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Graphical Abstract

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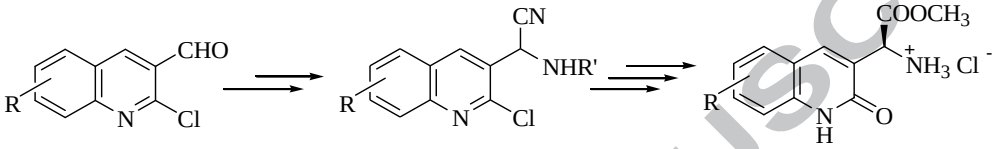

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Efficient synthesis and X-ray structures of new α-quinolin-3-yl-α-aminonitriles and derivatives.

Souheila Ladraa,[a] Fabienne Berrée,[b] Abdelmalek Bouraiou,[a] Sofiane Bouacida,[c] Thierry Roisnel,[d] Bertrand Carboni,[b] Ali Belfaitah*[a]

[a] Laboratoire des Produits Naturels d'Origine Végétale et de Synthèse Organique, Faculté des Sciences Exactes, Campus de Chaabat Ersas, Université Mentouri-Constantine, 25000, Algeria.
[b] Institut des Sciences Chimiques de Rennes, UMR 6226 CNRS-Université de Rennes 1, Campus de Beaulieu, 35042 Rennes CEDEX, France.
[c] Unité de Recherche de Chimie de l'Environnement et Moléculaire Structurale, Université Mentouri-Constantine, 25000, Algérie.
[d] Centre de Diffractométrie X, Sciences Chimiques de Rennes, UMR 6226 CNRS, Université de Rennes I, 35042 Rennes CEDEX, France

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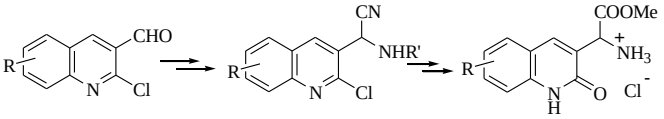
ABSTRACT

This study describes the synthesis of novel α-aminonitrile derivatives possessing a quinoline subunit via a Strecker reaction. Chiral α-methylbenzylamines were used to carry out the diastereoselective version of this sequence. Conversion of an enantiopure 2-chloroquinolin-3-yl derivative into the corresponding α-aminoester resulted in the concomitant formation of a 2(1*H*)-quinolinone moiety and a partial racemisation. Single crystal X-ray structures are reported for three compounds.

Amino acids are very important in biochemical, nutritional and biological research. In particular, the incorporation of non-proteinogenic α-amino acids into key positions of peptide chains has played a major role in drug discovery processes and constitutes one of the most effective methods to confer higher biological activity, as well as increasing biostability. These compounds have also been widely used as intermediates in the synthesis of drug candidates, natural products and ligands for asymmetric catalysis.[1] The three-component Strecker synthesis is one of the simplest methods for preparing α-amino acids and a great deal of effort has been devoted to the asymmetric version of this reaction. Enantioselective protocols have been reported in the case of chiral organo- or metal-based catalysts, [2] while, in alternative approaches, optically pure amines were successfully used as chiral auxiliaries in diastereoselective processes.[3]

On the other hand, quinoline derivatives have also received considerable interest due to the presence of this skeleton in a large number of bioactive compounds and natural products.[4] The introduction of a quinoline nucleus has been used successfully in a number of pharmacomodulations.[5] However, to our knowledge, no investigations involving the combination of a quinolinyl moiety and an α-amino acid unit have been reported.

In previous work, we reported that substituted 2-chloro-3-formylquinolines were key building blocks in the synthesis of various quinoline-containing heterocycles.[6] We describe herein our preliminary results concerning the synthesis of new α-aminonitriles possessing a quinoline unit using a diastereoselective Strecker reaction and their conversion into the corresponding α-amino esters (Scheme 1).

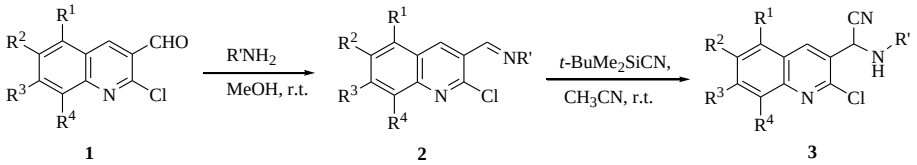


Scheme 1. Access to α-(quinolin-3-yl)-aminonitriles and their derivatives.

Initially, aldimines **2a-2i** were easily prepared in good yields from the corresponding 2-chloroquinolin-3-carboxaldehydes **1** in methanol in the presence of an amine (1.0 equiv).[7] Their conversion into the corresponding α-aminonitriles **3** proceeded cleanly in 83-96% yields by treatment with 1.2 eq. of *t*-$BuMe_2SiCN$ and a few drops of water in acetonitrile (Table 1).[8] Both the ^1H and ^{13}C NMR spectra of compounds **2** and **3** were in full agreement with the proposed structures.

The hydrolysis of the nitrile group was then studied under various conditions. No desired product was obtained from **3h**, selected as a model compound, either with aqueous KOH, NaOH in methanol/water, or *t*-BuOK at various temperatures (0 °C, r.t. or 60 °C).

Table 1: Synthesis of quinolin-3-yl imines **2** and α-aminonitriles **3**.

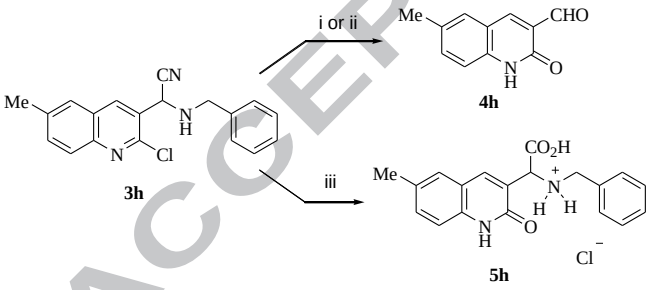


1 **2** **3**

R^1	R^2	R^3	R^4	R′	Product	Mp (°C)	Yield[a] (%)	Product	Mp (°C)	Yield[a] (%)
H	H	H	H	*i*-Pr	**2a**	63-65	90	**3a**	91-93	83
OMe	H	H	OMe	CH_2Ph	**2b**	120-121	77	**3b**	112-113	96
H	H	H	H	CH_2Ph	**2c**	55-57	98	**3c**	63-65	90
H	OMe	H	H	CH_2Ph	**2d**	60-61	97	**3d**	87	89
H	H	H	Me	CH_2Ph	**2e**	101-103	78	**3e**	120-122	93
H	H	OMe	H	3,5-$Me_2C_6H_3$	**2f**	201-202	76	**3f**	166-168	88
H	H	H	H	4-MeC_6H_4	**2g**	101-103	60	**3g**	134-136	92
H	Me	H	H	CH_2Ph	**2h**	68-70	93	**3h**	103-106	87
H	H	H	H	4-$MeOC_6H_4$	**2i**	102-105	87	**3i**	107-109	91

[a] Yield of isolated pure products.

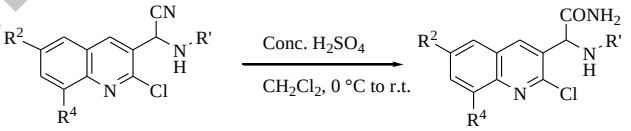
Acid-catalysed hydrolysis of **3h** with concentrated sulfuric acid in methanol or in AcOH furnished 2-oxoquinolin-3-carbaldehyde **4h** as the major product which resulted from simultaneous hydrolysis of the α-aminonitrile and 2-chloroquinoline moieties. At 0 °C, concentrated hydrochloric acid led to the *N*-benzyl α-amino acid hydrochloride **5h** as a white solid in a 93% yield (Scheme 2). Their structures were respectively established by comparison with NMR data from the literature for **4h** [9] and by ^1H, ^{13}C and IR spectroscopy and mass spectrometry for **5h**.[10] Unfortunately, attempted hydrogenolysis of α-amino acid **5h** using H_2/Pd-C mainly led to its decomposition (Scheme 2).



Scheme 2. Hydrolysis of aminonitrile **3h**. i. H_2SO_4/MeOH, reflux. ii. H_2SO_4 (80%)/AcOH, 75-80 °C. iii. Conc. HCl, 0 °C to rt, 93%.

Under slightly modified conditions [addition of concentrated H_2SO_4 to a pre-cooled (0 °C) solution of **3** in CH_2Cl_2],[11] α-aminonitriles **3c**, **3e, 3h** and **3i** were readily hydrolysed to give aminocarboxamides **6** after standard work-up with NH_4OH (pH=8-9) (Table 2). The ^1H and ^{13}C NMR spectra exhibited signals that confirmed these transformations, respectively, at 4.58 to 4.71 ppm for ArC<u>H</u>(CONH$_2$)NHBn, instead of 5.13 to 5.20 ppm for the ArC<u>H</u>(CN)NHBn protons, and 173.2 to 173.4 ppm for the ArCH(<u>C</u>ONH$_2$)NHBn carbons, instead of 117.6 to 117.8 ppm for ArCH(<u>C</u>N)NHBn.

Table 2: Synthesis of quinolin-3-ylcarboxamides **6.**

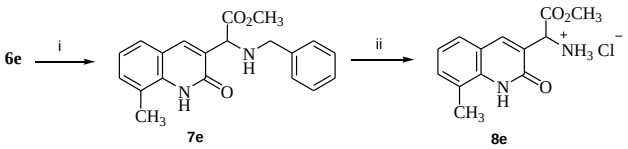


3 **6**

Entry	Product	R^2	R^4	R′	Yield [a] (%)
1	**6c**	H	H	CH_2Ph	67
2	**6e**	H	Me	CH_2Ph	75
3	**6h**	Me	H	CH_2Ph	70
4	**6i**	H	H	4-$MeOC_6H_4$	73

[a] Yield of isolated pure products.

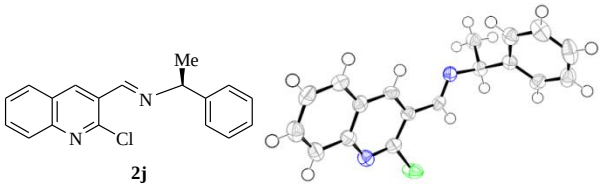
With these α-amino amides in hand, we next investigated the transformation of **6e**, chosen as model compound, into the corresponding α-amino ester. Treatment with methanol catalyzed by Amberlyst 15,[12] followed by hydrogenolysis with H_2 in the presence of $Pd(OH)_2$ and HCl yielded the racemic derivative **8e** in a 55% overall yield (Scheme 3).



Scheme 3. Synthesis of α-amino ester **8e**. i. MeOH, Amberlyst 15, reflux, 58%. ii. H_2, $Pd(OH)_2$ (0.1 eq.), HCl 1M (2 eq.), 95%.

To extend this work to the preparation of optically active derivatives containing a quinolin-3-yl moiety, we applied the Strecker reaction to enantiomerically pure amines. Chiral α-methylbenzylamines are commonly used as chiral auxilliaries in such processes [3a,c,d,e,g] which led us to synthesise the aldimine (+)

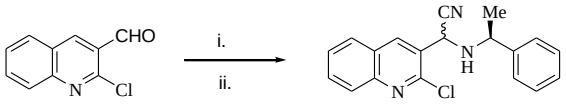
2j in 94% yield from 2-chloroquinolin-3-carboxaldehyde and (*S*)-α-methylbenzylamine [$[\alpha]_D^{20}$= +179.1 (*c* 1.02, CH_2Cl_2)].



2j

Figure 1: ORTEP plot of the X-ray crystal structure of **2j**. Displacement ellipsoids are drawn at the 50% probability level.[13]

Conversion into the corresponding α-aminonitrile **3j** was achieved in 84% yield with a 7/3 diastereoselectivity according to the previously described protocol (Scheme 4).



3j de : 40%

Scheme 4. Diastereoselective synthesis of α-aminonitrile **3j**. i. 1 eq. (*S*)-α-methylbenzylamine, MeOH, r.t. 94%. ii. 1.2 eq. *t*-$BuMe_2SiCN$, CH_3CN, H_2O, r.t. 84%.

While the separation of the two diastereomers failed using standard chromatographic methods, fractional crystallization from a CH_2Cl_2/petroleum ether (1:9) solution at room temperature afforded needles of the major isomer. Single-crystal X-ray analysis showed the major isomer to possess (*S*) configurations for the two stereocenters (Figure 3).[14] The structure of the minor diastereomer (2*R*,3*S*)-**3j** [15] was secured by X-ray crystallographic analysis (Figure 4).

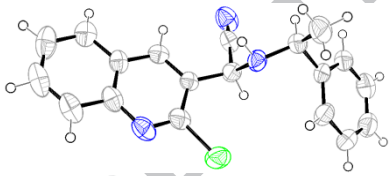


Figure 2: ORTEP plot of the X-ray crystal structure of (2*S*,3*S*)-**3j**. Displacement ellipsoids are drawn at the 50% probability level.[14]

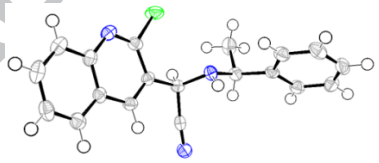


Figure 3: ORTEP plot of the X-ray crystal structure of (2*R*,3*S*)-**3j**. Displacement ellipsoids are drawn at the 50% probability level.[13]

Finally, the minor (*R*,*S*) derivative was converted into the corresponding amide **6j**[16] and methanolyzed before *N*-deprotection by hydrogenolysis (Scheme 5). Derivatization with *O*-acetyl-(*R*)-mandelic acid gave two diastereomers (ratio: 70/30) that revealed partial racemization. [17]

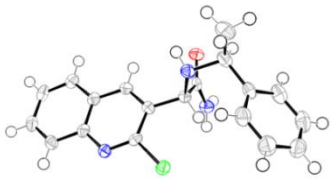
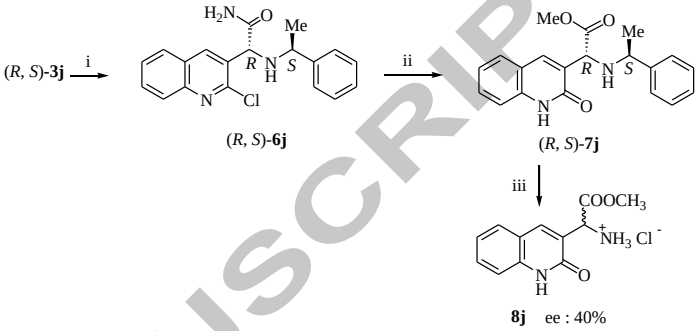
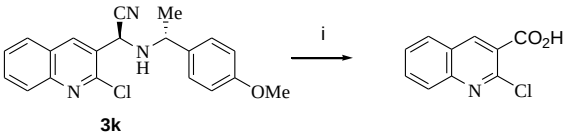


Figure 4: ORTEP plot of the X-ray crystal structure of (2*R*,3*S*)-**6j**. Displacement ellipsoids are drawn at the 50% probability level.[13]



Scheme 5. Synthesis of enantioenriched α-amino ester **8j**. [18] i. Conc. H_2SO_4 (33 eq.), CH_2Cl_2, 0 °C to r.t, NH_4OH, 65%. ii. MeOH, Amberlyst 15, reflux, 62%. iii. H_2, $Pd(OH)_2$ (0.1 eq.), HCl 1M (2 eq.), 92%.

In a parallel approach, to try to circumvent epimerization, imine **2k** derived from 1-(*R*)-(4-methoxyphenyl)ethanamine was similarly prepared in a 95% yield.[19] The Strecker reaction easily afforded the aminonitrile **3k**, albeit in a lower diastereomeric ratio (55/45) when compared with **3j**. After separation by crystallization, the major (*S*,*R*) isomer was directly treated with cerium ammonium nitrate to cleave the chiral auxiliary. Unfortunately, 2-chloroquinolin-3-ylcarboxylic acid was the only isolated product as a white solid in 93% yield,[20] which was attributed to decomposition of α-aminonitrile **3k** into the starting aldehyde and its further oxidation (Scheme 6).[21]



3k

Scheme 6. Oxidation of α-aminonitrile *(S,R)***3k.** i. CAN, CH_3CN/H_2O (4:1), 45 min, 0 °C-r.t., 93%.

In summary, we have described an easy access to new non-natural α-amino acid derivatives by cyanation of the corresponding quinolin-3-ylimines using *t*-$BuMe_2SiCN$ as the cyanide source. In most cases, quantitative yields and pure products were obtained without the need for chromatographic separation. When the asymmetric synthesis of an α-amino amide bearing a quinoline unit was successfully achieved from (*S*)-α-methylbenzylamine as the chiral auxiliary, partial epimerization occurred during the methanolysis and the *N*-deprotection steps.

Acknowledgements

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10. Selected spectral data for 2-benzylamino-2-(1,2-dihydro-6-methyl-2-oxoquinolin-3-yl)acetic acid hydrochloride **5h.** White solid. mp 218 °C. IR ν_{max} (KBr) 3421, 1743, 1651 cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6): δ 12.20 (br s, 1H), 9.60-10.00 (br s, 2H), 8.06 (s, 1H), 7.65-7.20 (m, 8H), 5.14 (s, 1H), 4.17 (s, 2H), 2.34 (s, 3H). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 168.6, 161.0, 142.4, 137.2, 133.3, 132.1, 131.7, 130.7, 130.7, 129.4, 128.9, 128.9, 128.2, 123.6, 118.7, 115.7, 58.2, 49.8, 20.7. HRMS (ESI): *m/z* $[M - HCl + Na]^+$ Calcd for $C_{19}H_{18}N_2O_3Na$: 345.1215. Found: 345.1212.
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13. Crystal structure analysis for 2-chloro-3-[(*S*)-α-methylbenzylimino] methylquinoline (**2j**): $C_{18}H_{15}ClN_2$, Mr = 294,7 $g.mol^{-1}$, monoclinic, space group $P2_1(4)$, a = 8.0353 (3) Å, b = 13.7059 (6) Å, c = 13.4665 (6) Å, β = 94.717 (2)°, V = 1478.06 (11) $Å^3$, Z = 4, ρ_c= 1.325 $g.cm^3$, F(0 0 0) = 616, crystal size: 0.24 x 0.13 x 0.03 mm. Crystal structure analysis for (*R*)-2-(2-chloroquinolin-3-yl)-2-[*N*-[(*S*)-α-methylbenzylamino]acetonitrile (**3j**): $C_{19}H_{16}ClN_3$, Mr = 321.8 $g.mol^{-1}$, orthorhombic, space group $P2_12_12_1(19)$, a = 5.9047(2)Å, b = 2.5394(6)Å, c = 21.3951(9)Å, V = 1584.12(11)$Å^3$, Z = 4, ρ_c= 1.349 $g.cm^3$, F(0 0 0) = 672, crystal size: 0.52 x 0.18 x 0.14 mm. Crystal structure analysis for: for *(R)*-2-(2-chloroquinolin-3-yl)-2-[*N*-(*S*)-α-methylbenzylamino]carboxamide (**6j**): $C_{19}H_{18}ClN_3O$, Mr = 339.81 g. mol^{-1}, monoclinic, space group $P2_1(4)$, a = 9.2574(2) Å, b = 6.6265(2) Å, c = 14.2529(4) Å, β = 104.0370(10)°, V = 848.22(4) $Å^3$, Z = 2, ρ_c=1.33 $g.cm^3$, F(0 0 0) = 356, crystal size: 0.51 x 0.13 x 0.12 mm. Crystallographic data (excluding structure factors) for these compounds have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 898280 for **2j**, CCDC 898281 for **3j** and CCDC 898282 for **6j**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif./cif.
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15. Selected properties and spectral data for (*R*)-2-(2-chloroquinolin-3-yl)-2-[*N*-[(*S*)-α-methylbenzylamino]acetonitrile **(+)-3j:** White crystals; mp. 145-146 °C. $[\alpha]_D^{20}$= + 9.6 (*c*=1.0, CH_2Cl_2). ^1H (300 MHz, $CDCl_3$): 8.31 (s, 1H), 8.05 (d, *J* =8.4 Hz, 1H), 7.95-7.75 (m, 2H), 7.71 (d, *J* =8.0 Hz, 1H), 7.45-7.20 (m, 5H), 5.25 (d, *J* =9.6 Hz, 1H), 4.12 (q, *J* =6.4 Hz, 1H), 2.08 (d, *J* =9.6 Hz, 1H), 1.51 (d, *J* =6.4 Hz, 3H). ^{13}C NMR (75.4 MHz, $CDCl_3$): 148.9, 147.4, 143.5, 141.9, 137.9, 131.4, 128.7, 128.3, 127.8, 127.7, 126.8, 126.7, 126.6, 117.7, 56.6, 49.9, 22.7. Anal. Calcd for $C_{19}H_{16}ClN_3$: C, 70.91; H, 5.01; N, 13.06. Found: C, 71.17; H, 4.99; N, 13.22.
16. Selected properties and spectral data for (*R*)-2-(2-chloroquinolin-3-yl)-2-[*N*-(*S*)-α-methylbenzylamino]carboxamide (-)-**6j**: 65% yield. $[\alpha]_D^{20}$ = -139.5 (*c* 1.08, CH_2Cl_2). IR ν_{max} (KBr) 3344, 1508 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): 7.89 (d, *J* = 8.5 Hz, 1H), 7.82 (s, 1H), 7.66 (d, *J* = 8.2 Hz, 1H), 7.60 (td, *J* =8.4, 1.5 Hz, 1H), 7.43 (td, *J* =8.4, 1.1 Hz, 1H), 7.25-715 (m, 5H), 6.74 (br s, 1H), 4.23 (s, 1H), 3.50 (q, *J* = 6.5 Hz, 1H), 1.21 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (75.47 MHz, $CDCl_3$): 173.2, 149.3, 147.0, 143.2, 140.0, 130.7, 130.0, 128.9, 128.2, 127.7, 127.5, 126.9, 62.3, 55.9, 24.1. HRMS : *m/z* $[M+Na]^+$ Calcd. for $C_{19}H_{18}N_3OClNa$: 362.1036; found: 362.1035.
17. Procedure for derivatization of **8j** with *O*-acetyl-(*R*)-mandelic acid.
To a solution of *O*-acetyl-(*R*)-mandelic acid (7 mg, 0.037 mmol) in dry CH_2Cl_2 (1 mL), were added, at 0 °C, EDCI (9 mg, 0.048 mml), HOBT (6 mg, 0.045 mmol) and *N*-methylmorpholine (16 mL, 0.14 mmol). After 30 min at 0 °C, a solution of **8j** (10 mg, 0.037 mmol) in dry CH_2Cl_2 (1 mL) was added to the reaction mixture. The reaction was stirred at rt overnight then Et_2O (3 mL) was added. The organic phase was washed with 0.1 M HCl (3x1 mL), H_2O (2x1 mL), brine (1 mL) then dried, filtered and concentrated under reduced pressure to give the corresponding product as a mixture of two diastereomers (ratio: 70/30).
Characteristic signals for the major diastereomer : ^1H NMR (500 MHz, $CDCl_3$): 6.20 (s, 1H), 5.58 (d, *J* = 8.4 Hz, 1H), 3.73 (s, 3H).
Characteristic signals for the minor diastereomer : ^1H NMR (500 MHz, $CDCl_3$): 6.15 (s, 1H), 5.71 (d, *J* = 8.5 Hz, 1H), 3.76 (s, 3H).
18. Selected properties and spectral data for (*R*)-2-(1,2-dihydro-2-oxoquinolin-3-yl)-2-aminomethyl acetate (-)-**8j**. 92% yield. $[\alpha]_D^{20}$ = -52.8 (*c* 0.75, MeOH). IR ν_{max} (KBr) 1749, 1652 cm^{-1}. ^1H NMR (400 MHz, MeOD): 8.28 (s, 1H), 7.80 (d, *J* = 7.8 Hz, 1H), 7.67 (t, *J* = 7.7 Hz, 1H), 7.44 (d, *J* = 7.9 Hz, 1H), 7.36 (t, *J* = 7.6 Hz, 1H), 5.29 (s, 1H), 3.86 (s, 3H). ^{13}C NMR (100 MHz, MeOD): 170.1, 163.7, 145.3, 141.1, 134.1, 130.8, 125.9, 125.3, 121.4, 117.6, 55.6, 55.0. HRMS : *m/z* $[M+H]^+$ Calcd. for $C_{12}H_{13}N_2O_3$: 233.0926; found: 233.0927**.**
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21. While this work was in progress, it was shown that treatment of (*S,S*)-α-aminonitriles derived from (*S*)-1-(4-methoxyphenyl)ethylamine and arylaldehydes in 6 M aqueous HCl at reflux resulted in cleavage of their chiral auxiliary fragments and concomitant hydrolysis of their nitrile groups. Perez-Fuertes, Y.; Taylor, J. E.; Tickell, D. A.; Mahon, M. F.; Bull, S. D.; James, T. D. *J. Org. Chem.* **2011**, *76*, 6038-6047.