

HETEROCYCLES, Vol. 89, No. 1, 2014, pp. 197 - 207. © 2014 The Japan Institute of Heterocyclic Chemistry
Received, 3rd November, 2013, Accepted, 2nd Decemeber, 2012, Published online, 12th December, 2013
DOI: 10.3987/COM-13-12878

SOLVENT-FREE SYNTHESIS OF NEW CHIRAL 3-PHENYLAMINO-3,5-DIHYDRO-4H-IMIDAZOL-4-ONE DERIVATIVES FROM α -AMINO ACID PHENYLHYDRAZIDES

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Abstract – Enantiopure 2,5-disubstituted 3-phenylamino-3,5-dihydro-4H-imidazol-4-one derivatives were obtained in good to excellent yields by condensation of chiral α -amino acid phenylhydrazides and triethyl orthoesters in the presence of dry acetic acid as catalyst. All reactions are performed under solvent-free and mild conditions.

The imidazol-4-one ring often appears as the core structure in many drug substances, covering a wide range of pharmaceutical activities.^{1,2} For example, 5,5-disubstituted imidazolones have shown antihypertensive and vasodilating properties.³ Anticonvulsant activity has been reported for 3-aminoimidazol-4-one derivatives.^{4,5} Whilst antibacterial activity was found for several benzylideneimidazol-4-ones.^{6,7} Moreover, the 2-aminoimidazolone derivatives isolated from the marine sponges such as Dispacamide, Polyandrocarpamine and Leucettamine B display various types of biological activities.⁸⁻¹⁰ Interest was further enhanced by the discovery of agrochemical activities of Imazaquin[®] as herbicide and the Fenamidone[®] as fungicide^{11,12} (Figure 1).

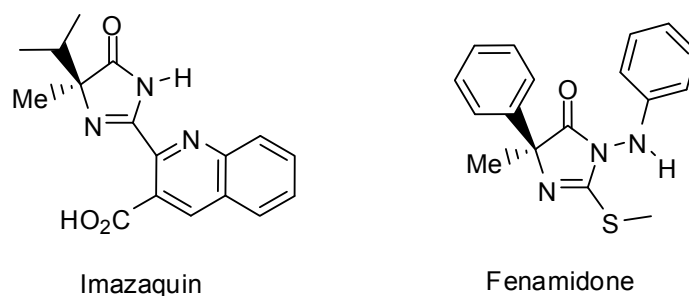
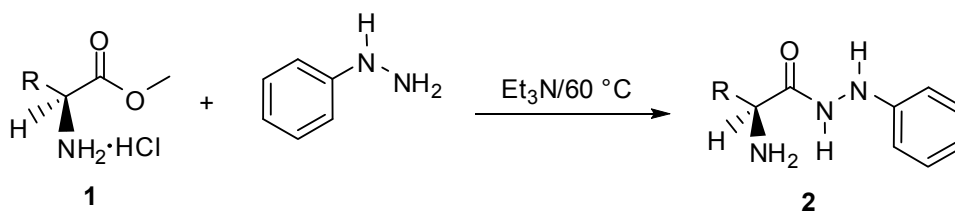


Figure 1. Agrochemical imidazolone derivatives

The imidazol-4-one ring was first synthesized by Finger.¹³ Three different pathways can be used for the synthesis of this heterocycle: route (a), condensation between an imidate and an amino ester,¹⁴ route (b), condensation of an orthoester and an amino amide,¹⁵⁻¹⁷ and route (c), acylation of the same amino amide and basic cyclization of the resulting product.¹⁸

As part of our ongoing efforts directed toward the synthesis of heterocyclic compounds starting from α -amino acids,¹⁹⁻²³ we report here an efficient method for the synthesis of 3-phenylamino-3,5-dihydro-4*H*-imidazol-4-ones utilizing α -amino acid phenylhydrazides and triethyl orthoesters. To the best of our knowledge, the synthesis of 3-phenylamino-3,5-dihydro-4*H*-imidazol-4-one derivatives making use of the above-mentioned reagents has not been reported. Moreover, the pharmacological activity of the imidazol-4-ones was influenced by both chirality and the nature of the substituents in the heterocycle. Surprisingly, a few reports have been published concerning the synthesis of chiral imidazol-4-ones in the chemical literature.^{1,2}

The starting (L)- α -amino acid phenylhydrazides **2a-e** were prepared in a manner similar to well-known procedures (Scheme 1).²⁴⁻²⁶ Thus, treatment under mild conditions of commercially available (L)- α -amino acid ester hydrochlorides **1a-e** with phenylhydrazine in the presence of triethylamine afforded the corresponding phenylhydrazides **2a-e** in good yields (Table 1). In each case, only one enantiomer was detectable by ¹H NMR using Eu(hfc)₃ as chiral shift reagent.



Scheme 1. Synthesis of the starting α -amino acid phenylhydrazides

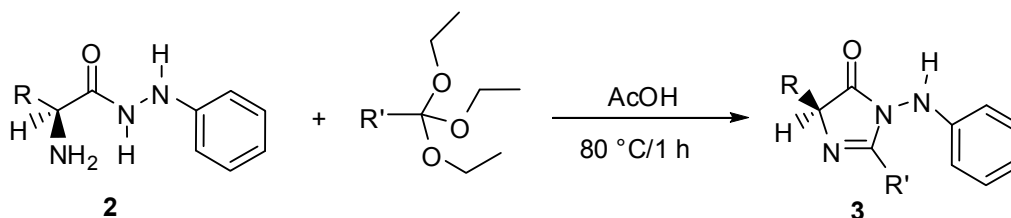
Table 1. Synthesis of α -amino acid phenylhydrazides **2a-e**

Product	R	Yield (%) ^a	mp (°C)	[α] _D ^b
2a	Me	80	122-124	+34.2
2b	<i>i</i> -Pr	65	152-154	+30.8
2c	Bn	85	142-144	+39.4
2d	CH ₂ OH	68	163-165	+42.6
2e	CH ₂ -CH ₂ -SMe	78	128-130	+29.8

^a Yield of the isolated product

^b (*c* 0.2, MeOH)

Phenylhydrazides **2a-e** were heated with two equivalents of triethyl orthoesters: orthoacetate, orthopropionate and orthobenzoate (Scheme 2) yielding the derivatives of 3-phenylamino-3,5-dihydro-4*H*-imidazol-4-one **3a-e**. The optimization of the reaction conditions revealed that the formation of the desired imidazol-4-ones **3** proceeded smoothly in the absence of solvent and in the presence of a catalytic amount of dry acetic acid (Table 2). Application of an equimolar amount of hydrazide **2a** and triethyl orthoacetate yielded only 33% of the cyclized product. Attempts to enhance the yield through the use of an alternative acid catalyst (PTSA) and higher reaction temperatures provided no significant benefit. Increasing the number of equivalents of the triethyl orthoacetate afforded the desired product **3a** along with a complex mixture of by-products.



Scheme 2. Synthesis of 3-phenylamino-3,5-dihydro-4*H*-imidazol-4-ones

Table 2. Optimization of the reaction conditions for the preparation of **3a**

Entry	Substrate ratio ^a	AcOH (equiv.)	Solvent	Yield (%) ^b
1	2/1	0.2	toluene	43
2	2/1	0.2	MeCN ^{''}	29
3	2/1	0.2	EtOH	36
4	2/1	-	toluene	11
5	2/1	0.1	-	81
6	1/1	0.1	-	33

^a Triethyl orthoacetate/**2a**

^b Yield of the pure product after flash chromatography

The results shown in Table 3 indicate the scope and potential limitations of this process. It was found that compounds possessing a phenyl group at position 2 were formed in respectable yields, whereas the corresponding products with alkyl groups (R' = Me, Et) reacted less efficiently. In addition, the steric hindrance caused by the R substituent in the starting phenylhydrazide also played an important role. The yields of imidazol-4-ones **3** obtained from (L)-valine phenylhydrazide were relatively lower than those

prepared from (L)-alanine, (L)-phenylalanine, (L)-serine and (L)-methionine phenylhydrazides. In addition, no racemization was observed by HPLC analysis.

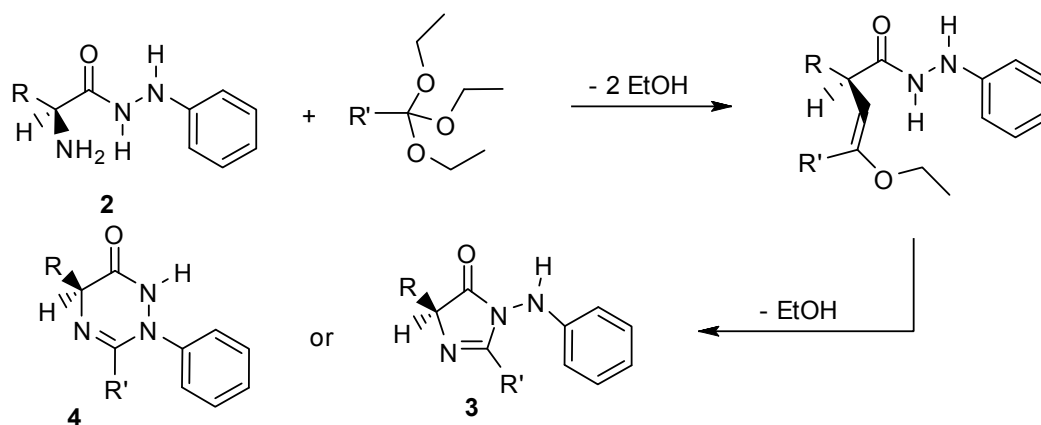
Analyzing the mechanism of the reaction between triethyl orthoesters and α -amino acid phenylhydrazides, we assumed that the first step, the amino group attacks the electrophilic carbon atom of the orthoester which leads to the iminoethers (Scheme 3). In the second step, two nucleophilic attacks on the iminoether carbon are possible resulting to either five-membered 3,5-dihydro-4*H*-imidazol-4-one **3** or six-membered 2,5-dihydro-1,2,4-triazin-6(1*H*)-one **4**. The products were characterized by HRMS, as well as ^1H NMR and ^{13}C NMR spectra. The three nitrogen containing ring structure was excluded considering the ^1H NMR features of the NHNHPh skeleton: these two protons usually resonate for α -amino acid phenylhydrazides at ≈ 6 ppm as singlet for the NH attached to the phenyl group and at ≈ 9 ppm as broad singlet for the NH attached to the carbonyl group.²⁷ In products **3** only the chemical shifts assigned to the NH attached to the phenyl group are present. Furthermore, this last signal showed HMBC correlation with the quaternary carbon signal of phenyl group at ≈ 147 ppm. Both facts give good evidence for the cyclic structure **3** and not **4**.

Table 3. Synthesis of 3-phenylamino-3,5-dihydro-4*H*-imidazol-4-one derivatives **3a-l**

Product	R	R'	Yield (%) ^a	$[\alpha]_D^b$
3a	Me	Me	63	-33.4
3b	Me	Et	68	-24.3
3c	Me	Ph	81	+22.6
3d	<i>i</i> -Pr	Me	52	-13.2
3e	<i>i</i> -Pr	Ph	61	+19.1
3f	Bn	Me	57	+32.5
3g	Bn	Ph	70	-11.6
3h	CH ₂ OH	Me	49	+21.9
3i	CH ₂ OH	Et	54	+36.7
3j	CH ₂ OH	Ph	75	-15.8
3k	CH ₂ -CH ₂ -SMe	Me	60	+25.4
3l	CH ₂ -CH ₂ -SMe	Ph	69	+30.1

^a Yield of the pure product after flash chromatography

^b (*c* 0.5, CHCl₃)



Scheme 3. Proposed mechanism of the cyclocondensation reaction

In summary, the efficient process described in this paper has enabled us to prepare chiral 2,5-disubstituted 3-phenylamino-3,5-dihydro-4*H*-imidazol-4-ones from inexpensive and readily available (L)- α -amino acid phenylhydrazides. Avoidance of solvents, short reaction times and good yields are the outstanding advantages of the present protocol. The potential antibacterial and fungicide activities of these new products are under investigation in our laboratory.

ACKNOWLEDGEMENTS

The authors thank the DGRST (Direction Générale de la Recherche Scientifique et de la Rénovation Technologique) of the Tunisian Ministry of Higher Education and Scientific Research for financial support of this research.

EXPERIMENTAL

General information: All reactions are carried under argon atmosphere in oven dried glassware equipped with a magnetic stirrer and a rubber septum unless otherwise indicated. All solvents are freshly distilled before use. All other commercial reagents were used without further purification. Reactions were monitored by thin layer chromatography (TLC) of aliquots using Merck 60F-254 silica gel plates (0.25 mm layered thickness). Column chromatographies were carried out with silica gel 60–120 mesh (Merck). ^1H and ^{13}C NMR spectra were recorded in deuterated solvents, on a Bruker AC-300 spectrometer. IR spectra were recorded with Biorad FTS-6000 spectrometer. HRMS were obtained on a Waters Micromass Q-Tof analytical instrument. Melting points were recorded on a Fisher Johns melting point apparatus. The shift reagent was $\text{Eu}(\text{hfc})_3$ (Aldrich Chem. Co.).

HRMS analysis

The samples were weighed, 0.5 mg of each compound, dissolved and diluted to 1 mL with MeOH. From each solution an aliquot of 5 μ L was injected on an analytical column, Ace C18 3 μ m, 150 \times 3.0 mm. Separated through a gradient (5–95% MeCN in 0.2% formic acid, flow rate 0.5 mL/min, column oven temperature 50 $^{\circ}$ C) and detected by a diode-array detector (190–350 nm) and quadrupole time-of-flight mass spectrometer (Q-Tof micro, Micromass Amiens, France) operated in electrospray ionization positive ion mode (capillary voltage 3.0 KV, cone voltage 40 V, ion energy 10 eV, mass range 80–1000 m/z, scan rate 1 s and inter scan delay 0.1 s).

HPLC analysis

HPLC analyses were performed on a JASCO (UV-2075 plus, PU-2080 plus, Japan) apparatus, using Supelco chiral phase column Chirobiotic V (4.6 mm \times 25.0 cm) with a flow of 0.7 mL/min, UV detection at λ = 254 nm and different mobile phase as follows: mixture of hexane/isopropanol in ratio 6/4 for **3a** (t_r = 8.2 min), **3b** (t_r = 6.5 min), **3c** (t_r = 8.9 min), hexane/isopropanol in ratio 5/5 for **3d** (t_r = 11.7 min), **3e** (t_r = 13.2 min), hexane/isopropanol in ratio 4/6 for **3f** (t_r = 9.2 min), **3g** (t_r = 9.8 min), **3h** (t_r = 16.3 min), **3i** (t_r = 15.4 min), **3j** (t_r = 17.6 min), **3k** (t_r = 13.5 min), **3l** (t_r = 14.9 min).

General procedure for the synthesis of L- α -amino acid phenylhydrazides 2a-e

Freshly distilled phenylhydrazine (12 mmol), triethylamine (10 mmol) and L- α -amino acid methyl ester hydrochloride (10 mmol) were mixed in a flask fitted with a condenser and a magnetic stirring bar. The mixture was stirred at 60 $^{\circ}$ C for 4 h under inert atmosphere. It was let cool down at room temperature and stirred overnight. Then, 100 mL of CHCl₃, 6 g of Na₂CO₃ and 5 mL of H₂O were added. The mixture was vigorously stirred for 3 h. After filtration of salts, the solvent was concentrated in *vacuo* and the unreacted phenylhydrazine was removed under reduced pressure. After addition of 50 mL of Et₂O and 5 mL of hexane, the mixture was stirred for 1 h and the solid product was filtered and washed with Et₂O. All products were obtained in spectroscopically pure form.

(L)-Alanine phenylhydrazide (2a)

Yield (80%); a white solid; mp 122–124 $^{\circ}$ C (lit.,²⁵ 116 $^{\circ}$ C); IR (cm⁻¹): 3275, 3215 (NH), 1665 (C=O); ¹H NMR (300 MHz, CDCl₃): δ 1.42 (d, 3H, J = 8.1 Hz, CH₃), 1.55 (sbr, 2H, NH₂), 3.63 (q, 1H, J = 8.1 Hz, CH-CH₃), 6.15 (s, 1H, NH-Ph), 6.84–7.24 (m, 5H, ArH), 8.20 (sbr, 1H, NH-CO); ¹³C NMR (75 MHz, CDCl₃): δ = 13.51, 13.67, 62.10, 127.30, 128.31, 132.53, 151.40, 167.37; [α]_D +34.2 (c 0.2, MeOH).

(L)-Valine phenylhydrazide (2b)

Yield (65%); a beige solid; mp 152–154 $^{\circ}$ C; IR (cm⁻¹): 3266, 3110 (NH), 1655 (C=O); ¹H NMR (300 MHz, CDCl₃): δ 0.90 (d, 3H, J = 6.9 Hz, CH₃), 1.02 (d, 3H, J = 6.9 Hz, CH₃), 1.70 (sbr, 2H, NH₂), 2.36 (m, 1H, CH-(CH₃)₂), 3.42 (d, 1H, J = 6.9 Hz, CH-NH₂), 6.20 (s, 1H, NH-Ph), 6.84–7.25 (m, 5H, ArH), 8.95 (sbr, 1H, NH-CO); ¹³C NMR (75 MHz, CDCl₃): δ = 16.19, 19.50, 30.86, 59.61, 113.71, 121.20,

129.17, 148.12, 174.05; $[\alpha]_D +30.8$ (*c* 0.2, MeOH); HRMS (ES) found MH^+ $m/z = 208.0619$, $C_{11}H_{18}N_3O$ requires 208.0624.

(L)-Phenylalanine phenylhydrazide (2c)

Yield (85%); a white solid; mp 142–144 °C (lit.,²⁵ 147 °C); IR (cm^{-1}): 3285, 3219 (NH), 1648 (C=O); 1H NMR (300 MHz, $CDCl_3$): δ 1.50 (sbr, 2H, NH_2), 3.22 (dd, 1H, $J = 9.6$ and 12 Hz, CH_2-Ph), 3.28 (dd, 1H, $J = 4.8$ and 12 Hz, CH_2-Ph), 3.76 (dd, 1H, $J = 9.6$ and 4.8 Hz, $CH-CH_2$), 6.15 (s, 1H, $NH-Ph$), 6.76–7.40 (m, 10H, ArH), 8.86 (sbr, 1H, $NH-CO$); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 40.94, 55.89, 113.70, 121.21, 127.00, 129.00, 129.12, 129.42, 137.24, 147.87, 173.71$; $[\alpha]_D +39.4$ (*c* 0.2, MeOH).

(L)-Serine phenylhydrazide (2d)

Yield (68%); an orange solid; mp 163–165 °C; IR (cm^{-1}): 3248 (NH), 3000 (OH), 2905 (NH), 1680 (C=O); 1H NMR (300 MHz, CD_3OD): δ 3.49 (t, 1H, $J = 5.7$ Hz, $CH-NH_2$), 3.74 (d, 2H, $J = 5.4$ Hz, CH_2-OH), 6.79–7.21 (m, 5H, ArH), 8.86 (sbr, 1H, $NH-CO$); ^{13}C NMR (75 MHz, CD_3OD): $\delta = 56.78, 65.61, 114.22, 121.09, 129.94, 149.76, 175.60$; $[\alpha]_D +42.6$ (*c* 0.2, MeOH); HRMS (ES) found MH^+ $m/z = 196.0512$, $C_9H_{14}N_3O_2$ requires 196.0503.

(L)-Methionine phenylhydrazide (2e)

Yield (78%); a pale-yellow solid; mp 128–130 °C; IR (cm^{-1}): 3230, 2918 (NH), 1647 (C=O); 1H NMR (300 MHz, $CDCl_3$): δ 1.86 (dt, 1H, $J = 6.9$ and 13.8 Hz, CH_2-CH), 2.10 (s, 3H, $-S-CH_3$), 2.16 (dt, 1H, $J = 6.9$ and 13.8 Hz, CH_2-CH), 2.62 (t, 2H, $J = 6.9$ Hz $S-CH_2$), 3.65 (t, 1H, $J = 13.8$ Hz, $CH-NH_2$), 6.27 (s, 1H, $NH-Ph$), 6.81–7.28 (m, 5H, ArH), 8.97 (sbr, 1H, $NH-CO$); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.84, 29.99, 33.43, 52.98, 113.11, 120.66, 128.68, 147.47, 173.70$; $[\alpha]_D +29.8$ (*c* 0.2, MeOH); HRMS (ES) found MH^+ $m/z = 240.0583$, $C_{11}H_{18}N_3OS$ requires 240.0586.

General procedure for the synthesis of 3-phenylamino-3,5-dihydro-4H-imidazol-4-ones 3a-l

An Argon-flushed, round-bottomed flask containing a mixture of L-(α)-amino acid phenylhydrazide (5 mmol), triethyl orthoester (10 mmol) and acetic acid (0.028 mL) was stirred at 80 °C for 1 h. The reaction mixture was diluted with EtOAc, washed with water, and dried over $MgSO_4$. The solvent was evaporated in vacuo and the residue was purified by flash column chromatography (EtOAc–hexane). The product was recrystallized from EtOAc–hexane.

(5S)-2,5-Dimethyl-3-phenylamino-3,5-dihydro-4H-imidazol-4-one (3a)

Yield (63%); a white solid; mp 103–105 °C; IR (cm^{-1}): 3218 (NH), 1725 (C=O), 1620 (C=N); 1H NMR (300 MHz, $CDCl_3$): δ 1.40 (d, 3H, $J = 7.4$ Hz, CH_3), 2.18 (s, 3H, CH_3), 3.98 (q, 1H, $J = 7.4$ Hz, $CH-CH_3$), 6.09 (s, 1H, $NH-Ph$), 6.85–7.36 (m, 5H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 17.90, 23.12, 57.63, 113.52, 122.85, 129.36, 147.11, 163.78, 175.72$; $[\alpha]_D -33.4$ (*c* 0.5, $CHCl_3$); HRMS (ES) found MH^+ $m/z =$

204.0518, C₁₁H₁₄N₃O requires 204.0510.

(5S)-2-Ethyl-5-methyl-3-phenylamino-3,5-dihydro-4H-imidazol-4-one (3b)

Yield (68%); a white solid; mp 116–118 °C; IR (cm⁻¹): 3221 (NH), 1712 (C=O), 1632 (C=N); ¹H NMR (300 MHz, CDCl₃): δ 1.25 (t, 3H, *J* = 7.0 Hz, CH₃), 1.39 (q, 2H, *J* = 7.0, CH₂) 1.43 (d, 3H, *J* = 7.1 Hz, CH₃), 4.05 (q, 1H, *J* = 7.1 Hz, CH-CH₃), 6.11 (s, 1H, NH-Ph), 6.82–7.25 (m, 5H, ArH); ¹³C NMR (75 MHz, CDCl₃): δ = 11.13, 19.02, 24.68, 62.41, 112.63, 123.54, 130.85, 147.52, 161.05, 172.55; [α]_D -24.3 (*c* 0.5, CHCl₃); HRMS (ES) found MH⁺ *m/z* = 218.0520, C₁₂H₁₆N₃O requires 218.0514.

(5S)-5-Methyl-2-phenyl-3-phenylamino-3,5-dihydro-4H-imidazol-4-one (3c)

Yield (81%); a pale-yellow solid; mp 135–137 °C; IR (cm⁻¹): 3355 (NH), 1658 (C=O), 1625 (C=N); ¹H NMR (300 MHz, CDCl₃): δ 1.45 (d, 3H, *J* = 6.9 Hz, CH₃), 4.24 (q, 1H, *J* = 6.9 Hz, CH-CH₃), 6.13 (s, 1H, NH-Ph), 6.87–7.83 (m, 10H, ArH); ¹³C NMR (75 MHz, CDCl₃): δ = 17.56, 63.21, 113.70, 122.68, 128.88, 129.26, 131.20, 131.57, 133.74, 147.08, 157.26, 174.52; [α]_D +22.6 (*c* 0.5, CHCl₃); HRMS (ES) found MH⁺ *m/z* = 266.0601, C₁₆H₁₆N₃O requires 266.0604.

(5S)-5-Isopropyl-2-methyl-3-phenylamino-3,5-dihydro-4H-imidazol-4-one (3d)

Yield (52%); a white solid; mp 139–141 °C; IR (cm⁻¹): 3248 (NH), 1723 (C=O), 1586 (C=N); ¹H NMR (300 MHz, CDCl₃): δ 0.94 (d, 3H, *J* = 6.8 Hz, CH₃), 1.07 (d, 3H, *J* = 6.8 Hz, CH₃), 2.17 (s, 3H, CH₃), 2.42 (m, 1H, CH-(CH₃)₂), 3.44 (d, 1H, *J* = 6.8 Hz, CH), 6.18 (s, 1H, NH-Ph), 6.91–7.33 (m, 5H, ArH); ¹³C NMR (75 MHz, CDCl₃): δ = 18.23, 18.59, 24.57, 30.85, 69.21, 114.12, 120.55, 129.39, 147.85, 165.22, 174.70; [α]_D -13.2 (*c* 0.5, CHCl₃); HRMS (ES) found MH⁺ *m/z* = 232.0521, C₁₃H₁₈N₃O requires 232.0516.

(5S)-5-Isopropyl-2-phenyl-3-phenylamino-3,5-dihydro-4H-imidazol-4-one (3e)

Yield (61%); a beige solid; mp 148–150 °C; IR (cm⁻¹): 3289 (NH), 1708 (C=O), 1612 (C=N); ¹H NMR (300 MHz, CDCl₃): δ 0.99 (d, 3H, *J* = 7.2 Hz, CH₃), 1.12 (d, 3H, *J* = 7.2 Hz, CH₃), 2.24 (m, 1H, CH-(CH₃)₂), 3.62 (d, 1H, *J* = 6.9 Hz, CH), 5.86 (s, 1H, NH-Ph), 6.80–7.77 (m, 10H, ArH); ¹³C NMR (75 MHz, CDCl₃): δ = 18.59, 19.05, 33.47, 76.10, 114.12, 121.66, 128.09, 129.77, 131.58, 131.96, 134.74, 147.36, 155.87, 176.04; [α]_D +19.1 (*c* 0.5, CHCl₃); HRMS (ES) found MH⁺ *m/z* = 294.0634, C₁₈H₂₀N₃O requires 294.0629.

(5S)-5-Benzyl-2-methyl-3-phenylamino-3,5-dihydro-4H-imidazol-4-one (3f)

Yield (57%); a white solid; mp 137–139 °C; IR (cm⁻¹): 3220 (NH), 1698 (C=O), 1596 (C=N); ¹H NMR (300 MHz, CDCl₃): δ 2.50 (s, 3H, CH₃), 2.79 (dd, 1H, *J* = 8.2 and 11 Hz, CH₂-Ph), 2.98 (dd, 1H, *J* = 4.9 and 11 Hz, CH₂-Ph), 4.12 (dd, 1H, *J* = 8.2 and 4.9 Hz, CH-CH₂), 6.01 (s, 1H, NH-Ph), 6.93–7.41 (m, 10H, ArH); ¹³C NMR (75 MHz, CDCl₃): δ = 25.20, 40.05, 69.11, 113.13, 122.87, 125.50, 127.63, 128.66,

129.17, 137.90, 147.88, 166.08, 174.89; $[\alpha]_D +32.5$ (c 0.5, CHCl_3); HRMS (ES) found MH^+ $m/z = 280.0592$, $\text{C}_{17}\text{H}_{18}\text{N}_3\text{O}$ requires 280.0605.

(5S)-5-Benzyl-2-phenyl-3-phenylamino-3,5-dihydro-4H-imidazol-4-one (3g)

Yield (70%); a white solid; mp 152–154 °C; IR (cm^{-1}): 3342 (NH), 1713 (C=O), 1621 (C=N); ^1H NMR (300 MHz, CDCl_3): δ 1.50 (sbr, 2H, NH_2), 3.14 (dd, 1H, $J = 8.0$ and 10 Hz, $\text{CH}_2\text{-Ph}$), 3.20 (dd, 1H, $J = 4.8$ and 10 Hz, $\text{CH}_2\text{-Ph}$), 3.96 (dd, 1H, $J = 8.0$ and 4.8 Hz, CH-CH_2), 6.13 (s, 1H, NH-Ph), 6.90–7.81 (m, 15H, ArH); ^{13}C NMR (75 MHz, CDCl_3): $\delta = 41.16, 68.21, 112.15, 121.69, 125.00, 127.51, 128.36, 128.89, 129.27, 131.04, 131.47, 133.63, 138.50, 147.78, 165.11, 176.82$; $[\alpha]_D -11.6$ (c 0.5, CHCl_3); HRMS (ES) found MH^+ $m/z = 342.0663$, $\text{C}_{22}\text{H}_{20}\text{N}_3\text{O}$ requires 342.0654.

(5S)-5-Hydroxymethyl-2-methyl-3-phenylamino-3,5-dihydro-4H-imidazol-4-one (3h)

Yield (49%); a yellow solid; mp 150–152 °C; IR (cm^{-1}): 3236 (NH), 1640 (C=O), 1566 (C=N); ^1H NMR (300 MHz, CDCl_3): δ 2.35 (s, 3H, CH_3), 3.72 (dd, 1H, $J = 6.7$ and 13 Hz, CH-OH), 3.94 (dd, 1H, $J = 7.1$ and 13 Hz, CH-OH), 4.12 (dd, 1H, $J = 6.7$ and 7.1 Hz, CH-CH_2), 5.92 (s, 1H, NHPh), 6.99–7.31 (m, 5H, ArH); ^{13}C NMR (75 MHz, CDCl_3): $\delta = 24.58, 63.60, 71.45, 120.24, 123.87, 130.44, 148.05, 160.53, 171.33$; $[\alpha]_D +21.9$ (c 0.5, CHCl_3); HRMS (ES) found MH^+ $m/z = 264.0554$, $\text{C}_{11}\text{H}_{14}\text{N}_3\text{O}_2$ requires 264.550.

(5S)-2-Ethyl-5-hydroxymethyl-3-phenylamino-3,5-dihydro-4H-imidazol-4-one (3i)

Yield (54%); a pale-yellow solid; mp 161–162 °C; IR (cm^{-1}): 3268 (NH), 1733 (C=O), 1627 (C=N); ^1H NMR (300 MHz, CDCl_3): δ 1.28 (t, 3H, $J = 6.7$ Hz, $\text{CH}_3\text{-CH}_2$), 1.42 (q, 2H, $J = 6.7$ Hz, $\text{CH}_2\text{-CH}_3$), 3.72 (dd, 1H, $J = 7.1$ and 13.2 Hz, $\text{CH}_2\text{-OH}$), 3.93 (dd, 1H, $J = 6.8$ and 13.2 Hz, $\text{CH}_2\text{-OH}$), 4.11 (dd, 1H, $J = 7.1$ and 6.8 Hz, CH-CH_2), 5.81 (s, 1H, NHPh), 6.89–7.47 (m, 5H, ArH); ^{13}C NMR (75 MHz, CDCl_3): $\delta = 11.17, 25.36, 66.74, 72.58, 117.89, 122.83, 129.36, 147.55, 163.12, 172.08$; $[\alpha]_D +36.7$ (c 0.5, CHCl_3); HRMS (ES) found MH^+ $m/z = 233.0541$, $\text{C}_{12}\text{H}_{15}\text{N}_3\text{O}_2$ requires 233.0532.

(5S)-5-Hydroxymethyl-2-phenyl-3-phenylamino-3,5-dihydro-4H-imidazol-4-one (3j)

Yield (75%); an orange solid; mp 172–174 °C; IR (cm^{-1}): 3255 (NH), 1719 (C=O), 1609 (C=N); ^1H NMR (300 MHz, CDCl_3): δ 3.96 (dd, 1H, $J = 7.3$ and 14.1 Hz, $\text{CH}_2\text{-OH}$), 4.20 (dd, 1H, $J = 6.9$ and 14.1 Hz, $\text{CH}_2\text{-OH}$), 4.32 (dd, $J = 7.3$ and 6.9 Hz, CH-CH_2), 5.74 (s, 1H, NHPh), 6.91–7.87 (m, 10H, ArH); ^{13}C NMR (75 MHz, CDCl_3): $\delta = 63.12, 72.58, 115.25, 123.45, 128.23, 129.89, 131.02, 131.97, 133.85, 148.25, 155.77, 174.26$; $[\alpha]_D -15.8$ (c 0.5, CHCl_3); HRMS (ES) found MH^+ $m/z = 282.0617$, $\text{C}_{16}\text{H}_{16}\text{N}_3\text{O}_2$ requires 282.0611.

(5S)-2-Methyl-5-(2-methylthioethyl)-3-phenylamino-3,5-dihydro-4H-imidazol-4-one (3k)

Yield (60%); a pale-yellow solid; mp 101–102 °C; IR (cm^{-1}): 3198 (NH), 1684 (C=O), 1617 (C=N); ^1H

NMR (300 MHz, CDCl₃): δ 1.93 (dt, 1H, $J = 6.9$ and 13.8 Hz, CH₂-CH), 2.19 (s, 3H, -S-CH₃), 2.17 (s, 3H, CH₃), 2.26 (dt, 1H, $J = 6.9$ and 13.8 Hz, CH₂-CH), 2.64 (t, 2H, $J = 6.9$ Hz S-CH₂), 3.81 (t, 1H, $J = 13.8$ Hz, CH-CH₂), 6.06 (s, 1H, NH-Ph), 6.85–7.38 (m, 5H, ArH); ¹³C NMR (75 MHz, CDCl₃): $\delta = 15.12, 23.55, 30.71, 33.78, 59.90, 117.56, 124.65, 130.17, 146.13, 163.25, 170.59$; $[\alpha]_D +25.4$ (c 0.5, CHCl₃); HRMS (ES) found MH⁺ $m/z = 264.0554$, C₁₃H₁₈N₃OS requires 264.0558.

(5S)-5-(2-Methylthioethyl)-2-phenyl-3-phenylamino-3,5-dihydro-4H-imidazol-4-one (31)

Yield (69%); a white solid; mp 112–114 °C; IR (cm⁻¹): 3203 (NH), 1711 (C=O), 1642 (C=N); ¹H NMR (300 MHz, CDCl₃): δ 2.15 (s, 3H, -S-CH₃), 2.26 (dt, 1H, $J = 6.9$ and 13.8 Hz, CH₂-CH), 2.31 (dt, 1H, $J = 6.9$ and 13.8 Hz, CH₂-CH), 2.62 (t, 2H, $J = 6.9$ Hz S-CH₂), 4.08 (t, 1H, $J = 13.8$ Hz, CH-CH₂), 5.92 (s, 1H, NH-Ph), 6.85–7.88 (m, 10H, ArH); ¹³C NMR (75 MHz, CDCl₃): $\delta = 15.45, 31.23, 33.98, 60.83, 113.74, 122.56, 128.99, 129.68, 132.47, 133.12, 135.65, 148.25, 153.09, 174.86$; $[\alpha]_D +30.1$ (c 0.5, CHCl₃); HRMS (ES) found MH⁺ $m/z = 326.0658$, C₁₈H₂₀N₃OS requires 326.0642.

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