Synthesis of *trans/cis*-3,4-Disubstituted 1,2,3,4-Tetrahydroisoquinolines by Nucleophilic Acyl Substitution of Homophthalic Anhydride with Aldimines

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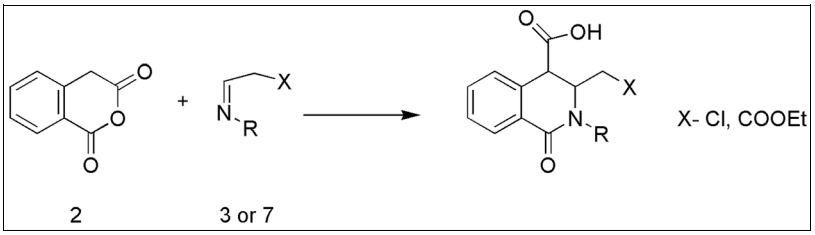

The reaction of the functionalized *N*-protected imines **3** and **7** containing either the chloromethyl or ethyl ester moieties, respectively, attached to the imine carbon with homophthalic anhydride **2** afforded *cis/tran*-3-subsituted-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-caboxylic acids appropriate for further synthetic elaboration.

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INTRODUCTION

Imine–anhydride condensations have proven to be a valuable method for the synthesis of a variety of functionalized tetrahydroisoquinolines and as such, the reaction has been utilized for the synthesis of nitidine chloride, corynoline, 6-oxocorynoline, 14-epicorynoline, chelidonine, fagaronine chloride, and decumbenine, Figure 1 [1–6].

These substituted 1,2,3,4-tetrahydroisoquinolines with stereogenic centers at C-3 and C-4 exist in both cis and trans forms that may be obtained as mixtures or as a single diastereomer depending upon the temperature, the solvent used, the substituents in positions 2 and 3, and the use of various catalysts such as Lewis acids. At room temperature, the reaction is considered as kinetically controlled and mixtures of cis and trans acids are obtained [7,8].

As part of a project directed at the synthesis of sequence, selective DNA alkylating agents related to compound **1**, imine–anhydride condensations have been used as a key reaction in the synthesis of the heterocyclic frame (Fig. 2) [9–11]. Although this reaction is quite convenient for the synthesis of these compounds, it is limited due to the synthetic difficulty associated with heterocyclic imines that can be utilized, which contain additional functionality. In order to expand the scope of the reaction, it was hoped that functionalized imines could be utilized and could be subsequently converted into nitrogen containing heterocycles fused to the isoquinolinic acid that results from the imine–anhydride condensation. Toward this end, the reaction of compounds **3** and **7** with homophthalic anhydride, **2**, have been investigated. Both compounds contain electrophilic functionality at the alpha carbon of the imine, which may be further elaborated, as well as removable nitrogen protecting groups.

RESULTS AND DISCUSSION

The reaction of compounds **3a** and **3b** with homophthalic anhydride **2** is shown in Scheme 1. The α-chloroimines were prepared *in situ* by condensation of the amine with chloroacetaldehyde in alcohol-free chloroform according to the procedure reported by Teutsch *et al*.,[12]. The α-chloroimines are unstable and were therefore not isolated but used immediately in the subsequent reaction with **2** to afford the desired isoquinolinic acids **4**. The results are presented in Table 1. The imine anhydride condensation is complete within 10 min to give primarily the cis and trans acids **4a** and **4b** with small amounts of the lactones **5**. The presence of the cis and trans acids was determined by GC/MS analysis that revealed the presence of two peaks (60/40 ratio) with the same fragmentation pattern showing (M^+–CO_2–HCl). Further characterization was not possible however because of the rapid conversion of the initial products to the lactones. The lactones form as a result of further reaction by displacement of the chloride by the initially formed carboxyl group. Upon standing, or the use of longer reaction times results in nearly complete conversion to the lactones. To prevent conversion to the lactones, the acids were immediately converted to the esters **6a** and **6b** via reaction with diazomethane or $NaHCO_3/CH_3I$. Alternatively, Fisher esterification could be utilized but this method resulted in increased lactone formation. Characterization of the esters **6a** and **6b** by NMR revealed a coupling constant of $J_{3-4} = 1.6$ Hz between the C-3 and C-4 protons indicating exclusive formation of the trans isomer. The small coupling constant is due to the pseudo-axial orientation of the ester and chloromethylene groups to minimize steric interaction that gives a dihedral angle for the C-3 and C-4 protons of approximately

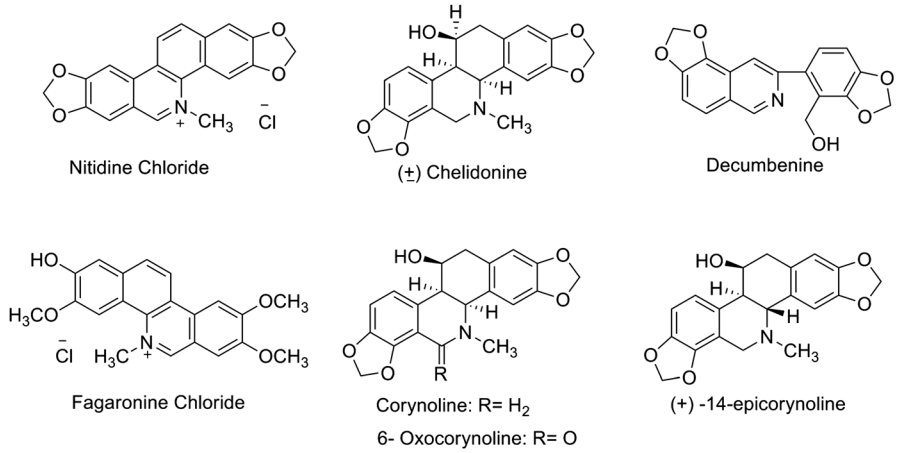


Figure 1. Natural products synthesized utilizing imine-anhydride condensations as a key step.

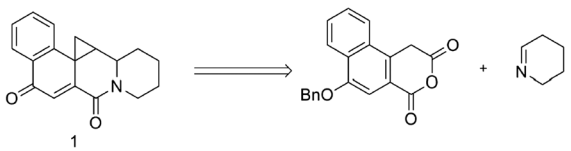


Figure 2. Retrosynthetic synthesis of compound **1**.

60°. Molecular mechanics calculations (SYBYL) suggested the diaxial orientation of the ester and chloromethylene functions to be 2.0 kcal more stable than the diequatorial arrangement. The isolation of only the trans isomer occurred as a result of isomerization of the cis acid to give the more stable trans isomer during esterification. The lactones exhibited a coupling constant of $J = 7$ Hz between C3-H and C4-H indicating exclusive formation of the cis isomer.

Recently, Lewis acids have been shown to be useful in promoting imine–anhydride condensations [13]. A procedure reported by Azizian *et al.* does not pre-form the imine as was performed in the procedure mentioned earlier but combines the anhydride, the aldehyde, and the appropriate amine in a single pot and utilizes $KAl(SO_4)_2.12H_2O$ (alum) as the Lewis acid (Scheme 2). This procedure has been reported for unfunctionalized imines so it was therefore of interest to determine if it offered any advantages over pre-forming the imine for these unstable alpha-functionalized imines. When chloroacetaldehye and benzylamine were utilized in this reaction, the resulting products and yields were similar to those obtained by pre-forming the imine.(Table 2)

Utilization of the imines **7a** and **7b** in the condensation was also investigated as both a means of extending the versatility of the reaction and to investigate the incorporation of an electron withdrawing ester functionality at the alpha position of the imine (Scheme 3, Table 2). The imines **7a** and **7b** were found to be much more stable than **3a** and **3b** and were stable upon storage. Reaction times were longer in the case of **7a** and **7b** compared with **3a** and **3b**. In the case of **7a**, reaction with homophthalic anhydride gave the isoquinolinic acid **8a** in high yield (85%) exclusively as the cis isomer as revealed from the 6 Hz

Scheme 1

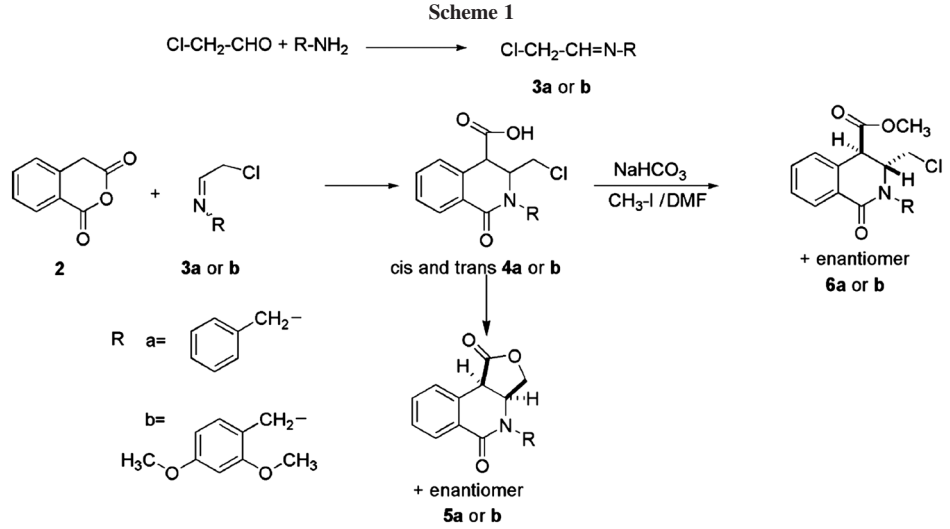


Table 1

Reaction of Homophthalic anhydride with **3a,b**.

Compound	% Yield		Reaction time in minutes	
	Procedure A	Procedure B	Procedure A	Procedure B
6a	70	60	10 imine + 10 acid	5
6b	80	–	10 imine + 10 acid	–
5a	20	25	10 imine + 10 acid	5
5b	15	–	10 imine + 10 acid	–

Procedure A involved formation of the imine prior to condensation with the anhydride. Procedure B involved combining the amine, aldehyde, and anhydride so that the imine was formed *in situ* with alum as a catalyst.

coupling constant for the C-3 and C-4 protons. There was also a small amount of **9a** produced as well. Compound **9a** apparently arises as a result of breakdown of the imine during the reaction. In the case of **7b**, yields of **8b** were modest (53%) and there was an increased amount of **9b** formed. Utilization of Azizain's procedure gave similar yields in the case of **8a** along with a small amount of **9a**. In the case of **7b**, the yield of **8b** was slightly lower and longer reaction times were necessary. (Scheme 4).

To summarize, these studies have served to show that functionality can be introduced into the C3 position of the isoquinolinic-acids that is suitable for further manipulation with the goal of synthesizing more complex heterocycles by cyclization of the C3 and C4 positions. The stereochemistry of the imine–anhydride cyclization product is dependent in part upon the functionality present at the alpha carbon of the imine. The utilization of alum as a Lewis acid did not prove superior with regard to product yields to pre-forming the imines in the examples investigated here.

EXPERIMENTAL

Materials and methods. Melting points were recorded on a Thomas–Hoover melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian MR400 (operated at 400 or 100 MHz, respectively). All ^{1}H chemical shifts are reported in δ relative to the internal standard tetramethylsilane (TMS, δ 0.00). ^{13}C chemical shifts are reported in δ relative to $CDCl_3$ (center of triplet, δ 77.23) or relative to DMSO-d_6 (center of septet, δ 39.51). The spin multiplicities are indicated by the symbols s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad). Atlantic Microlabs, Norcross, and Georgia performed elemental analyses. Reactions were monitored by thin layer chromatography (TLC) using 0.25 mm E. Merck silica gel 60-F_{254} pre-coated silica gel plates with visualization by the irradiation with Mineralight UVGL-25 lamp or exposure to iodine vapor. Column chromatography was performed on Whatman silica gel (average particle size 2–25 μm, 60 Å) and elution with the indicated solvent system. Spinning band chromatography was performed on a Chromatotron 8900 (Harrison Research, Palo Alto, CA) sing Merck silica gel 7749 with gypsum binder and fluorescent indicator. Yields refer to the spectroscopically (^{1}H NMR and ^{13}C NMR) and chromatographically homogeneous materials. GC-MS was performed with an HP-5890 GC coupled with an HP-5970 mass selective detector (Hewlett Packard, Palo Alto, CA) using Helium (grade 5.0) as carrier gas. The mass spectrometer was operated on the electron impact (EI) mode using ionization voltage of 70 eV and a source temperature of 230°C. Samples were dissolved in HPLC grade acetonitrile (Fisher Scientific, NJ, USA) and manually introduced (1 μL) individually.

Table 2

Reaction of Homophthalic anhydride with **7a,b**.

Compound	% Yield		Reaction time in hours	
	Procedure A	Procedure B	Procedure A	Procedure B
8a	85	85	2	7
8b	53	40	0.5	8
9a	8	10	2	2
9b	15	0	0.3	0.3

9b was formed then completely converted to **8b** in case of procedure B.

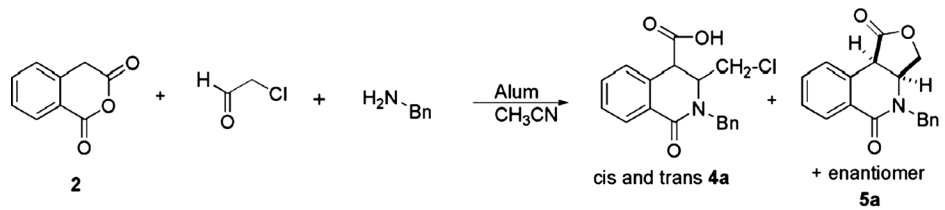
Experimental procedures.

Procedure A.

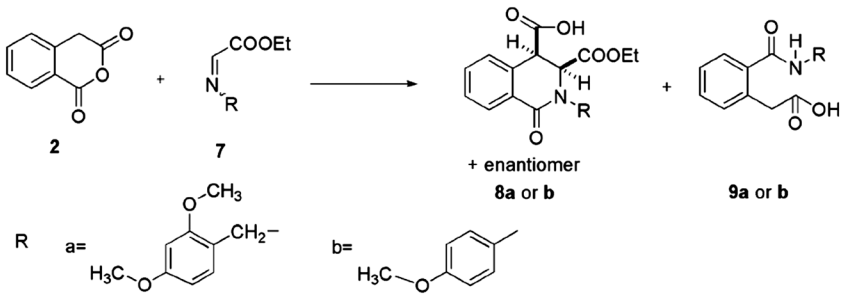
1- General procedure for the synthesis of Imines *N*-(2-chloroethylidene)-1-phenylmethanamine (**3a**) and *N*-(2-chloroethylidene)-1-(2,4-dimethoxyphenyl)methanamine (**3b**)

To chloroacetaldehyde (60 mmoles, 10.5 mL, 1.2 equivalent) (45% in aqueous solution), 10 ml of water was added and the resulting solution was stirred in an ice-methanol bath at −5°C. To this solution, the appropriate amine (50 mmoles, 1 equivalent)

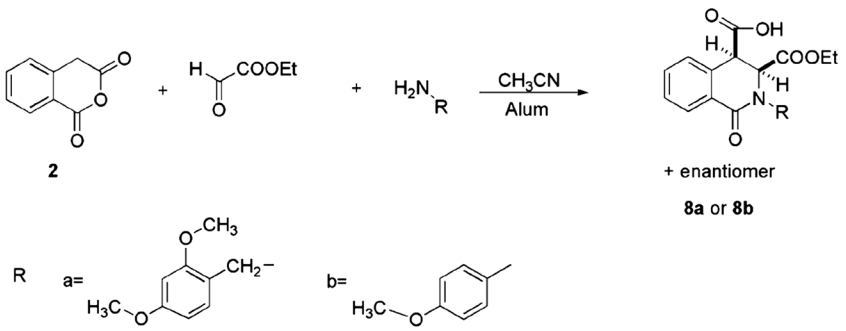
Scheme 2



Scheme 3



Scheme 4



in one portion was added and the reaction mixture was allowed to stir for 10 min. After removal of the cooling bath, alcohol-free chloroform (10 mL) was added twice to extract the imine. The combined organic extracts were rapidly dried with anhydrous sodium sulfate and used without further purification in the next step.

2- General procedure for the synthesis of the acids 2-benzyl-3-(chloromethyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (**4a**) and 3-(chloromethyl)-2-(2,4-dimethoxybenzyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (**4b**) and the lactones 4-benzyl-3a,4-dihydrofuro[3,4-c]isoquinoline-1,5(3H,9bH)-dione (**5a**) and 4-(2,4-dimethoxybenzyl)-3a,4-dihydrofuro[3,4-c]isoquinoline-1,5(3H,9bH)-dione (**5b**).

The imine **3a** or **3b** (50 mmoles, 1.2 equivalents) in alcohol-free chloroform (15 mL) was added to **2** (41 mmoles, 6.64 g, 1 equivalent) suspended in methylene chloride (10 mL) and the resulting solution was allowed to stir at room temperature for 15 min. The solvents were evaporated under reduced pressure and the oily residue was washed twice with petroleum ether (10 mL) to give a brown gum that was further dried under vacuum to give a yellowish-brown fluffy powder of acid **4a** or **4b** and the lactone **5a** or **5b**, respectively. These were used without further purification to maximize the yield. The acids **4a** and **4b** were characterized in the form of their methyl esters that were obtained from the next esterification step.

Procedure B. A mixture of homophthalic anhydride, **2** (162 mg, 1 mmole), chloroacetaldehyde (45% in aqueous solution) (1.2 mmoles, 0.21 mL), benzylamine (107 mg, 1 mmole), and alum (0.24 g, 0.5 mmoles) in acetonitrile (10 mL) in a 25-mL flask was stirred at room temperature for 15 min. After completion of the reaction (monitored by TLC, ethyl acetate/pet-ether 1/1), the solvent was evaporated under reduced pressure, the product was washed with petroleum ether (25 mL), and the resulting gum was dried under vacuum. The crude product contained the acid **4a** in the form of a mixture of diastereomers (60% yield calculated by GC-MS and the lactone **5a** in 25% yield) and the crude product was used in the subsequent esterification step without purification.

3- General procedure for the synthesis of the esters: methyl 2-benzyl-3-(chloromethyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (**6a**) and methyl 3-(chloromethyl)-2-(2,4-dimethoxybenzyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (**6b**).

To a DMF solution (15 mL) of the mixture of the acid **4a** or **4b** and the lactone **5a** or **5b** (50 mmoles), respectively, sodium bicarbonate (4.3 g, 51 mmoles) was added and the formed suspension was allowed to stir at room temperature for 15 min. To this, methyl iodide (7.1 g, 50 mmoles) was added and stirring was continued for an additional 15 min. Brine (5 mL) was added and the product was extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were evaporated under vacuum and purified by column chromatography (silica gel) using petroleum ether and ethyl acetate in a 4:1 ratio as the eluting system to give esters **6a** and **6b** in 56.4% and 65% overall yields, respectively, and the lactones **4a** and **4b** in 20% and 15% yields, respectively.

4-Benzyl-3a,4-dihydrofuro[3,4-c]isoquinoline-1,5(3H,9bH)-dione (5a). This compound was obtained as white crystals, mp:146–148°C; ^{1}H-NMR $CDCl_3$: δ 3.97 (dd, 1H,, 2H OCH_{2a}, J = 8.02, J = 9.2 Hz), 4.05 (d, 1H, C4-H, J = 8.41 Hz), 4.09 (dd, 1H, OCH_{2b}, J = 6.65, J = 9.2 Hz), 4.50 (sextet, 1H. C3-H, J = 6.65, J = 8.26, 8.30), 4.8–4.95 (dd, 2H, –CH_2–Ar, J = 15 Hz), 7.25–7.35 (m, 5H, Ar–H), 7.45–7.65 (m,3H, Ar–H), 8.3 (d, 1H, Ar–H, J = 12 Hz); ^{13}C-NMR ($CDCl_3$): δ 40.60, 49.77, 55.16, 70.52, 127.29, 127.54, 127.55, 128.13, 128.26, 128.67, 128.70, 128.90, 129.11, 129.17, 133.29, 136.66, 162.16 and 173.51; GC-MS (EI): 293(M^+ and100%), 236, 106, 91 and 65. *Anal.*

Calcd. for $C_{18}H_{15}NO_3$: C, 73.71; H, 5.15; N, 4.78. Found: C, 73.73; H, 5.15; N, 4.75.

4-(2,4-Dimethoxybenzyl)-3a,4-dihydrofuro[3,4-c]isoquinoline-1,5(3H,9bH)-dione (5b). This compound was obtained as a white powder, mp:124–126°C; ^{1}H-NMR ($CDCl_3$): δ 3.81 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 4.01 (d, 1H, C4-H, J = 8.3 Hz), 4.04 (dd,1H, OCH_{2a}, J = 8.02, J = 9.2 Hz), 4.22 (dd, 1H, OCH_{2b}, J = 6.65, J = 9.2 Hz), 4.57 (sextet, 1H, C3-H, J = 6.65, J = 8.02, J = 9.2 Hz), 4.75–4.90 (dd, 2H, –CH_2–Ph, J = 16 Hz), 6.49 (d,2H, Ar–H), 7.26–7.63 (m,4H, Ar–H) and 8.23 (d,1H, Ar–H, J = 12 Hz); ^{13}C-NMR-4b $CDCl_3$: δ 40.67, 43.27, 54.75, 55.40, 55.54, 70.87, 76.68, 77.00, 77.32, 98.54, 104.85, 116.93, 127.19, 127.91, 128.70, 128.72, 128.94, 131.71, 132.94, 158.50, 160.90, 162.03 and 173.91; GC-MS (EI): 353(M^+ and100%), 322, 166, 151, 121, 91 and 77. *Anal*. Calcd. for $C_{20}H_{19}NO_5$: C, 67.98; H, 5.42; N, 3.96. Found: C, 67.80; H, 5.45; N, 3.85.

Methyl 2-benzyl-3-(chloromethyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (6a). This compound was obtained as yellow crystals, mp 128–130°C; ^{1}H-NMR ($CDCl_3$): δ 3.15 (t, 1H, CH–Cl, J = 11 Hz), 3.39 (s, 3H, –$COOCH_3$), 3.47 (dd, 1H, CH–Cl, J = 6.8, J = 14 Hz), 4.13 (1H, d, C4-H, J = 1.6 Hz), 4.24 (ddd, 1H, C3-H, J = 1.6, J = 4.1, J = 10.6 Hz), 4.5–5.1 (dd, 2H, –CH_2–Ph, J = 14.8 Hz), 7.25–7.38 (6H, m, Ar–H), 7.45–7.55 (2H, m, Ar–H), and 8.15 (d, 1H, Ar–H, J = 6.4 Hz); ^{13}C-NMR ($CDCl_3$): δ 41.01, 43.85, 48.98, 51.61, 58.04, 126.9, 127.47,127.58, 127.75 (3 carbons), 127.92 (2 carbons), 128.71, 131.01, 131.53, 136.05, 161.78 and 169.55. GC-MS (EI): 343(M^+), 394, 248, 91 (100%) and 65. *Anal.* Calcd. for $C_{19}H_{18}ClNO_3$: C, 66.38; H, 5.28; N, 4.07. Found: C, 66.15; H, 5.16; N, 4.06.

Methyl 3-(chloromethyl)-2-(2,4-dimethoxybenzyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (6b). This compound was obtained as pinkish-white crystals, mp 125–127°C; ^{1}H-NMR ($CDCl_3$): δ 3.1 (t, 1H, CH–Cl, J = 11 Hz), 3.40 (s, 3H, OCH_3), 3.50 (dd, 1H, CH–Cl, J = 3.8, J = 11 Hz), 3.80 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 4.13 (1H, d, C4-H, J = 1.6 Hz), 4.36 (ddd, 1H, CH–N, J = 1.6, J = 3.6, J = 11 Hz), 4.5–5.0 (dd, 2H, –CH_2–Ph, J = 14 Hz), 6.5 (2H, d, Ar–H), 7.2–7.6 (4H, m, Ar–H), 8.14(1H, d, Ar–H, J = 6.4 Hz). ^{13}C-NMR ($CDCl_3$): δ 42.14, 43.39, 44.74, 52.51, 55.38, 55.44, 58.89, 98.23, 104.56, 117.54, 128.44, 128.58, 128.77, 129.55, 132.08, 132.23, 132.50, 158.73, 160.71, 162.67 and 170.74, GC-MS (EI): 403(M^+), 368, 340, 151 (100%), 121, 91 and 77. *Anal*. Calcd. for $C_{21}H_{22}ClNO_5$: C, 62.45; H, 5.49; N, 3.74; Cl, 8.78. Found: C, 62.53; H, 5.50; N, 3.48; Cl, 8.83.

Procedure A to form the acids 8a, **8b**, **9a**, and **9b**.

Synthesis of the imines ethyl 2-(2,4-dimethoxybenzylimino) acetate (7a) and ethyl 2-(4-methoxyphenylimino)acetate (7b). To a stirred solution of ethyl glyoxalate (12 mmoles, 1.2 equivalents) in dry methylene chloride (20 mL) in one portion, the amine either 2,4-dimethoxybenzylamine or *p*-anisidene (10 mmoles, 1 equivalent) was added and the reaction mixture was allowed to stir for 3 h in the presence of molecular sieves. After filtering off the molecular sieves, the imine dissolved in methylene chloride was added to **2** in the next reaction without further purification.

2-Synthesis of the acids 8a/ 8b and **9a/9b**. To a stirred suspension of **2** (1.62 g, 10 mmoles, 1 equivalent) in dry methylene chloride (10 mL), the imine either **7a** or **7b** dissolved in methylene chloride (20 mL) was added and the reaction was allowed to stir at room temperature for 2 h and the precipitated acids **9a** or **9b** were filtered off and dried in 8% and 15% yields, respectively. The filtrate containing acid **8a** or **8b** was concentrated under vacuum and crystallized from ethanol/ether/water in 85% and 53% yields, respectively. All yields were calculated with respect to **2**.

Procedure B to form the acid 8b. A mixture of **2** (162 mg, 1 mmole), ethyl glyoxalate (123 mg, 1.2 mmoles), *p*-anisidene (123 mg, 1 mmole), and alum (0.24 g, 0.5 mmoles) in acetonitrile (10 mL) in a 25-mL flask was stirred at room temperature for 8 h. After completion of the reaction (monitored by TLC, ethyl acetate/pet-ether 1/1), the solvent was evaporated under reduced pressure, and petroleum ether (25 mL) was added. This resulted in the formation of a gum from which the petroleum ether was decanted and the gum was dried under vacuum. The crude product containing the acid **8b** was dissolved in 2N $NaHCO_3$ (5 mL) and washed with ethyl acetate. The aqueous solution was acidified with 0.6N HCl and the precipitated acid was extracted with ethyl acetate to give the pure acid in the form of a mixture of diastereomers (50/50) in 40% overall yield.

2-(2,4-Dimethoxybenzyl)-3-(ethoxycarbonyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (8a). This compound was obtained as a white powder, mp 146–148°C; ^{1}H-NMR (DMSO-d_6): δ 1.0 (t, 3H, –CH_2–CH_3), 3.80 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.90 (q, 2H, –CH_2–CH_3), 4.53 (d, 1H, C4-H, J = 5.5 Hz), 4.61 (d, 1H, C3-H, J = 5.7 Hz), 4.24 and 4.92 (dd, 2H, –CH_2–Ar, J = 15 Hz), 6.48 (d, 1H, Ar–H), 6.57 (s, 1H, Ar–H), 7.2 (d, 1H, Ar–H), 7.4 (t, 1H, Ar–H), 7.51 (t, 1H, Ar–H), 7.66 (d, 1H, Ar–H) and 7.92 (d, 1H, Ar–H); ^{13}C-NMR-DMSO-d_6: δ 13.25, 44.71, 45.43, 55.12, 55.35, 59.55, 60.81, 98.14, 104.56, 116.38, 126.63, 127.12, 127.23, 128.77, 130.88, 131.56, 133.36, 158.37, 160.13, 163.16, 169.01 and 170.12. *Anal*. Calcd. for $C_{22}H_{23}NO_7$: C, 63.91; H, 5.61; N, 3.39. Found: C, 63.74; H, 5.62; N, 3.52.

3-(Ethoxycarbonyl)-2-(4-methoxyphenyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (8b). This compound was obtained as white crystals, mp 186–188°C; ^{1}H-NMR (DMSO-d_6): δ 1.0 (t, 3H, –CH_2–CH_3), 3.8 (s, 3H, O–CH_3), 4.0 (q, 2H, –CH_2–CH_3), 4.8 (d, 1H, C4-H, J = 6 Hz), 5.0 (d, 1H, C3-H, J = 5.6 Hz), 7.0 (d, 2H, Ar–H), 7.3 (d, 2H, Ar–H), 7.5 (dd, 1H, Ar–H), 7.6 (dd, 1H, Ar–H), 7.7 (d, 1H, Ar–H), 8.0 (d, 1H, Ar–H) and 13.35 (s,1H, –COOH); ^{13}C-NMR (DMSO-d_6): δ 13.53, 45.81, 55.22, 61.02, 63.28, 114.05, 126.38, 127.26, 127.58, 128.09, 128.85, 132.0, 133.81, 134.53, 157.93, 162.81, 169.1 and 170.16. *Anal*. Calcd. for $C_{20}H_{19}NO_6$: C, 65.03; H, 5.18; N, 3.79. Found: C, 64.94; H, 5.26; N, 3.83.

[2-(2,4-Dimethoxy-benzylcarbamoyl)-phenyl]-acetic acid (9a). This compound was obtained as white flakes, mp 150–152°C; ^{1}H-NMR (DMSO-d_6): δ 3.3 (1H, br.s, NH), 3.74 (s, 3H, OCH3), 3.76 (s, 3H, OCH3), 3.90 (s, 2H, –CO–CH_2), 4.15 (d, 2H, –NH–CH_2), 6.4 (d, 1H, Ar–H), 6.52 (s, 1H, Ar–H), 7.08 (d, 1H, Ar–H), 7.3 (dd, 1H, Ar–H), 7.46 (t, 1H, Ar–H), 7.8 (d, 1H, Ar–H) and 8.09 (t, 1H, Ar–H).

^{13}C-NMR (DMSO-d_6): δ 55.07, 55.25, 98.04, 104.16, 118.87, 126.51, 128.61, 130.03, 131.03, 131.41, 131.58, 136.9, 157.52, 159.52, 168.53 and 169.92. LC-HRMS: calculated for $C_{18}H_{19}NO_5$ (M-H): 328.1190. Found: 328.1197.

[2-(4-Methoxy-phenylcarbamoyl)-phenyl]-acetic acid (9b). This compound was obtained as a pale violet powder, mp 174–176°C; ^{1}H-NMR (DMSO-d_6): δ 3.3 (1H, br. s, NH), 3.70 (s, 3H, OCH3), 4.05 (s, 2H, –CH_2), 6.85 (d, 2H, Ar–H), 7.35 (m, 2H, Ar–H), 7.50 (m, 3H, Ar–H), 7.86 (d, 1H, Ar–H) and 9.93 (s, 1H,–COOH). ^{13}C-NMR (DMSO-d_6): δ 41.46, 55.04, 113.67 (2 carbons), 120.34 (2 carbons), 126.64, 130.04, 131.10, 131.49, 132.04, 132.56, 136.79, 154.84 and 168.45 (2 overlapped carbonyls).LC-HRMS: calculated for $C_{16}H_{14}NO_4$ (M-H): 284.0928. Found: 284.0935.

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