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Regioselectivity in isoquinoline alkaloid synthesis

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ABSTRACT

Regioselectivity in isoquinoline alkaloid synthesis is analyzed here. Our experiments have shown that substituents on the aromatic ring of the starting amine are determinant in isoquinoline synthesis. The use of dicyclohexylcarbodiimide in activating carboxylic acids for electrophilic aromatic substitution reactions is presented for the first time.

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1. Introduction

The Pictet–Spengler reaction involves adding a phenylethylamine to an aldehyde to form an iminium ion; the resulting electrophile is suitable for aromatic substitution and ring closure. This methodology has been used in alkaloid synthesis as the key step in tetrahydroisoquinoline formation.[1] Such reaction is usually carried out in an aprotic solvent in the presence of an acid catalyst and proceeds most smoothly when the phenylethylamine aromatic ring is activated by an electron-donating substituent. Poor regioselectivity may be observed in some cases.[2]

It has been demonstrated recently that this reaction does not occur when tyrosine or tyramine is involved,[3,4] that regioselectivity in Pictet–Spengler cyclization for isoquinoline synthesis depends on activating the aromatic ring of phenylethylamine and that the least sterically hindered *ortho* position is the predominant cyclization site.[5] It has also been proposed that using some catalyst and dehydrating agents has increased the yield and regioselectivity and that Brønsted acids, such as trifluoromethanesulfonic acid, acetic acid, and trifluoroacetic acid, have not been effective.[6] No relationship has been established between this reaction's pH and yield or regioselectivity.[7,8]

The dopamine reaction was carried out in this work with some aromatic aldehydes to establish the importance of substituents on the aromatic ring of the starting phenylethylamine during the course of the Pictet–Spengler reaction when working with protic solvents and Brønsted acids as catalyst.

The dopamine hydrobromide reaction was carried out with selected aldehydes, methanol as solvent, and acetic acid as catalyst; the respective isoquinoline hydrobromide was obtained in all cases in high yields and with complete regioselectivity (Table 1); the formation of any other regioisomer was not detected. Starting phenylethylamine was recovered in all cases; this did not react. Product formation was not observed when an acid was not used as a catalyst in the experimental conditions used here. These results showed that the Pictet–Spengler reaction occurred in polar solvents when the starting phenylethylamine's aromatic ring had a substituent in position 3 activating the ring. It should be stressed that the existence of electron-donating and electron-withdrawing groups on aldehydes did not have an effect on regioselectivity.

The presence of two strongly activated positions on the dopamine ring favored the formation of two isoquinoline regioisomers; however, only the product of electrophilic aromatic substitution on carbon 6 of phenylethylamine was obtained in all cases in the conditions used here (Table 1). Such complete regioselectivity suggested that the activating group in position 3 of the aromatic ring was necessary for the Pictet–Spengler reaction to occur and, in turn, direct the course of the reaction toward aromatic electrophilic substitution in position 6. The distribution of Mulliken atomic charges[9] from intermediary imine arising from the Pictet–Spengler reaction showed greater electronic density on carbon 6 (−0.0559) than on carbon 2 (−0.0262) of the ring when calculated using PC-GAMESS software, B3LYP/6-31G** basis set and suggested that the reaction was favored at this point (Fig. 1). Calculations for Schiff bases from different aldehydes with electron-donating or electron-withdrawing groups presented a similar pattern; differences regarding the distribution of the charge between C-2 and C-6 did not change appreciably. These results correlated with those of the isolated products.

The same methodology was used for the 6,7-dimethoxyphenylethylamine reaction with 3-nitrobenzaldehyde; this reaction did not lead to the expected isoquinoline but to the respective intermediary Schiff base **8** (Scheme 1).

Calculations for compound **8** revealed a Mulliken charge distribution similar to that observed for the Schiff bases from the dopamine reaction with aldehydes. Such results led to proposing that the 6,7-dimethoxyphenylethylamine reaction did not occur because the activation energy for cyclization was greater for the Schiff base with methoxy groups on the aromatic ring.

Schiff base **8** was refluxed in 37% HCl to overcome the energy barrier and obtain 6,7-dimethoxyphenylethylamine-derived tetra-

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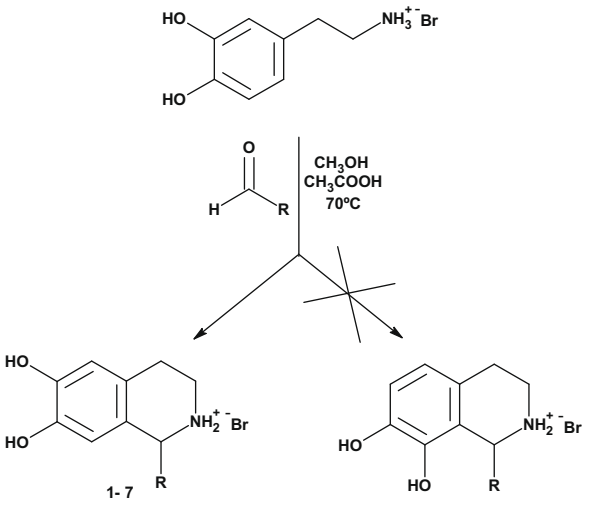
Table 1
Dopamine reaction with aldehydes



	R	Yield (%)
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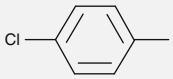
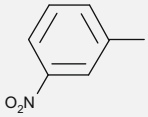
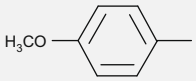
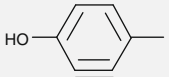
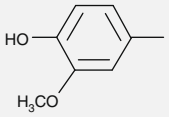
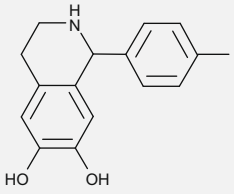
2		78
3		90
4		63
5		52
6		38
7		35

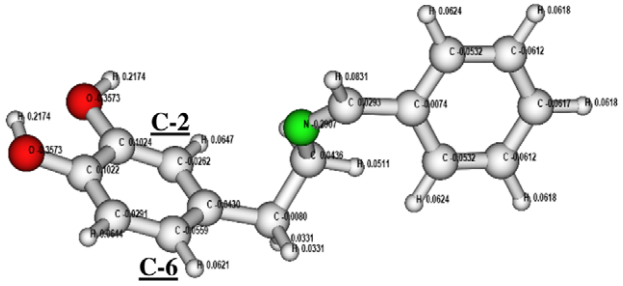


Figure 1. Mulliken atomic charge distribution for imine.

hydroisoquinolines **9** and little time was taken to precipitate the respective isoquinoline (Scheme 2).[10] This experiment demonstrated that isoquinoline not being obtained with methoxy groups in the initial conditions was due to the high activation energy required for electrophilic aromatic substitution. The same as in earlier cases, the reaction occurred with complete regioselectivity.

The results presented up to this point have shown that Pictet–Spengler cyclization yield depended only on the starting aldehydes' electrophilic capacity, that activating the phenylethylamine aromatic ring was important in the course of the reaction and that the high electron density on carbon 6 of dopamine favored substitution at this point. We propose that using protic solvents (such as methanol) increases cyclization regioselectivity due to greater intermediary Schiff base solvation on phenol hydroxyls; such solvation generates greater steric impediment and directs the reaction toward carbon 6, this being the least sterically hindered due to the presence of other substituents.

6,7-Dimethoxy-1,4-dihydro-(2*H*)-isoquinoline-3-one **10** was synthesized from 3,4-dimethoxybenzylamine (Scheme 3) to demonstrate that isoquinoline synthesis regioselectivity depends only on factors which can increase steric impediment regarding the electrophile, that it is not exclusive to the Pictet–Spengler reaction and that it does not depend on the catalyst used. The same as in Pictet–Spengler cyclization, only one of the expected regioisomers was formed. The steric impediment generated by the alkyl halide–aluminum chloride complex could provide a possible explanation for total regioselectivity in this alkylation, confirming that previously proposed for obtaining tetrahydroisoquinolines.

6,7-Dimethoxy-1,2-dihydroisoquinolin-3,4-dione **11** was synthesized from 3,4-dimethoxybenzylamine to observe whether total regioselectivity also occurred in acylation reactions (Scheme 4).

The same as in the previous reactions, the acylation reaction regioselectively produced the respective isoquinoline and (unexpectedly) in a single step. The strategy used showed that *N*,*N*-dicyclohexylcarbodiimide commonly used as a carboxylic acid activator for amide formation is also useful for activating carboxylic acids in electrophilic aromatic substitution reactions on strongly activated rings and (as in previous cases) cyclization was completely regioselective.

This work has thus presented a simple and economic methodology which does not require the synthesis and purification methods which are completely isoquinoline regioselective. It has been shown that electrophilic aromatic substitution reactions for isoquinoline formation only occurred on carbon 6 of the starting phenylalkylamine when solvent, catalyst, or activator conditions increased steric impediment at reaction sites; such regioselectivity was not restricted to the Pictet–Spengler reaction. Using dicyclohexylcarbodiimide as a carboxylic acid activator for electrophilic aromatic substitution reactions has also been presented for the first time. Applying this strategy to isoquinoline compound synthesis is currently being investigated and will be reported in due course.

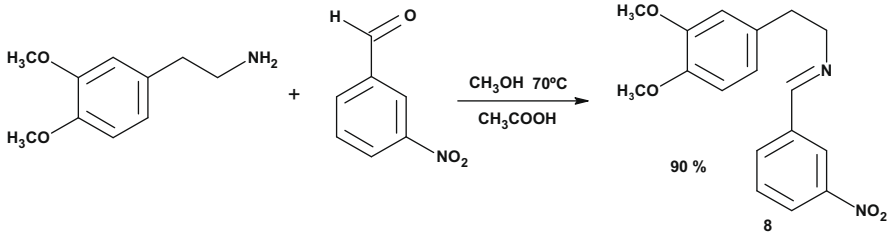
2. Experimental

2.1. General procedure for dopamine reaction with aldehydes

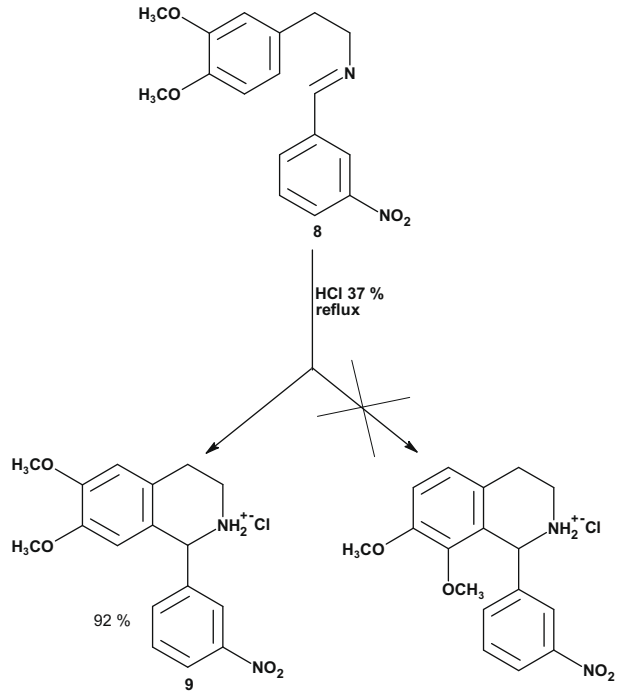
Acetic acid (0.1× mol) was added to a solution of dopamine hydrobromide (× mol) and the respective aldehyde (× mol) in methanol; the mixture was refluxed for 48 h. The precipitated product was filtered and washed with methanol.

2.2. 6,7-Dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrobromide 1

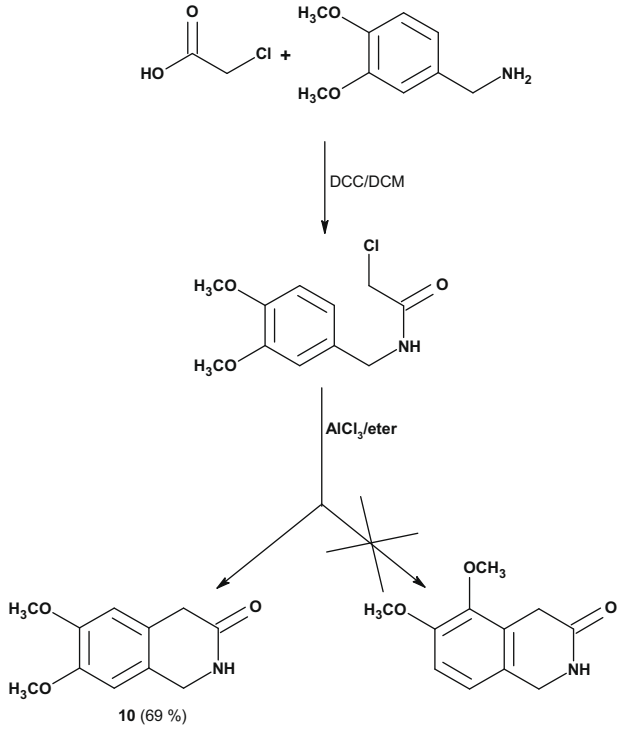
(50%, white solid, mp 256–257 °C). ^{1}H NMR (D_2O, 400 MHz): 2.88 (2H, t, J = 6.4 Hz), 3.38 (2H, t, J = 6.4 Hz), 4.13 (2H, s), 6.61 (1H, s), 6.66 (1H, s). ^{13}C NMR (D_2O, 100 MHz): 23.8 (C-4), 41.7 (C-3), 44.0 (C-1), 113.7 (C-8), 115.8 (C-5), 119.6 (C-9), 123.7 (C-10), 143.0 (C-7), 143.8 (C-6).



Scheme 1. 3,4-Dimethoxyphenylethylamine and 3-nitrobenzaldehyde reaction.



Scheme 2. 1-(3-Nitrophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **9** synthesis.



Scheme 3. 6,7-Dimethoxy-1,4-dihydro-(2*H*)-isoquinolin-3-one **10** synthesis.

2.3. 6,7-Dihydroxy-1-(4-chlorophenyl)-1,2,3,4-tetrahydroisoquinoline hydrobromide 2

(78%, cream-colored solid, mp 232–234 °C) ^{1}H NMR (D_2O, 400 MHz): 3.01 (2H, m), 3.37 (2H, m), 5.60 (1H, s), 6.29 (1H, s), 6.76 (1H, s). 7.23 (2H, d, J = 8.0 Hz), 7.40 (2H, d, J = 8.0 Hz). ^{13}C NMR (D_2O, 100 MHz): 23.9 (C-4), 39.2 (C-3), 58.1 (C-1), 114.9 (C-8), 115.5 (C-5), 122.4 (C-10), 124.6 (C-9), 143.2 (C-7), 144.5 (C-6), 129.2 (C-12, C-16), 131.3 (C-13, C-15),134.7 (C-14), 135.3 (C-11).

2.4. 6,7-Dihydroxy-1-(3-nitrophenyl)-1,2,3,4-tetrahydroisoquinoline hydrobromide 3

(90%, cream-colored solid, mp 259–260 °C) ^{1}H NMR (D_2O, 400 MHz): 3.00 (2H, m), 3.38 (2H, m), 5.72 (1H, s), 6.23 (1H, s), 6.73 (1H, s). 7.59 (1H, t, J = 8.0 Hz), 7.67 (1H, d, J = 8.0 Hz), 8.00 (1H, d, J = 8.0 Hz), 8.22 (1H, d, J = 8.0 Hz).

2.5. 6,7-Dihydroxy-1-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline hydrobromide 4

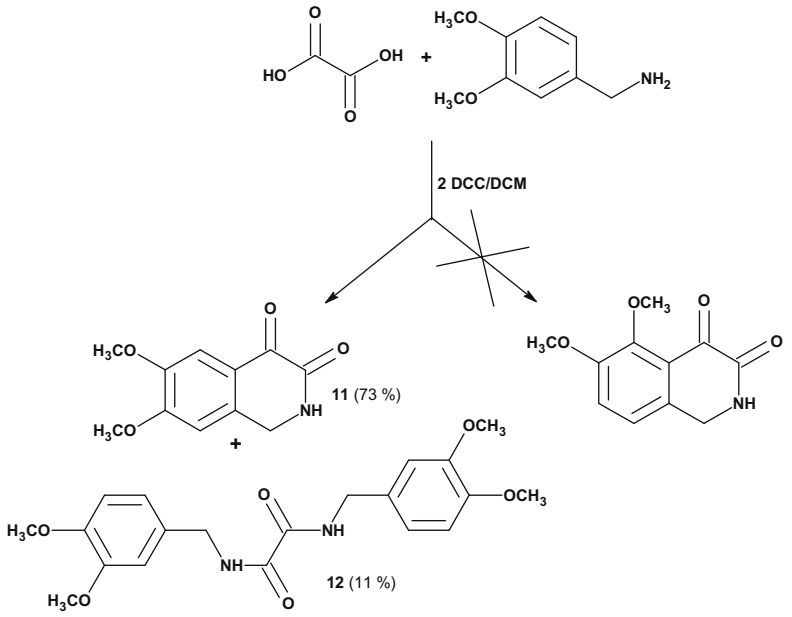
(63%, white solid, mp 238–239 °C) ^{1}H NMR (D_2O, 400 MHz): 3.02 (2H, m), 3.37 (2H, m), 3.78 (3H, S), 5.57 (1H, s), 6.32 (1H, s), 6.77 (1H, s). 6.98 (2H, d, J = 8.8 Hz), 7.22 (2H, d, J = 8.8 Hz). ^{13}C NMR (D_2O, 100 MHz): 23.9 (C-4), 39.0 (C-3), 55,4 (CH_3–O), 58.3 (C-1), 114.9 (C-8), 115.4 (C-5), 123.0 (C-10), 128.6 (C-9), 143.1 (C-7), 144.5 (C-6), 114.5 (C-13, C-15), 124.6 (C-11),132.3 (C-12, C-16), 159.9 (C-14).

2.6. 6,7-Dihydroxy-1-(4-hydroxyphenyl)-1,2,3,4-tetrahydroisoquinoline hydrobromide 5

(52%, coffee-colored solid, mp 257–259 °C) ^{1}H NMR (D_2O, 400 MHz): 2.93 (2H, m), 3.30 (2H, m), 5.44 (1H, s), 6.23 (1H, s), 6.68 (1H, s). 6.78 (2H, d, J = 8.4 Hz), 7.06 (2H, d, J = 8.4 Hz). ^{13}C NMR (D_2O, 100 MHz): 24.0 (C-4), 39.1 (C-3), 58.4 (C-1), 115.0 (C-8), 115.5 (C-5), 124.6 (C-10), 133.1 (C-9), 143.1 (C-7), 144.3 (C-6), 115.9 (C-13, C-15), 128.0 (C-11), 131.5 (C-12, C-16),156.8 (C-14).

2.7. 6,7-Dihydroxy-1-(4-hydroxy-3-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline hydrobromide 6

(38%, cream-colored solid, mp 230 °C) ^{1}H NMR (D_2O, 400 MHz): 3.02 (2H, m), 3.40 (2H, m), 5.53 (1H, s), 6.35 (1H, s), 6.78 (1H, s). 6.80 (1H, d, J = 8.0 Hz), 6.86 (1H, s), 6.90 (1H, d, J = 8.0 Hz).



Scheme 4. 6,7-Dimethoxy-1,2-dihydroisoquinoline-3,4-dione **11** synthesis

2.8. 6,7-Dihydroxy-1-[4-(6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline-1-yl)phenyl]-1,2,3,4-tetrahydroisoquinoline dihydrobromide 7

(35%, cream-colored solid, mp 235–236 °C) ^{1}H NMR (D_2O, 400 MHz): 2.97 (4H, m), 3.30 (4H, m), 5.59 (2H, s), 6.15 (2H, s), 6.74 (2H, s), 7.15 (4H, s). ^{13}C NMR (D_2O, 100 MHz): 23.9 (C-4,C-4′), 39.0 (C-3, C-3′), 58.1 (C-1, C-1′), 115.0 (C-8, C-8′), 115.6 (C-5, C-5′), 122.2 (C-10, C-10′), 124.6 (C-9, C-9′), 143.2 (C-7, C-7′), 144.5 (C-6, C-6′), 130,5(C-12, C-13, C-15, C-16).

2.9. Procedure for 6,7-dimethoxyphenylethylamine reaction with 3-nitrobenzaldehyde

A solution of 6,7-dimethoxyphenylethylamine (× mol) and 3-nitrobenzaldehyde (× mol) in methanol was refluxed for 72 h. The solvent was evaporated and the crude product was treated with 37% HCl; the resulting mixture was refluxed for 1 h. The precipitated product was filtered and washed with methanol.

2.10. *N*-[2-(3,4-Dimethoxyphenyl)ethyl]-*N*-[(3-nitrophenyl) methylene]amine 8

(90%, yellow solid, mp 91–92 °C) ^{1}H NMR ($CDCl_3$, 400 MHz): 3.00 (2H, t, J = 6.8 Hz), 3.91 (2H, t, J = 6.8 Hz), 6.76 (1H, s), 6.79 (1H, d, J = 7.6 Hz). 6.81 (1H, d, J = 7.6 Hz), 7.60 (1H, t, J = 8.0 Hz), 8.03 (1H, d, J = 8.0 Hz), 8.21 (1H, s), 8.27 (1H, d, J = 8.0 Hz), 8.57 (1H, s).

2.11. 6,7-Dihydroxy-1-(3-nitrophenyl)-1,2,3,4-tetrahydroisoquinoline hydrobromide 9

(92%, cream-colored solid, mp 258–260 °C) ^{1}H NMR (D_2O, 400 MHz): 3.22 (2H, m), 3.51 (2H, m), 3.63 (3H,s), 3.91 (3H,s), 5.94 (1H, s), 6.44 (1H, s), 7.03 (1H, s). 7.70 (1H, t, J = 8.0 Hz), 7.82 (1H, d, J = 8.0 Hz), 8.19 (1H, s), 8.40 (1H, d, J = 8.0 Hz).

2.12. Synthesis of 6,7-dimethoxy-1,4-dihydro-(2*H*)-isoquinoline-3-one 10 (Scheme 3)

3,4-Dimethoxybenzylamine (0.50 g, 3 mmol) was added to a solution of chloroacetic acid (0.57 g, 6 mmol) and dicyclohexylcarbodiimide (DCC) (1.24 g, 6 mmol) in 5 mL dichloromethane (DCM). The resulting mixture was shaken at room temperature for 3 h and filtered. The solvent was evaporated and the product extracted with isopropyl acetate. The isopropyl acetate was evaporated off; the crude product was dissolved in 5 mL ethyl ether and treated with 0.03 g $AlCl_3$. The resulting mixture was shaken for 6 h; once this time had elapsed, the product was isolated and purified by silica gel column chromatography, eluted with isopropyl acetate.

2.13. 6,7-Dimethoxy-1,4-dihydro-(2*H*)-isoquinoline-3-one 10

(0.43 g, 69%, white solid, mp 118–120 °C). ^{1}H NMR (400 MHz, $CDCl_3$): 4.44 (2H, s), 3.89 (6H, s), 4.11 (2H, s), 6.81 (1H, s), 6.84 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$): 42.6 (C-4), 43.7 (C-1), 55.9 (CH_3–O), 56.0 (CH_3–O), 11.2 (C-8), 111.3 (C-5), 129.8 (C-9, C-10), 148.7 (C-7), 149.3 (C-6), 165.7 (C-3).

2.14. Synthesis of 6,7-dimethoxy-(1*H*)-isoquinoline-3,4-dione 11 (Scheme 4)

3,4-Dimethoxybenzylamine (0.50 g, 3 mmol) was added to a solution of oxalic acid (0.30 g, 3,3 mmol) and dicyclohexylcarbodiimide (DCC) (1.38 g, 6,7 mmol) in 5 mL dichloromethane (DCM). The resulting mixture was shaken at room temperature for 3 h and filtered; the DCM was evaporated. Product **11** was extracted with isopropyl acetate; sub product **12** corresponded to an insoluble solid in isopropyl acetate.

2.15. 6,7-Dimethoxy-1,2-dihydroisoquinoline-3,4-dione 11

(0.49 g, 73%, white solid, mp 213–214 °C). ^{1}H NMR (400 MHz, $CDCl_3$/CD_3OD (5:5)): 3.88 (3H, s), 3.89 (3H, s), 4.34 (2H, d, J = 5.68 Hz), 4.73 (1H, s), 6.82 (1H, s), 6.84 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$/CD_3OD (5:5)): 43.6 (C-1), 55.2 (CH_3–O), 55.4 (CH_3–O), 110.9 (C-5), 111.5 (C-8), 119.4 (C-10), 132.7 (C-9), 148.0 (C-6), 149.0 (C-7), 158.5 (C-3, C-4).

2.16. *N*,*N*′-Bis(3,4-dimethoxybenzylethanodiamide) 12

(0.06 g, 11%, white solid, mp 160–162 °C). ^{1}H NMR (400 MHz, CD_3OD): 3.83 (3H, s), 3.84 (3H, s), 4.28 (2H, s), 4.65 (2H, s), 6.84

(2H, d, J = 8.0 Hz), 6.86 (2H, s), 6.89 (2H, d, J = 8 Hz). ^{13}C NMR (101 MHz, CD_3OD): 43.7 (C-Ph), 55.9 (CH_3–O), 111.2 (C-2), 111.3 (C-5), 119.4 (C-6), 129.8 (C-1), 148.7 (C-4), 149.3 (C-3), 165.7 (CO).

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