained using a combination of CP/MAS and total sideband suppression (TOSS) methods (CP/MAS/TOSS) with SPINAL64 proton decoupling. Non Quaternary Suppression (NQS) technique was applied to distinguish unambiguously the quaternary carbons. 128 transients for ^{13}C and 3072 for ^{15}N were accumulated with a 5 s relaxation delay.

Computational Method

Calculations were done on Spartan 08 program package v. 1.2.0 [37]. The structures were first optimized using the MMFF94 field. The geometry optimization was performed with DFT calculations using B3LYP/6-31G(d) basis set. Energies and NMR chemical shifts were calculated from the DFT derived structures, using the SM8 routine for solvation with chloroform [38]. ^{13}C NMR chemical shifts are corrected from an empirical relationship in Spartan for the effects of local chemical environment. Referencing to TMS (0 ppm) and CH_3NO_2 (381.7) is done internally in the Spartan package.

RESULTS AND DISCUSSION

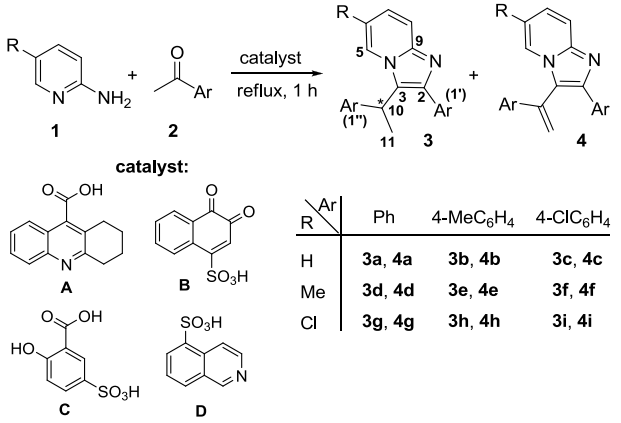
Catalyst's efficiency

In our previous study [32,33], we achieved a direct acid catalyzed conversion of 2-aminopyridines and acetophenones into an easy separable mixtures of 2-aryl-3-(1-arylethyl) (**3**) and 2-aryl-3-(1-arylethenyl)imidazo[1,2-a]pyridines (**4**), shown on Scheme 1. It was found that acetic and trifluoroacetic acid did not catalyze the transformation significantly, while *p*-toluenesulfonic and sulfuric acid led to considerable conversion of 2-aminopyridines. The products were isolated in 42-91% total yields depending on the 2-aminopyridine and acetophenone substituents [33].

A possible way to improve the reaction yield is to find more effective catalysts. Various acids were checked, which can be divided in two general groups: sulfonic acids and carboxylic acids. Their efficiency was first studied on a model reaction, the formation of imidazopyridines **3a** and **4a** by refluxing (202°C) a mixture of 2-aminopyridine and 5-fold excess acetophenone in solventless conditions for 1 h in the presence of 10 mol % catalyst.

As expected, sulfonic acids led to better conversions than carboxylic. Among the latter, the aromatic acids 1-naphthoic acid, 5-methylthiophe-

ne-3-carboxylic acid, and pyridine-3-carboxylic acid catalyzed poorly the transformation, 5-12% total yields, while aliphatic mono- and poly-carboxylic acids were not efficient in general. The best conversion was achieved with 1,2,3,4-tetrahydro-9-acridinecarboxylic acid (**A**, Scheme 1, Table 1). Contrary, the sulfonic acids tested, 3,4-dioxo-3,4-dihydronaphthalene-1-sulfonic acid (**B**), 2-hydroxy-5-sulfobenzoic acid (**C**), and isoquinoline-5-sulfonic acid (**D**), showed moderate to excellent efficiency. As seen on Table 1, the poly-functionalized catalyst **C** showed commensurable efficacy with *p*-toluenesulfonic acid, while isoquinoline sulfonic acid **D** led to almost complete conversion with significant superior of 2-aryl-3-(1-arylethyl) substituted product **3a**.



Scheme 1. Synthesis of imidazo[1,2-a]pyridines **3** and **4**.

Table 1. Formation of imidazo[1,2-a]pyridines **3a** and **4a** in the presence of various catalysts.

Entry	Catalyst	Reaction yield, %*			**3a**:**4a**
		Total	**3a**	**4a**	ratio
1	p-TSA [33]	76	72	4	95:5
2	H_2SO_4 [33]	61	50	11	82:18
3	**A**	34	33	1	97:3
4	**B**	54	47	7	87:13
5	**C**	77	73	4	95:5
6	**D**	94	86	8	92:8

*Isolated yields by flash chromatography.

The most effective catalyst, isoquinoline-5-sulfonic acid **D**, was further applied in the formation of imidazopyridines **3b**-**3i** and **4b**-**4i**. The results are summarized on Table 2. As seen, significant improvement of the reaction yield was achieved in all cases compared to *p*-TSA and sulfuric acid [33]. This effect is most clearly demonstrated on the example of **3c**/**4c** mixture formation (Entry 3), where the products were isolated in 99% total yield when catalyst **D** was used, while *p*-TSA and sulfuric acid led only to 83% and 81% yield, respectively. Similarly to the previous results, the lowest yields were obtained from 5-chloro-2-aminopyridine and 4-methylacetophenone; 71% with **D** (Entry 8), 66% with *p*-TSA and 68% with H_2SO_4.

Table 2. Formation of imidazo[1,2-a]pyridines **3** and **4** in the presence of catalyst **D**.

Entry	Total	Compound **3**		Compound **4**		**3**:**4**
	yield*	Prod	Yield	Prod	Yield	ratio
1	94	**3a**	86	**4a**	8	92:8
2	96	**3b**	80	**4b**	16	82:18
3	99	**3c**	87	**4c**	12	87:13
4	93	**3d**	83	**4d**	10	89:11
5	96	**3e**	80	**4e**	16	83:17
6	92	**3f**	79	**4f**	13	86:14
7	94	**3g**	71	**4g**	23	76:24
8	71	**3h**	41	**4h**	30	58:42
9	87	**3i**	65	**4i**	22	75:25

*Isolated yields by flash chromatography.

From the other side, isoquinoline sulfonic acid **D** accelerated the Ortoleva-King type intermediated transformation better than *p*-toluenesulfonic acid [33], i.e. more like sulfuric acid in terms of **3**:**4** ratio. The latter was most significant when 4-methylacetophenone was used. The reaction output was similar from 2-aminopyridine and 5-methyl-2-aminopyridine, 94% of 82:18 **3a**:**4a** and 96% of 83:17 **3e**:**4e** catalyzed by **D** *vs* 76% of 95:5 **3a**:**4a** and 86% of 90:10 **3e**:**4e** catalyzed by *p*-TSA *vs* 61% of 82:18 **3a**:**4a** and 80% of 86:14 **3e**:**4e** catalyzed by sulfuric acid, while lower yields with significant percentage of vinylated product were observed from 5-chloro-2-aminopyridine, 71% of 58:42 **3h**:**4h** with **D** *vs* 66% of 70:30 **3h**:**4h** with *p*-TSA *vs* 68% of 62:38 **3h**:**4h** with H_2SO_4.

Enantioseparation

The main reaction products, 2-aryl-3-(1-arylethyl)imidazo[1,2-a]pyridines (**3**), are racemic compounds due to the presence of a chiral center in the substituent at position 3. We were interested to achieve the transformation enantioselectively despite the relative low prospects because the chiral center is not sufficiently close to any nitrogen. Several chiral acids were examined in the formation of **3a**. The carboxylic acids (L)-mandelic, (L)-malic, N-Z-(D)-norleucine, N-Boc-(L)-glutamic acid 5-benzyl ester, O,O'-dibenzoyl-(L)-tartaric acid led to insignificant conversion (up to 17%), while **3a**/**4a** were obtained in 85% total yield in 94:6 ratio with (+)-camphor-10-sulfonic acid. Surprisingly, (R)-1,1'-binaphthyl-2,2'-diyl hydrogen phosphate efficiently catalyzed the reaction; the products were isolated in 89% total yield in 96:4 ratio.

The products were analyzed by HPLC on chiral stationary phase. Sufficient separation of the enantiomers was achieved, as illustrated on Fig. 1, but no enantioselectivity was induced with all acids tested. All attempts to separate the enantiomers by salts formation were also unsuccessful.

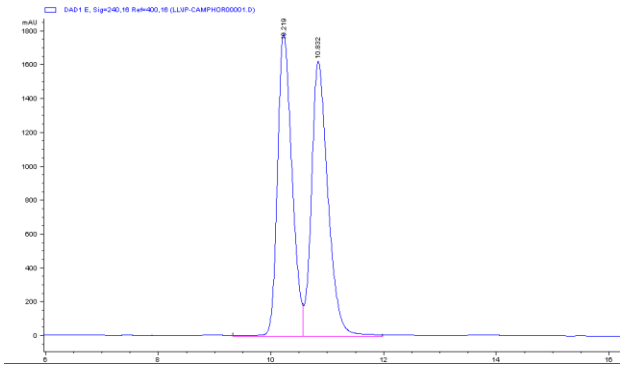


Fig. 1. Resolution of **3a** enantiomers by HPLC; eluent: hexane/*i*-PrOH 80:20; flow rate 1 ml/min; retention times: t_R-1 10.22 min, t_R-2 10.83 min.

Solid State NMR Study

Contrary to the liquid state spectra ^{15}N solid state NMR experiments of 2-phenyl-3-(1-phenyl-ethyl)imidazo[1,2-a]pyridine (**3a**) reveal doubling of the signals for both nitrogen atoms, indicating the presence of two species with different structure (Fig. 2).

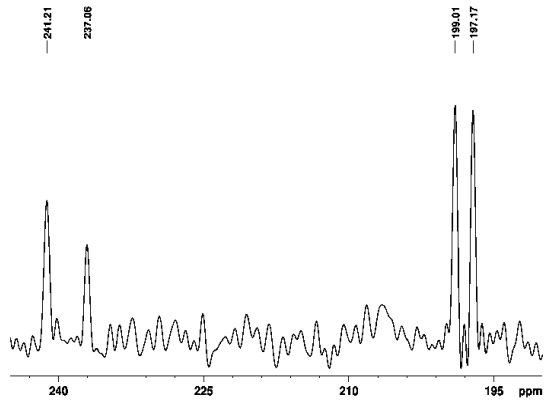


Fig. 2. ^{15}N CPMAS spectrum of **3a**.

^{13}C CPMAS spectra for **3a** are also compatible with two different species since most of the carbon atoms are doubled as revealed in Fig. 3. Using the unambiguous assignment of the liquid state spectra [32] and the technique of nonquaternary atom suppression the quaternary atoms could be unambiguously recognized, along with some rest signals for the methyl groups. The small difference between the experimental NMR chemical shifts of the two species precludes differentiation of the two species.

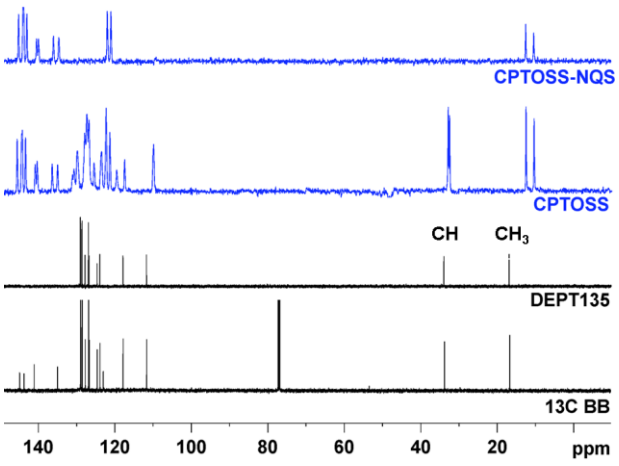


Fig. 3. Comparison of liquid state (^{13}C BB and DEPT135) with ^{13}C CPMAS (CPTOSS and CPTOSS-NQS) spectra of **3a**.

Two main alternatives are possible: polymorphic structures or different chemical shifts for two enantiomers in the solid state. Two conformational isomers in the solid state could also not be excluded. The energy difference between the major and minor isomers of **3a** in chloroform amounts only 2.4 kcal/mol (Fig. 4), making the minor isomer also a possible alternative for the solid state. The major conformer corresponds to the atom arrangement in the solid X-ray structure [32]. Theoretical NMR chemical shifts were calculated for both isomers.

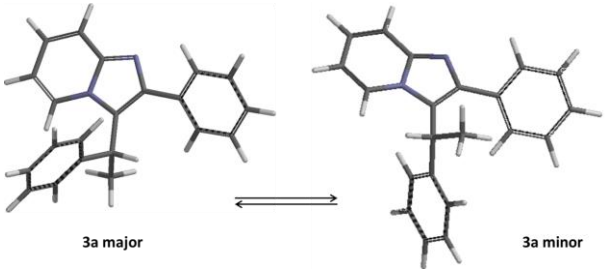


Fig. 4. Theoretical structures of the major and minor conformers of **3a**.

Table 3 and Fig. 5 reveal the close resemblance of the experimentally determined in the liquid and the solid state and the theoretically predicted NMR chemical shifts. This precludes unambiguous determination of the differences between the two species in the solids state based on the so far available data. Further experiments are in progress.

Table 3. Experimentally determined ^{13}C and ^{15}N NMR chemical shifts in $CDCl_3$ and the two solid state forms (**SS1** and **SS2**), along with theoretically calculated values.

No.	Experimental			Theoretical	
	$CDCl_3$	**SS1**	**SS2**	**3a** major	**3a** minor
1	-	241.20	237.06	243.14	246.62
2	143.76	144.50	143.67	136.91	136.02
3	122.96	122.61	121.63	124.98	125.31
4	198.66	197.17	199.01	205.74	212.99
5	124.53	125.72	122.61	125.42	121.53
6	111.56	110.15	110.35	111.43	112.80
7	123.74	123.99	123.75	122.54	122.51
8	117.78	119.81	117.76	117.21	117.59
9	144.86	145.85	144.70	144.78	144.33
10	33.78	32.77	33.14	32.42	32.72
11	16.17	12.78	10.68	12.40	13.51
1′	135.02	136.69	135.27	130.49	129.30
2′	128.92	130.18	130.18	133.20	132.13
6′	128.92	129.87	128.18	129.15	131.53
3′	128.42	127.61	127.08	127.67	126.70
5′	128.42	127.61	127.08	127.08	126.70
4′	127.68	131.37	130.95	125.39	125.22
1″	141.11	141.10	140.61	141.23	144.00
2″	126.80	130.18	130.18	129.43	128.07
6″	126.80	129.87	128.18	124.88	124.58
3″	128.81	127.61	127.08	128.14	127.98
5″	128.81	127.61	127.08	127.26	127.85
4″	126.61	131.37	130.95	125.07	127.97

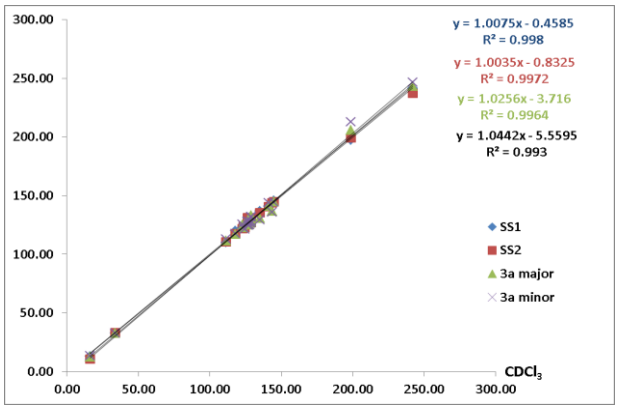


Fig. 5. Comparison of experimental data in $CDCl_3$ with experimental solid state ^{13}C NMR shifts and theoretically predicted shifts for the two possible conformers of **3a**.

CONCLUSION

The catalytic efficiency of various sulfonic and carboxylic acids in the direct acid catalyzed conversion of 2-aminopyridines and acetophenones into 2,3-disubstituted imidazo[1,2-a]pyridines was tested aiming to improve the reaction yields. It was observed that the carboxylic acids tested catalyzed the transformation insignificantly, while the sulfonic acids led to moderate to excellent yields. It was found that isoquinoline-5-sulfonic acid was the most efficient catalyst, up to 99% total yield. The latter was applied in the reaction between substituted aminopyridines and acetophenones. Significant improvement of the reaction yield was achieved in all cases compared to *p*-TSA and sulfuric acid [33] but the ratios 2-aryl-3-(1-arylethyl) to 2-aryl-3-(1-arylethenyl)imidazo[1,2-a] pyridines were more similar to that obtained with sulfuric acid, i.e. isoquinoline-5-sulfonic acid accelerated the Ortoleva-King type intermediated transformation better than *p*-toluenesulfonic acid. Several chiral acids were also examined but no enantioselectivity was induced. It was found that (*R*)-1,1'-binaphthyl-2,2'-diyl hydrogen phosphate was a very effective catalyst in the transformation studied. Comparison of experimental and theoretically predicted NMR chemical shifts does not allow assignment of the two observed species in the solid state.

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2,3-ДИЗАМЕСТЕНИ ИМИДАЗО[1,2-a]ПИРИДИНИ ОТ 2-АМИНОПИРИДИНИ И АЦЕТОФЕНОНИ. ЕФЕКТИВНИ КАТАЛИЗАТОРИ И ЯМР ИЗСЛЕДВАНЕ В ТВЪРДО СЪСТОЯНИЕ.

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(Резюме)

Проверена е ефективността на редица сулфо и карбоксилови киселини като катализатори в директно кисело катализирано превръщане на 2-аминопиридини и ацетофенони в 2,3-дизаместени имидазо[1,2-a]пиридини с цел подобряване на реакционните добиви. Най-ефективният катализатор е използван и при реакция между заместени аминопиридини и ацетофенони. Дискутирани са ефективността на катализаторите и влиянието им върху разпределението на продуктите. Изследвани са и хирални киселини, но стереоселективност не е индуцирана. ЯМР спектрите показват наличие на две форми в твърдо състояние, чието надеждно отнасяне не е възможно с наличните експериментални и теоретични данни.