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Imidazolidin-1-oles, *N*-2-aminoethyl nitrones and 1,2,5-oxadiazinanes. A novel ring–chain tautomerism

Necdet Coşkun[a,*] and Oktay Asutay[b]

[a]*Uludağ University, Department of Chemistry, 16059 Bursa, Turkey*
[b]*Namık Kemal University, Muratlı Vocational School, Department of Chemistry, Muratlı-Tekirdağ, Turkey*

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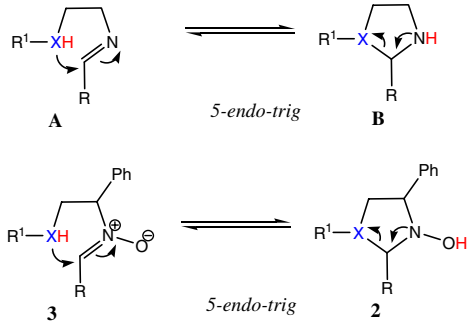
Abstract—Imidazolin-3-oxides **1** were reduced with $NaBH_4$ in THF at reflux to give the corresponding 2,3,5-triarylimidazolidin-1-oles **2**, which are proved to be in a ring–chain–ring tautomeric equilibrium with *N*-2-aminoethyl nitrones **3** and 3,5,6-triphenyl-1,2,5-oxadiazinanes **4**. The ratios of the ring and chain form are determined by the substituent at the reaction centre and can be described by the equation $\log K_X = \rho\sigma^+ + \log K_{X=H}$. These are the first examples of a novel three-component ring–chain–ring tautomeric equilibrium characterized by a Hammett-type equation. The stability of the ring form was favoured by electron-withdrawing substituents. Treatment of the equilibrium mixture of **2**, **3** and **4** with phenylisocyanate in refluxing toluene gives selectively the corresponding O-carbamoylated imidazolidines **5**; *cis*-**5** was shown to isomerize to *trans*-**5** on heating.

1. Introduction

The reversible intramolecular addition of an XH (X = O, S, NR) group to a C=N double bond in structure **A** to form a cyclic structure **B** is a well-known phenomenon. While the 5-*endo-trig* process has been investigated in detail in N-unsubstituted 1,3-X,*N*-heterocycles,[1] including N-alkyl or aryl substituted 2-arylimidazolidines,[2] there are no examples of ring–chain tautomerism in 1,3-X,*N*-OE (E = H in the present case) heterocyclic systems **2** (Scheme 1). 1–4 Hydrogen shift in the latter case would give the corresponding aminonitrone tautomer **3**. These ring–chain tautomeric processes are expected to influence the reactivity, and therefore the synthetic applicability, of these compounds.

Here we report the ring–chain tautomeric equilibrium between imidazolidin-1-oles **2**, *N*-2-aminoethyl nitrones **3** and 1,2,5-oxadiazinanes **4**. These are examples of a novel three-component ring–chain tautomeric equilibrium characterized by a Hammett-type equation. Treatment of the equilibrium mixture of **2**,**3** and **4** with phenylisocyanate in refluxing toluene gives selectively the corresponding O-carbamoylated products **5**.



Scheme 1. 5-*endo-trig* cyclization with 1–3 and 1–4 hydrogen migration.

2. Effect of substituents on the ring–chain tautomeric equilibria of imidazolidin-1-oles, aminonitrones and oxadiazinanes

Nitrones[3] **1a–f** were subjected to reduction[4] with $NaBH_4$ in THF and the products were characterized as the corresponding imidazolidin-1-oles[5] **2a–f** in equilibrium with *N*-(1-aryl-2-arylaminoethyl) nitrones **3a–f** and oxadiazinanes **4a–f** (Scheme 2, Table 1).

The compounds in equilibrium were characterized by analytical and spectroscopic methods. The most characteristic spectral parameters distinguishing aminals **2** and

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* Corresponding author. E-mail: coskun@uludag.edu.tr

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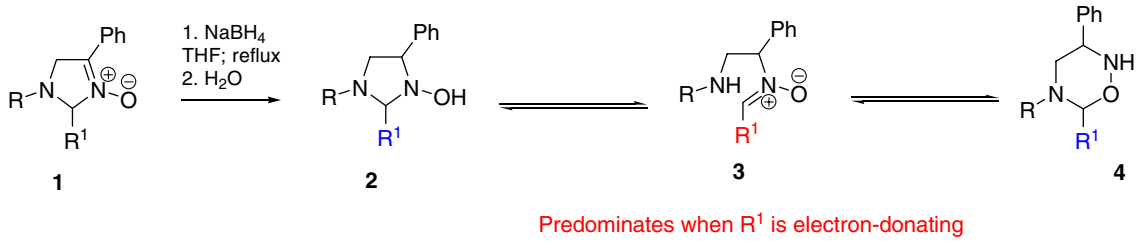


Scheme 2. Ring–chain tautomers **2**–**4a**–**f**.

Table 1. Ring–chain equilibria of compounds **2**–**4** in $CDCl_3$ at 25 °C

			Products in equilibrium[a] (%)					
1–**4**	R	R^1	rt (h)	**4**	**3**	**2**	*trans*-**5**/*cis*-**5**[d]	Mp (°C)
a	4-MeC_6H_4	4-ClC_6H_4	22	21.8	58.8[b]	19.4	39:39	159–160
b	4-MeC_6H_4	4-$NO_2C_6H_4$	2.5	30	24[c]	46	16:11	
c	4-MeC_6H_4	Ph	22	15.3	69.4	15.3	22:10	144–145
d	4-MeC_6H_4	3,4-$(MeO)_2C_6H_3$	17	3.6	91	5.4	40:32	152–153
e	4-$MeOC_6H_4$	3,4-$(MeO)_2C_6H_3$	17	4	90	6		154–155
f	4-MeC_6H_4	4-$MeOC_6H_4$	17	6	86.2	7.8	53:31	98[e]

[a] The yields of **2**, **3** and **4** were determined by ^1H NMR based on the integral areas of the singlets at ca. 5.12, and 5.70, for **2** and **4** and a doublet of doublets at 5.20 ppm for **3**, respectively.
[b] The crude reaction mixture contains 24% of *N*-(4-chlorobenzylidene)-4-methylbenzenamine and 8% *N*-(4-chlorobenzyl)-4-methylbenzenamine.[6]
[c] The reaction mixture contained only 32.5% of **2**–**4b**.
[d] The contents (%) after 3 h reflux in toluene; the singlets at ca. 5.87 and 5.50 and doublets of doublets at 5.33, 5.00 and 5.20 ppm were used for the determination of the ratios of *trans*-**5** and *cis*-**5**, the other products were 2-, and 3-imidazolines and the unreacted nitrone **3**.
[e] Crystallized from petroleum ether.

N,*O*-acetals **4** were the resonances at ca. 85.3 and 91.8 in their ^{13}C NMR spectra and the signals for the attached hydrogens at ca. 5.12 and 5.70 ppm. All other spectral patterns were in agreement with the proposed structures. Protons appearing as a doublet of doublets at ca. 5.20 attached to a carbon at ca. 77.6 are characteristic of nitrones **3**. The presence of a signal in the ^1H NMR spectra at 8.20 ppm was due to the *ortho* protons of a C-phenyl group being affected by the anisotropic field of the nitrone oxygen. Nitrones **3** have a characteristic ABX system with the AB part at ca. 4 ppm and the X part at 5.20 with $J = 14.4$; 9.6; 3.6 Hz. The nitrone C–H resonates as a singlet at ca. 7.30 ppm. The ratios were determined in $CDCl_3$ at 25 °C and are given in Table 1. The mixtures from the reduction of nitrones **1** were subjected to crystallization from ethanol and afforded crystalline products with sharp melting points.

Samples crystallized from ethanol were dissolved in $CDCl_3$ and equilibrated at 25 °C until constant concentrations were measured (Table 1). The equilibrium constants for the cases with electron-donating groups were lower than those with electron-withdrawing groups. Calculated $\log(K_X/K_{X=H})$ values based on the equilibrium constants for the total ring products and the chain is in linear correlation[7] with lit.[8] σ^+ constants (Fig. 1). $\text{Log}(K_X/K_{X=H})$ for the equilibria of **2** and **3**, and **4** and **3** were again in good correlation with the same equilibrium constants (Table 2). Similar interpretations for the **2**/**4** ratios showed that the latter were not substituent sensitive.

Crystallized or crude reaction mixtures containing tautomers **2**–**4** were treated with phenylisocyanate in toluene at reflux. Inspection of the resulting mixtures revealed that the main reaction pathway proceeded through imidazolidines **2**, which are carbamoylated to give *cis*- and *trans*-**5** (Scheme 3, Table 1). The ratio of diastereomers was determined after 3 h at reflux. The products crystallized from ethanol were characterized to be *cis*-**5** by 1D and 2D NMR experiments. The C-2H chemical shifts were ca. 5.86 and 5.50 ppm, respectively, for the trans and cis isomers. The IR spectra of *cis*-**5** showed characteristic absorptions at 3330 and 1740 cm^{-1} typical for ν_{N-H} and $\nu_{C=O}$ of a *O*-phenylcarbamoyl group.[9] Compounds **5** undergo elimination to give the corresponding 2- and 3-imidazolines.[10] Heating of the compounds during GC–MS injection produced phenylisocyanate and the corresponding 2- and 3-imidazolines. The products isolated by crystallization from ethanol were shown to be the corresponding *cis*-**5** iso-

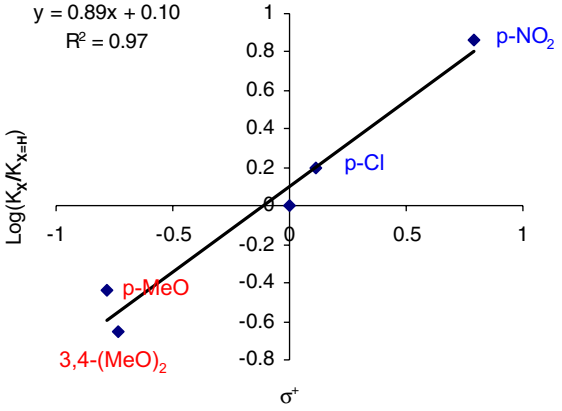
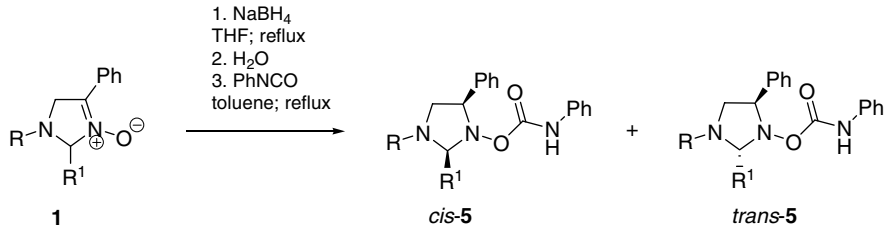


Figure 1. Plot of σ^+ constants versus $\log(K_X/K_{X=H})$.

Table 2. Linear free-energy relationships for the total ring–chain, **2**–**3** and **4**–**3** equilibria

S	R/C	**2/3**	**4/3**	$\log(K_X/K_{X=H})_{R/C}$	$\log(K_X/K_{X=H})_{2/3}$	$\log(K_X/K_{X=H})_{4/3}$	lit. σ^+
Cl	0.7	0.33	0.37	0.20	0.18	0.23	0.11
NO_2	3.17	1.92	1.25	0.86	0.94	0.75	0.79
H	0.44	0.22	0.22	0	0	0	0
3,4(MeO)$_2$	0.10	0.06	0.04	−0.65	−0.57	−0.74	−0.73[a]
3,4(MeO)$_2$	0.11	0.07	0.04	−0.60	−0.50	−0.74	
MeO	0.16	0.09	0.07	−0.44	−0.38	−0.50	−0.78

[a] Calculated as $\sigma_p^+ + \sigma_m^+$.



Scheme 3. Selective O-carbamoylation of tautomeric mixtures **2**–**4a**–**f**.

mers, except in the case of **4a** where the $CDCl_3$ solution of the compound revealed the presence of *cis*- and *trans*-**5**. NOESY 1D experiments performed on **5c** confirmed the cis orientation of the aromatic rings at C-2 and C-5. Irradiation of the C-2H singlet at 5.50 ppm led to signal enhancement of the triplet at C-5, and *ortho* protons of C-2 and N-3 aromatic rings by 1.4, 4.6 and 5.1%, respectively. Irradiation of the triplet at C-5 enhanced the *ortho* proton signal of the aromatic ring at C-5 as well as the singlet at C-2. The C-5H peaks of *trans*-**5** isomers overlapped with the triplets of *cis*-**5** at ca. 4.72 ppm. N-Carbamoylation of oxadiazinanes **4** would give a downfield peak for C-3H.

2.1. Thermal isomerization of *cis*-5a to *trans*-5a

The ^1H NMR spectrum at 25 °C in $CDCl_3$ of the crystalline product with a sharp melting point revealed the presence of *cis*- and *trans*-**5a**, where the cis isomer predominates. The spectra recorded at higher temperatures (Fig. 2) showed that the cis isomer converts to *trans*-**5** and the ratio remains nearly constant in the 30–40 °C range. Pure *cis*-**5c** was treated in the same way, however, no isomerization to *trans*-**5c** was observed.

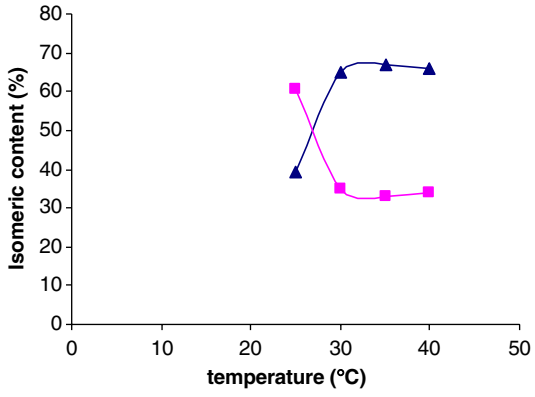


Figure 2. Temperature dependence of the cis–trans equilibrium for compound **5a** *trans*-**5a**, ▲; *cis*-**5a**, ■.

The isomerization of *cis*- and *trans*-**5** may involve resonance stabilized iminium **A**–**B** or carbamoylated nitrone type dipoles **C**–**D** (Scheme 4). The other possibility is decarbamoylation to nitrone **3**, recyclization to imidazolidine **2** and recarbamoylation to give isomeric **5**. 4-Chlorobenzaldehyde, 3%, was detected in the $CDCl_3$ solution of *cis*- and *trans*-**5**, which could result from hydrolysis of both **A**–**B** and **C**–**D** intermediates although our observations are that iminium species are more sensitive to moisture.

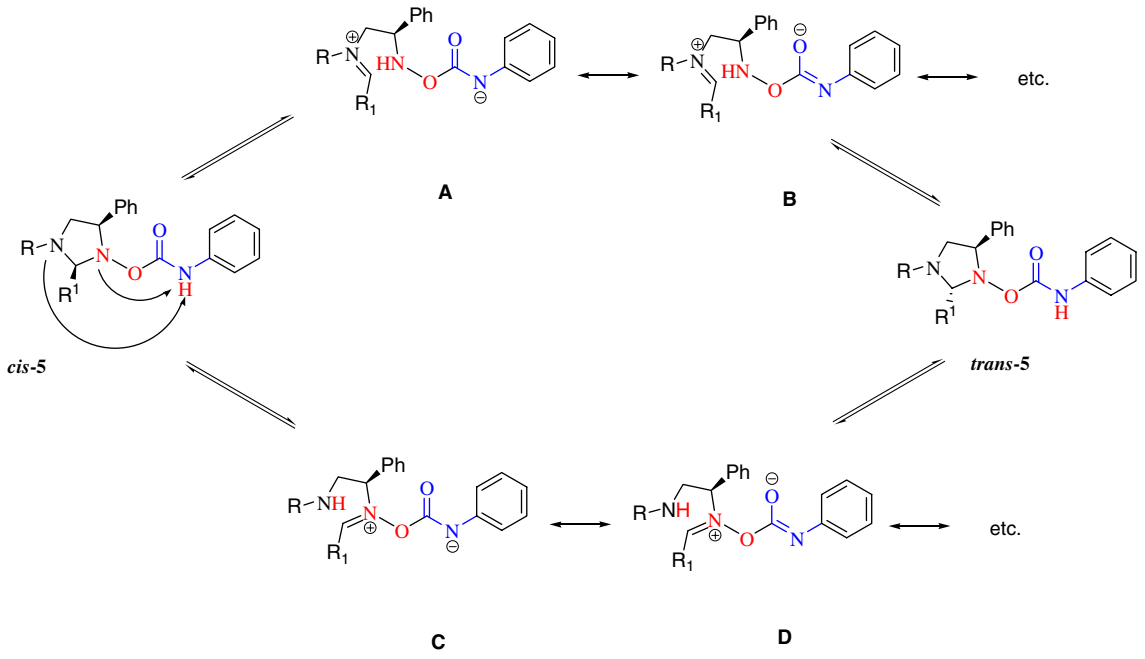
The effect of temperature on the cis–trans equilibrium may be rationalized by assuming that the cis isomer is the kinetic product, which converts slowly at room temperature but rapidly reaches equilibrium at higher temperatures. The ^1H NMR spectrum of the latter mixture was recorded at 20 °C after several days standing at room temperature and showed that the ratio remains the same as for that recorded at 40 °C.

2.2. Synthesis of 2–4a–f

General procedure. To a solution of nitrone **1a**–**f** (0.5 mmol) in THF (20 mL) $NaBH_4$ (5 mmol) was added and the reaction mixture refluxed with stirring for a specified time. The solvent was evaporated under vacuum and the residue suspended in water and extracted with chloroform (2×15 mL). The combined extracts were washed with water (2×15 mL), dried over anhydrous sodium sulfate, filtered and the solvent evaporated under reduced pressure. The residue was dissolved in ethanol with heating and left to crystallize at room temperature.

2.3. C-Phenyl-*N*-(1-phenyl-2-*p*-tolylaminoethyl) nitrone 3c

The spectrum is elicited from those of the equilibrated tautomeric mixture. ^1H NMR (400 MHz, $CDCl_3$): δ 2.25 (3H, s), 3.63 (1H, dd, $J = 14.4$; 3.6), 4.04 (1H, br s), 4.33 (1H, dd, $J = 14.4$; 9.6), 5.20 (1H, dd, $J = 9.6$;



Scheme 4. Possible mechanisms for the isomerization of *cis*- and *trans*-**5**.

3.2), 6.56 (2H, d, $J = 8.4$), 7.02 (2H, d, $J = 8.4$), 7.37–7.58 (8H, m), 8.18–8.20 (2H, m). Anal. Calcd for $C_{22}H_{22}N_2O$ (330.42) C, 79.97; H, 6.71; N, 8.48. Found C, 79.85; H, 6.62; N, 8.39.

2.4. C-(3,4-Dimethoxyphenyl)-*N*-(1-phenyl-2-*p*-tolyl-aminoethyl) nitrone 3d

IR (KBr) ν_{NH} 3309; $\nu_{C=N}$ 1596 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.26 (3H, s), 3.64 (1H, dd, $J = 14.4$; 3.6), 3.91 (3H, s), 3.93 (3H, s), 4.34 (1H, dd, $J = 14.4$; 9.6), 5.17 (1H, dd, $J = 9.6$; 3.2), 6.58 (2H, d, $J = 8.8$), 6.86 (1H, d, $J = 8.4$), 7.01 (2H, d, $J = 8.8$), 7.32 (1H, s), 7.38–7.44 (4H, m), 7.57–7.59 (2H, m), 8.32 (1H, d, $J = 2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 20.4; 46.1; 55.9 (2 carbons); 77.2; 110.5; 111.0; 113.3; 123.2; 123.6; 127.3; 127.5; 128.9; 129.0; 130.0; 135.2; 136.0; 144.6; 148.4; 150.7. Anal. Calcd for $C_{24}H_{26}N_2O_3$ (390.47) C, 73.82; H, 6.71; N, 7.17. Found C, 73.70; H, 6.65; N, 7.10.

2.5. C-(3,4-Dimethoxyphenyl)-*N*-(1-phenyl-2-*p*-methoxy-phenylethyl) nitrone 3e

IR (KBr) ν_{NH} 3313; $\nu_{C=N}$ 1596 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.61 (1H, dd, $J = 14.4$; 3.6), 3.76 (3H, s), 3.91 (3H, s), 3.94 (3H, s), 4.31 (1H, dd, $J = 14.4$; 9.6), 5.15 (1H, dd, $J = 9.6$; 3.6), 6.62 (2H, d, $J = 8.4$), 6.79 (2H, d, $J = 8.4$), 6.87 (1H, d, $J = 8.8$), 7.31 (1H, s), 7.38–7.44 (4H, m), 7.57–7.59 (2H, m), 8.33 (1H,d, $J = 2$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 46.8; 55.8; 55.9 (2 carbons); 77.2; 110.6; 111.0; 114.7; 115.0; 123.2; 123.6; 127.5; 128.9; 129.0; 135.3; 136.1; 141.0; 148.4; 150.8; 152.5. Anal. Calcd for $C_{24}H_{26}N_2O_4$ (406.47) C, 70.92; H, 6.45; N, 6.89. Found C, 70.80; H, 6.50; N, 6.70.

2.6. 3,6-Diphenyl-5-*p*-tolyl-1,2,5-oxadiazinane 4c

IR (KBr) ν_{NH} 3255 cm^{-1}. The spectrum was elicited from the crystalline product immediately upon dissolution in $CDCl_3$. The solution consisted of nearly 80% of **4c**. ^1H NMR (400 MHz, $CDCl_3$): δ 2.25 (3H, s), 3.88 (1H, dd, $J = 10.8$; 4.0), 4.10 (1H, br s), 4.48 (1H, dd, $J = 10.4$; 6.4), 5.59 (1H, s), 6.00 (1H, br s), 6.45 (2H, d, $J = 8.4$), 7.03 (2H, d, $J = 8.4$), 7.25–7.38 (10H, m).

2.7. Synthesis of 1-phenylcarbamoyloxy-2,3,5-triaryl-imidazolidines 5

A mixture of **2**–**4a**–**f** (0.15 mmol) in toluene (10 mL) was refluxed in the presence of phenylisocyanate (0.30 mmol, 0.036 g) for 3 h. The product mixture was analyzed for the ratio of *cis* and *trans*-**5** (See Table 1).

2.8. *cis*-1-Phenylcarbamoyloxy-2,5-diphenyl-3-*p*-tolyl-imidazolidine 5c

A mixture of **2**–**4c** (2.5 mmol) in acetonitrile (15 mL) was refluxed in the presence of phenylisocyanate (5 mmol, 0.596 g) for 1.5 h. The solvent was evaporated and the residue was treated with petroleum ether (2×10 mL) and the remaining part was dissolved in ethanol (25 mL) and refluxed under condenser for 10 min. The resulting precipitate was filtered to give 0.126 g, 11% of **5c**. A further crop of 0.066 g, 6%, crystallized from the mother liquor upon cooling in a fridge. Mp 169 °C with decomposition; IR (KBr) ν_{NH} 3330, $\nu_{C=O}$ 1737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.21 (3H, s), 4.02–4.11 (2H, m), 4.72 (1H, t, $J = 8.8$), 5.50 (1H, s), 6.42 (2H, d, $J = 8.0$), 6.80 (2H, d, $J = 7.6$), 6.95–7.00 (3H, m), 7.13 (2H, t, $J = 7.2$), 7.28–7.37 (6H, m), 7.50 (2H, d, $J = 7.2$), 7.57 (2H, d, $J = 7.2$), 7.77 (1H,

s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.3 (Me); 54.7 (CH_2); 68.9 (CH); 84.7 (CH); 113.6; 119.7; 124.1; 127.2; 127.5; 127.9; 128.7; 128.9 (2 carbons); 129.3; 129.4; 129.6; 135.7; 136.3; 137.9; 143.4; 152.7. Anal. Calcd for $C_{29}H_{27}N_3O_2$ (449.54) C, 77.48; H, 6.05; N, 9.35. Found C, 77.40; H, 5.95; N, 9.40.

2.9. *cis*-1-Phenylcarbamoyloxy-2-(3,4-dimethoxyphenyl)-5-phenyl-3-*p*-tolylimidazolidine 5d

The product was recrystallized from ethanol; mp 130–132 °C; IR (KBr) ν_{NH} 3303, $\nu_{C=O}$ 1737 cm^{-1}; IR (KBr) ν_{NH} 3330; $\nu_{C=O}$ 1736 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.22 (3 H, s), 3.76 (3H, s), 3.81 (3H, s), 4.01–4.11 (2H, m), 4.70 (1H, t, $J = 8.8$), 5.42 (1H, s), 6.45 (2H, d, $J = 8.8$), 6.80 (1H, d, $J = 8.0$), 6.85 (2H, d, $J = 8.0$), 6.95–7.00 (4H, m), 7.15 (3H, t, $J = 7.2$), 7.31–7.38 (3H, m), 7.50 (2H, d, $J = 7.2$), 7.86 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.3 (Me); 54.8 (CH_2); 55.9 (Me); 56.1 (Me); 68.7 (CH); 84.8 (CH); 109.6; 111.7; 113.8; 119.3; 119.4; 119.6; 124.2; 127.6; 127:8; 128.7; 128.9; 129.0; 129.5; 135.5; 136.4.143.7; 149.6; 149.7; 152.8. Anal. Calcd for $C_{31}H_{31}N_3O_4$ (509.6) C, 73.06; H, 6.13; N, 8.25. Found C, 73.15; H, 6.20; N, 8.10.

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