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PAPER

Preparation of 1-methyl-3-phenylisoquinoline derivatives from oximes by using polyphosphoric esters

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We show a beneficial new approach to the preparation of 1-methyl-3-phenylisoquinoline derivatives. This method involves heating polyphosphate ester and the appropriate oximes, obtained from 3,4-diphenylbut-3-en-2-one derivatives. The isoquinolines were synthesized with yields mainly from about 50 to 70% and their structures were confirmed by proton and carbon nuclear magnetic resonance spectroscopy and elemental analysis. This newly developed procedure is particularly suitable for the synthesis of 1-methyl-3-phenylisoquinoline derivatives with chlorine, methyl, and methoxy substituents on the aromatic ring.

Introduction

Plants containing various alkaloids based on the isoquinoline structure are well-known for many hundreds of years and have been successfully used in the medicine as drugs different afflictions. Because of the high intensity and diversity of physiological activities, the synthesis of these compounds has become a very important aim of chemical science.[1-4] Among many alkaloids containing an isoquinoline structure, the most important of them belong to the opium group of compounds, such as papaverine, which is an antispasmodic agent, commonly used in the medicine to decrease tension, as well as the activity of smooth muscles.[5,6] Moreover, also used are some benzophenanthridine derivatives, e.g. sangwinaryna or chelidonine.[7-12] Many alkaloids, particularly 3-phenylisoquinoline and its derivatives demonstrate an anticancer or antirheumatic activity, and can prevent the symptoms of hypertension and neuralgia. It has been proved that 1-(4-methylpiperazinyl)-3-phenylisoquinoline hydrochloride works as an anticarcinogenic agent against various sorts of cancer cells. Furthermore, the natural alkaloid known as Decumbenine b has been applied in medicine as a very effective drug against hypertension and neuralgia for many decades.[13-16]

In 1893, Bischler and Napieralski described the method of synthesis of isoquinoline derivatives based on the cyclization of phenylethylamides in presence of phosphorus pentoxide as a dehydrogenation agent.[17] The Bischler - Napieralski reaction occurs according to a mechanism of an intramolecular electrophilic substitution reaction between an aromatic ring and a nitrilium ion that is generated in situ from a reacting amide. The yield of the reaction depends on both the presence and the amount of electron donating groups in the aromatic ring comprising the nitrogen atom.[18,19] In the period 1936-41, Krabbe and co-workers studied a cyclization reaction of N-styrylamide.[20-22] Later, Goszczyński and Zieliński investigated the effect of the structure of N-styrylamides on their ability for cyclization to the isoquinoline systems.[23] Subsequent research demonstrated that 1-methyl-3-phenylisoquinoline derivatives could not be obtained via the Pictet and Grams method. The cyclization of 2-acetamido-1,2-diphenylethan-1-ol derivatives in boiling decalin by using phosphorus pentoxide or chlorophosphoric acid at 150°C resulted in formation of 1-methyl-4-phenylisoquinoline derivatives instead of expected products, substituted with a phenyl group on the third carbon atom. [24]

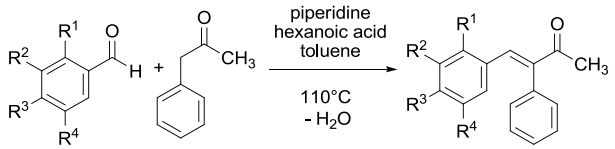
Isoquinoline derivatives can be obtained likewise from unsaturated oximes of ketones and aldehydes, without the necessity of isolation of intermediate products. Thomas and coworkers described a synthesis of isoquinoline starting from an oxime of the cinnamic aldehyde in the presence of rare-earth metals ions implanted in zeolites. However, small quantities of byproducts (cinnamonitrile and cinnamaldehyde) were formed in the process and contaminated the reaction product.[25,26] The synthesis of isoquinoline derivatives can be performed in common solvents as well as in ionic liquids.[27-30]

The ethyl ester of polyphosphoric acid (polyphosphate ester, PPE) is a dehydrogenation agent with a structure containing cyclic esters, and may be obtained in the reaction between phosphorus pentoxide and diethyl ether in the presence of chloroform. PPE is often used as a substitute for polyphosphoric acid (PPA), due to the better solubility in the organic solvents and higher safety of using as a reagent in organic synthesis. Moreover, the reaction can be conducted under milder conditions, and therefore PPE improves the economic viability of synthesis.[31-33] PPE was successfully applied as a reagent in the Beckmann rearrangement[31] and in the Bischer - Napieralski reaction.[18,19] PPE can be likewise applied in the Biginelli cyclocondensation reaction[33], the Fischer indole synthesis[34], reactions of alkylation or N-alkylation[35], and a bioparticles condensation.[36] In presence of this substance aminoacids and

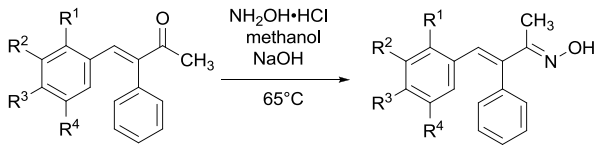
peptides undergo conversion into macromolecular peptides.[36]

Results and discussion

The aim of this work was the preparation of a simple method for synthesis of 1-methyl-3-phenylisoquinoline derivatives from the oximes of unsaturated ketones, without the necessity of separation of N-styrylamides as intermediates. Structures of all synthesized compounds were confirmed by proton and carbon nuclear magnetic resonance spectroscopy and the purity of products was determined by elemental analysis (CHN) as well as thin layer chromatography (TLC). 3,4-Diphenylbut-3-en-2-one derivatives were obtained via the condensation reaction of benzaldehyde derivatives with 1-phenylpropan-2-one, followed by dehydration of the formed hydroxy ketones (Scheme 1). A solution of the benzaldehyde derivative and 1-phenylpropan-2-one in toluene was heated in presence of catalytic amounts of hexanoic acid and piperidine for 12 h.



Scheme 1 The synthesis of 3,4-difenylobut-3-en-2-one derivatives



Scheme 2 The synthesis of oximes from ketones

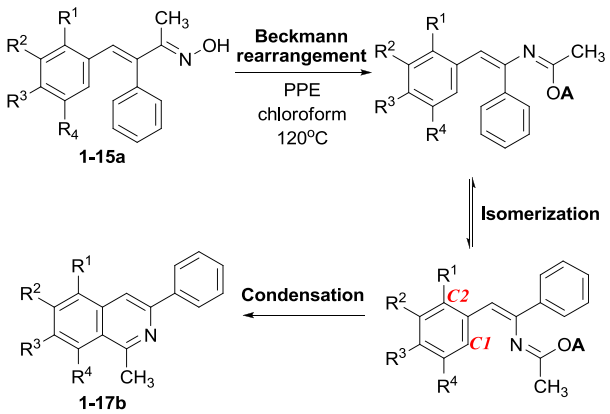
Afterwards, all required oximes were formed by reaction of the 3,4-diphenylbut-3-en-2-one derivatives and hydroxylamine hydrochloride in an alkaline environment, wherein methanol was used as a solvent. In table 1 are listed yields and melting points of the oximes, synthesized according to the reaction presented in Scheme 2. The oximes of unsaturated ketones were obtained in the form of crystals during the slow cooling of the post-reaction mixture with a yield from 51 to 90%.

As a result of these studies, we found that heating the obtained oximes of 3,4-diphenylbut-3-en-2-one derivatives with polyphosphate ester at 120ºC leads to a formation of 1-methyl-3-phenylisoquinoline derivatives. This observation proves that three different reactions occur in the reaction mixture - Beckmann rearrangement, isomerization of intermediates, and finally condensation. The proposed mechanism of this process is shown in Scheme 3.

An /E/ isomer of the amide should be formed in the rearrangement reaction of the selected oxime. However, this compound is not able to cyclize to an isoquinoline derivative due to the presence of the double bond, which is unable to rotate freely. In presence of PPE as reaction medium, isomerization of the /E/ isomer of the amide to the /Z/ isomer occurs. However, all amides exist in the form of nitrylium cations in the reaction mixture, which strongly facilitates the cyclization reaction. In order to confirm the assumed reaction mechanism, oximes (**2a**, **11a**) were heated with PPE at 70ºC for 5 minutes and then water was slowly added to the post-reaction mixture. In effect the mixture of isoquinoline and both amides was obtained, which was confirmed by IR spectroscopy. In the spectrum of the resulting mixture we identified the absorption bands from N-H (3200-3300 cm^{-1}) and C=O (1650-1700 cm^{-1}) stretching vibrations of an amide group.

Table 1 Prepared oximes

Oxime	R^1	R^2	R^3	R^4	Yield (%)	Mp (ºC)
1a	H	H	H	H	77	157-158
2a	CH_3	H	H	H	81	142-144
3a	H	CH_3	H	H	57	132-134
4a	H	H	CH_3	H	90	178-180
5a	Cl	H	H	H	87	138-140
6a	H	Cl	H	H	85	145-149
7a	H	H	Cl	H	80	193-194
8a	OCH_3	H	H	H	89	147-150
9a	H	OCH_3	H	H	74	132-136
10a	H	H	OCH_3	H	63	185-188
11a	OCH_3	OCH_3	H	H	81	182-187
12a	H	OCH_3	OCH_3	H	51	184-186
13a	OCH_3	H	OCH_3	H	55	194-196
14a	OCH_3	H	H	OCH_3	71	185-187
15a	H	OCH_3	H	OCH_3	51	166-168



Scheme 3 A proposed mechanism of isoquinolines synthesis, where A is a fragment of the PPE molecule

Moreover, thin layer chromatography (TLC) analysis clearly proved that the post-reaction mixture consists of an isoquinoline structure and two isomers of the amide.

The oxime **4a** was used for determination of the influence of reaction temperature on the synthesis efficiency. The mixture of the substrate and PPE was heated for three hours at temperatures ranging from 100 to 140ºC (Table 2). The highest yield of isoquinoline was observed at 120ºC and this temperature was selected to perform all syntheses. The deterioration of the reaction yield above the temperature of 120ºC may be related to the decomposition of PPE, which is unstable at high temperatures. Table 3 shows that the yield depends on the type as well as the position of the substituent on the phenyl group of the

starting oxime. The unsubstituted 1-methyl-3-phenylisoquinoline **1b** (where R^1, R^2, R^3, R^4 = H) is known in the literature[23, 37] and was obtained with a 68% yield from the 3,4-diphenylbut-3-en-2-one.[23] The location of a methyl group in the *para* position causes the cyclization of the oxime to the isoquinoline **4b** with the similar yield (67%). However, when the methyl group was located in the *ortho* position the isoquinoline **2b** was obtained with lower efficiency (48%). This indicates that a steric hindrance occurs during the cyclization of oxime **2b** to this isoquinoline. The highest yield was observed for isoquinoline **3b**, where the methyl group is substituted in the *meta* position (76%).

Table 2 PPE catalyzed synthesis of 1,7-dimethyl-3-phenyl-isoquinoline (**4b**) in various temperatures

NO.	Temperature (°C)	Yield (%)
1	100	58
2	110	60
3	120	67
4	130	61
5	140	56

Table 3 Prepared isoquinoline derivatives

Product	R^1	R^2	R^3	R^4	Yield (%)	Mp (°C)
1b	H	H	H	H	68	47-48[a]
2b	CH_3	H	H	H	48	73-75
3b	H	CH_3	H	H	76	47-49
4b	H	H	CH_3	H	67	64-65
5b	Cl	H	H	H	45	60-61
6b	H	Cl	H	H	19	95-98
7b	H	H	Cl	H	47	99-100
8b	OCH_3	H	H	H	61	116-118
9b	H	OCH_3	H	H	72	132-134
10b	H	H	OCH_3	H	36	121-122
11b	OCH_3	OCH_3	H	H	71	109-112
12b	H	OCH_3	OCH_3	H	74	144-145
13b	OCH_3	H	OCH_3	H	13	154-156
14b	OCH_3	H	H	OCH_3	53	80-81
15b	H	OCH_3	H	OCH_3	77	116-118
16b	H	H	OH	H	5	275-278
17b	OCH_3	H	OH	H	10	151-154

[a] Mp 48°C, reference[37]

The yield of syntheses of isoquinolines from oximes containing one methoxy group also depend on the location of this group on the phenyl substituent of the substrate. The oxime **8a** with the methoxy group in the *ortho* position undergoes transformation to the isoquinoline with a yield lower by about 11% than the oxime **9a** containing the methoxy group in the *meta* position, which was obtained in 72% yield. However, when the methoxy group is located in *para* position, isoquinoline **10b** was synthesized with the lowest yield – only 36%. Moreover, it was found that besides the expected main product, small amounts (5%) of 7-hydroxy-1-methyl-3-phenylisoquinoline (**16b**) were formed.

On the other hand, the presence of two methoxy groups in the oxime generally does not negatively affect the synthetic efficiency. As a result of transformation of oximes **11a** and **12a,** compounds **11b** (5,6-dimethoxy-1-methyl-3-phenylisoquinoline) and **12b** (6,7-dimethoxy-1-methyl-3-phenylisoquinoline) were obtained with yields of 71% and 74%, respectively. The exception was the synthesis of the compound **13b**, which also contained two methoxy groups. The low yield of this reaction (13%) was caused by the formation of by-products (e.g. 7-hydroxy-5-methoxy-1-methyl-3-phenylisoquinoline (**17b**) during the reaction. A similar efficiency was observed for cyclization of the oxime **6a**, wherein 6-chloro-1-methyl-3-phenylisoquinoline (**6b**) was obtained in only 19% yield. This also implies that the presence of a substituent which causes a reduction in total electron density of the aromatic ring affects the efficiency of the entire process adversely. This phenomenon confirms also the yields of isoquinolines substituted with a chlorine in the *ortho* (**5b**) or *para* (**7b**) position, which reached similar values (slighty less than 50%).

The oximes **3a**, **6a**, **9a**, **12a** and **15a** may theoretically be converted into two different products, which are structural isomers. Scheme 3 shows that during the cyclization of these five amides, the carbon of the carbonyl group can attack the carbon *C1* as well as the carbon *C2*. The analysis of ^{1}H and ^{13}C NMR spectra revealed that of only one reaction product was obtained. By comparing the location and multiplicity of the signals of the formed isoquinoline with theoretical spectra of the two isomers, we discovered that the obtained products were formed by attack on the *C1* carbon.

Further research proved that the use of other reagents such as phosphoryl chloride, phosphorus pentoxide, or chlorophosphoric acid instead of PPE does not result in formation of isoquinoline structures from oximes. Moreover, the PPE is an effective condensing reagent only for oximes of ketones containing the aryl group on the third carbon atom in their structure. The reaction does not occur in case of replacing this group with a hydrogen or alkyl group.

Conclusions

The ethyl ester of polyphosphoric acid (PPE) applied in our studies proved to be an efficient reagent for the cyclization of oximes to isoquinolines substituted by one or two functional groups. PPE allowed 1-methyl-3-phenylisoquinoline derivatives to be obtained with high efficiency and purity. Moreover, three different reactions occur in the reaction mixture - Beckmann rearrangement, isomerization and condensation - and all are promoted by only one reagent. As a result, we eliminate the necessity of isolating the reaction intermediates as well as the use of various catalysts suitably selected for each reaction. The studied reaction of cyclocondensation turned out to be a selective process. As the result of all syntheses only one isomer of isoquinoline was formed.

Experimental

General

Melting points were measured with a Büchi melting point B-540 apparatus. The IR spectra were made by the use of a Bruker FT-IR EQUINOX 55 spectrophotometer. ^{1}H NMR and ^{13}C NMR

analyses were performed on a Gemini Varian 300 VT spectrometer with tetramethylsilane as an internal standard. CHN elemental analyses were performed at the Adam Mickiewicz University, Poznan (Poland). The TLC chromatograms were made on KIESEGEL 60 GF_{254} plates and a mixture of toluene - ethyl acetate (1:1) was used as a mobile phase.

Synthesis of PPE

The reagent was prepared by refluxing a mixture of 150 g of phosphorus pentoxide (P_40_{10}), 150 mL of diethyl ether and 300 mL of chloroform until the solution was clear (15-30 hours). Then, the mixture was filtered through glass wool and concentrated on a rotary evaporator. The obtained PPE was diluted with anhydrous chloroform to a density of 2.7 $g \cdot ml^{-1}$ before use.

Condensation of 1-phenylprop-2-one with benzaldehyde derivatives

The appropriate benzaldehyde derivative (0.1 mol), 1-phenylprop-2-one (0.11 mol) and toluene (100 mL) as a solvent and catalytic amounts of hexanoic acid and piperidine were added to a reaction flask. Next, the solution was heated in a Dean Stark apparatus for 12 hours at 110ºC. The reaction mixture was cooled to room temperature and toluene was evaporated under reduced pressure. The obtained raw product was recrystallized from ethanol.

Oximation of 3,4-diphenylbut-3-en-2-one derivatives

In a round-bottom flask a selected ketone (0.05 mol) and hydroxylamine hydrochloride (0.08 mol) were dissolved in 50 mL of methanol. Afterwards, sodium hydroxide (0.06 mol) dissolved in aqueous-methanolic solution (1:1) was added into the reaction mixture. The solution was heated in a round-bottom flask equipped with a reflux condenser for 1 hour. The obtained precipitate was filtered off under reduced pressure and recrystallized from ethanol.

General procedure for the synthesis of 3-phenylisoquinoline derivatives

A cyclization of a selected oxime (0.02 mol) was carried out in a solution of PPE (0.035 mol) in chloroform at 120ºC for 3 hours. The post-reaction mixture was acidified with hydrochloric acid and both chloroform and contaminations were separated by a steam distillation. Then, an excess of sodium hydroxide was added to the flask containing the isoquinoline hydrochloride in order to isolate of the reaction product. Next, the mixture was extracted three times with diethyl ether and the organic phase was dried over sodium sulfate. Afterwards, the solvent was removed and the crude product was recrystallized from ethanol.

In the synthesis of 7-methoxy-1-methyl-3-phenylisoquinoline (**10b**) and 5,7-dimethoxy-1-methyl-3-phenylisoquinoline (**13b**) the separated aqueous phase was acidified with a 10% solution of hydrochloric acid and as a result by-products comprising a hydroxyl substituent (**16b**, **17b**) precipitated. Then, the aqueous mixture was extracted three times with diethyl ether and the organic phase was dried over sodium sulfate. Afterwards, the solvent was removed.

1-Methyl-3-phenylisoquinoline (**1b**). White cryst. solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.15-6.74 (10H, m), 2.88 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.4, 150.0, 139.8, 136.5, 129.6, 128.6, 128.2, 127.5, 126.9, 126.6, 125.5, 115.1, 22.5; Anal. Calcd for $C_{16}H_{13}N$: C, 87.64; H, 5.98; N, 6.39. Found: C, 87.44; H, 6.21; N, 6.12.

1,5-dimethyl-3-phenylisoquinoline (**2b**). White cryst. solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.18 (2H, m), 8.04 (1H, s), 7.42 (6H, m), 3.05 (3H, s) 2.73 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.9, 149.9, 140.3, 136.1, 134.3, 130.4, 128.7, 128.2, 127.1, 126.5, 126.2, 111.7, 23.0, 19.0; Anal. Calcd for $C_{17}H_{15}N$: C, 87.52; H, 6.48; N, 6.00. Found: C, 87.71; H, 6.33; N, 5.89.

1,6-dimethyl-3-phenylisoquinoline (**3b**). White cryst. solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.18 (2H, m), 7.97 (1H, s), 7.43 (6H, m), 3.02 (3H, s) 2.36 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.4, 149.9, 140.1, 137.0, 130.1, 129.9, 129.3, 127.0, 125.9, 126.8, 125.9, 115.9, 22.5, 21.7; Anal. Calcd for $C_{17}H_{15}N$: C, 87.52; H, 6.48; N, 6.00. Found: C, 87.64; H, 6.55; N, 6.09.

1,7-dimethyl-3-phenylisoquinoline (**4b**). White cryst. solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.16 (2H, m), 7.88 (1H, s), 7.38 (6H, m), 3.03 (3H, s) 2.57 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.7, 149.2, 140.0, 137.0, 134.9, 132.1, 128.6, 128.1, 127.4, 126.8, 126.7, 124.5, 115.0, 22.6, 22.0; Anal. Calcd for $C_{17}H_{15}N$: C, 87.52; H, 6.48; N, 6.00. Found: C, 87.45; H, 6.59; N, 6.14.

5-chloro-1-methyl-3-phenylisoquinoline (**5b**). White cryst. solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.29 (1H, s), 8.18-7.39 (8H, m), 3.04 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.9, 151.1, 139.5, 134.7, 132.0, 130.0, 128.8, 128.7, 127.5, 127.2, 126.4, 124.6, 111.4, 22.9; Anal. Calcd for $C_{16}H_{12}ClN$: C, 75.74; H, 4.77; N, 5.52. Found: C, 75.61; H, 4.83; N, 5.59.

6-chloro-1-methyl-3-phenylisoquinoline (**6b**). White cryst. solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.14-7.39 (9H, m), 2.99 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.5, 151.1, 139.3, 137.6, 136.1, 128.7, 128.6, 127.5, 127.3, 127.0, 126.2, 124.7, 114.1, 22.6; Anal. Calcd for $C_{16}H_{12}ClN$: C, 75.74; H, 4.77; N, 5.52. Found: C, 75.58; H, 4.64; N, 5.62.

7-chloro-1-methyl-3-phenylisoquinoline (**7b**). White cryst. solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.15-7.36 (9H, m), 3.00 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.7, 150.3, 139.3, 135.0, 132.2, 130.9, 129.2, 128.7, 128.5, 127.0, 126.9, 124.7, 114.5, 22.5; Anal. Calcd for $C_{16}H_{12}ClN$: C, 75.74; H, 4.77; N, 5.52. Found: C, 75.80; H, 4.71; N, 5.67.

5-methoxy-1-methyl-3-phenylisoquinoline (**8b**). White cryst. solid. ^{1}H NMR (300 MHz, $CDCl_3$): 8.36 (1H, s), 8.22-8.20 (2H, m), 7.65 (1H, m), 7.54-7.26 (4H, m), 6.97 (1H, m), 4.01 (3H, s), 3.03 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.8, 155.2, 149.5, 140.1, 129.3, 128.6, 128.1, 127.2, 126.9, 126.5, 117.4, 109.4, 107.2, 55.6, 23.0; Anal. Calcd for $C_{17}H_{15}NO$: C, 81.90; H, 6.06; N, 5.62. Found: C, 81.79; H, 6.01; N, 5.74.

6-methoxy-1-methyl-3-phenylisoquinoline (**9b**). White cryst. solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15-6.74 (9H, m), 3.91 (3H, s), 2.95 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.6, 157.9, 150.6, 140.0, 138.8, 136.1, 128.6, 128.2, 127.8, 127.0, 122.2, 119.3, 114.7, 105.1, 55.4 22.5; Anal. Calcd for $C_{17}H_{15}NO$: C, 81.90; H, 6.06; N, 5.62. Found: C, 81.97; H, 6.14; N, 5.53.

7-methoxy-1-methyl-3-phenylisoquinoline (**10b**). White cryst. solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.12-8.09 (2H, m), 7.84 (1H, s), 7.50-7.24 (5H, m), 6.97 (1H, m), 3.95 (3H, s), 2.99 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.2, 156.8, 148.1, 139.7, 132.2, 129.2, 128.7, 128.0, 127.5, 126.7, 122.8, 115.1,

103.6, 55.4 22.6; Anal. Calcd for $C_{17}H_{15}NO$: C, 81.90; H, 6.06; N, 5.62. Found: C, 81.81; H, 6.23; N, 5.49.

5,6-dimethoxy-1-methyl-3-phenylisoquinoline (**11b**). White cryst. solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.19-8.16 (3H, m), 7.90 (1H, d, *J* = 9.0 Hz), 7.86 (1H, m), 7.53-7.26 (3H, m), 4.02 (6H, m), 2.99 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.3, 151.2, 150.1, 142.2, 140.1, 132.8, 128.6, 128.2, 127.1, 122.5, 114.5, 108.8, 61.2, 56.5, 22.7; Anal. Calcd for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 5.01. Found: C, 77.29; H, 6.23; N, 5.10.

6,7-dimethoxy-1-methyl-3-phenylisoquinoline (**12b**). White cryst. solid. (^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10-7.10 (8H, m), 4.04 (6H, m), 2.96 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.8, 152.5, 149.7, 149.1, 133.4, 128.6, 127.6, 126.7, 122.2, 114.3, 105.6, 103.8, 55.9, 22.7; Anal. Calcd for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 5.01. Found: C, 77.52; H, 6.15; N, 4.97.

5,7-dimethoxy-1-methyl-3-phenylisoquinoline (**13b**). Brown cryst. solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.23 (1H, s), 7.65-7.21 (7H, m), 3.99 (3H, s), 3.96 (3H, s), 2.95 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.7, 156.5, 156.2, 147.8, 140.0, 128.6, 127.9, 127.7, 126.8, 125.6, 109.8, 101.0, 95.2, 55.7, 55.4, 22.9; Anal. Calcd for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 5.01. Found: C, 77.64; H, 6.01; N, 4.85.

5,8-dimethoxy-1-methyl-3-phenylisoquinoline (**14b**). White cryst. solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.22-6.71 (8H, m), 3.96 (3H, s), 3.91 (3H, s), 3.19 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.9, 151.8, 149.6, 148.7, 139.7, 131.4, 128.6, 128.2, 126.9, 119.5, 108.8, 107.4, 105.2, 55.8, 55.6, 28.9; Anal. Calcd for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 5.01. Found: C, 77.23; H, 6.28; N, 5.30.

6,8-dimethoxy-1-methyl-3-phenylisoquinoline (**15b**). White cryst. solid. ^{1}H NMR (300 MHz, acetone-d_6): δ 8.15-8.12 (3H, m), 7.71 (1H, s), 7.52-7.37 (4H, m), 3.92 (6H, m), 3.12 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.9, 159.4, 157.8, 150.3, 140.1, 139.7, 128.5, 128.2, 126.8, 115.6, 114.3, 98.9, 97.8, 55.4, 55.3, 28.6; Anal. Calcd for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 5.01. Found: C, 77.11; H, 5.87; N, 5.14.

7-hydroxy-1-methyl-3-phenylisoquinoline (**16b**). Yellow cryst. solid. ^{1}H NMR (300 MHz, acetone-d_6): δ 11.40 (1H, s), 7.59-7.37 (9H, m), 2.54 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.4, 177.1, 159.5, 139.0, 133.3, 132.3, 129.3, 129.2, 128.7, 127.6, 121.0, 119.9, 111.2, 19.0; Anal. Calcd for $C_{16}H_{13}NO$: C, 81.68; H, 5.57; N, 5.95. Found: C, 81.79; H, 5.21; N, 5.75.

7-hydroxy-5-methoxy-1-methyl-3-phenylisoquinoline (**17b**). Yellow cryst. solid. ^{1}H NMR (300 MHz, acetone-d_6): δ 11.33 (1H, s), 7.67-7.28 (6H, m), 6.17 (2H, m), 4.07 (3H, s), 2.51 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 179.5, 178.5, 168.9, 166.4, 136.9, 134.5, 132.0, 130.8, 128.1, 127.8, 119.0, 117.7, 112.4, 57.7, 18.8; Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 77.23; H, 5.99; N, 4.94.

Notes and references

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