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Synthesis of new enantiomerically pure *N*-methyl-*N*-arylsulfonyl-α-aminonitriles from amino acids

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Abstract

New enantiomerically pure *N*-methyl-*N*-arylsulfonyl-α-aminonitriles were prepared starting from the corresponding α-amino acids by way of *N*-methyl-*N*-arylsulfonyl-α-amino amides. The key step of this sequence consists of the dehydration of amides by thionyl chloride which proceeded without a significant racemization. Enantiomeric purity of nitriles was determined by HPLC analysis. ***To cite this article: N. Tka et al., C. R. Chimie 12 (2009).***

Résumé

Des nouveaux *N*-methyl-*N*-arylsulfonyl-α-aminonitriles enantiomériquement purs sont préparés au départ des acides α-aminés correspondant en passant par les *N*-methyl-*N*-arylsulfonyl-α-aminoamides. L'étape clé de cette séquence consiste en une déshydratation des amides par l'intermédiaire du chlorure de thionyle qui a lieu sans racémisation. La pureté enantiomérique des nitriles a été déterminée par HPLC. ***Pour citer cet article : N. Tka et al., C. R. Chimie 12 (2009).***

Keywords: α-Amino acids; *N*-Methyl-*N*-arylsulfonyl-α-aminoamides; Thionyl chloride; *N*-Methyl-*N*-arylsulfonyl-α-aminonitriles

Mots-clés : Acides α-aminés ; *N*-methyl-*N*-aryksulfonyl-α-aminoamides ; Chlorure de thionyle ; *N*-methyl-*N*-arylsulfonyl-α-aminonitriles

1. Introduction

α-Aminonitriles have gained an increasing interest in recent years thanks to their versatile utility as precursors and intermediates in the preparation of numerous biologically-active compounds [1–9]. In particular, the synthesis of optically-active α-aminonitriles constitutes an area of considerable interest in asymmetric organic synthesis. The preparation of chiral *N*-monosubstituted and *N*-unsubstituted α-aminonitriles is very well documented. These compounds can be obtained by resolution of racemates with tartaric acid [10], through enantioselective enzymatic transformation [11], *via* catalytic enantioselective Strecker reaction [12,13] or by dehydration of optically-active amides derived from amino acids [14–17]. However, the literature is bereft of reports on the preparation of *N*,*N*-disubstituted α-aminonitriles in an enantiomerically enriched form. This is also significantly contrasted with the vast number

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of examples of non-racemic aminonitriles having two or more stereogenic centers [18,19]. Indeed, we are aware of only three such reports: (*R*)-2-alkyl-2-(1-piperidinyl)alkanenitrile (ee 6–84%) obtained *via* dehydration of the corresponding commercially carboxamides using various dehydrating agents [20], (*S*)-1-benzyl-α-cyanopiperidine (ee 91%) prepared in several steps from non-racemic cyanohydrin [21] and *N*-allyl-*N*-trifluoroacetyl-α-aminonitriles (ee 37–95%) obtained *via* addition of hydrogen cyanide to imines, catalyzed by a chiral (Salen)Al(III) complex and followed by the trifluoroacetylation of the *N*-monosubstituted α-aminonitriles [22].

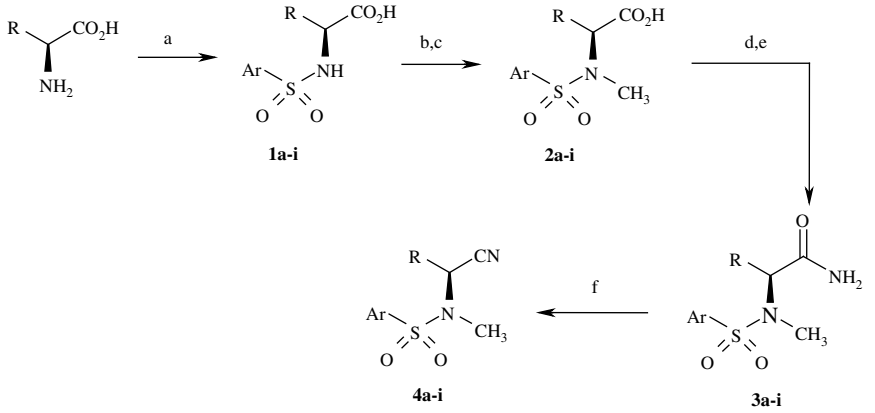
Herein, we report the synthesis of enantiomerically pure *N*-methyl-*N*-arylsulfonyl-α-aminonitriles from the corresponding (L)- and (D)-α-amino acids by means of *N*-methyl-*N*-arylsulfonyl-α-amino amides. These compounds are new and represent the first example of enantiomerically pure *N*,*N*-disubstituted α-aminonitriles.

2. Results and discussion

The synthetic route to target compounds **4a–k** is outlined in Schemes 1 and 2. The commercially available (D)- and (L)-amino acids, used as starting materials, were converted to the corresponding *N*-arylsulfonyl-α-amino acids **1a–k** according to the procedure described in the literature [23]. Compounds **1a–i** were converted to *N*-methyl-*N*-arylsulfonyl-α-amino acids **2a–i** in two steps, following a similar method reported by Freindinger et al. [24–26] The treatment of **2a–i** and **1j**,**k** with thionyl chloride followed by treatment with aq. NH_3 led to the corresponding α-amino amides **3a–k**. The last step is the dehydration of aminoamides **3a–k** with thionyl chloride which led to the corresponding α-aminonitriles **4a–k**.

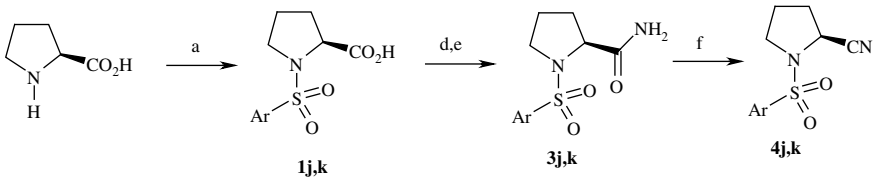
α-Aminonitriles **4a–k**, prepared by dehydration of the corresponding amides **3a–k**, were obtained with excellent yields. Moreover, the reaction occurred without a significant racemization of the stereogenic center. Indeed, we have analyzed the enantiomeric *ratio* of compounds **4a–c**,**f** prepared from both optically pure and racemic amino acids, by chiral HPLC analysis. We have found that racemization did not occur for compound **4a–c**,**f** prepared from optically pure amino acids.

In this work, thionyl chloride is used as a dehydrating agent to convert amides into the corresponding aminonitriles. This agent appeared to be convenient to provide α-aminonitriles without a significant racemization of the α-bearing carbon. However, as described in the literature, the use of other dehydrating agents such as $POCl_3$/Py, TsCl/PyTf_2O/Et_3N and Burgess' salt [20] involved racemization of the *N*,*N*-disubstituted α-aminonitriles. Within this work, we have found that the use of $POCl_3$ instead of $SOCl_2$, to convert the amide **3a** into the corresponding nitrile **4a**, occurred with total racemization of the α-bearing carbon. As described by Sheldon et al. [10] in α-aminonitriles, the α-proton is somewhat acidic due to the electron-withdrawing effect of the cyano group. Then, the presence of a basic site would catalyze the racemization process. Accordingly, we think that the use of $SOCl_2$, which frees HCl (g) and SO_2 (g) during the reaction, is convenient to avoid the racemization, since there is no possible acid–base interaction between the acidic α-proton of nitriles and these compounds.



a : R = Me, Ar = Ph; **b** : R = i - Pr, Ar = Ph; **c** : R = i - Bu, Ar = Ph; **d** : R = *sec*- Bu, Ar = Ph; **e** : R = Bn, Ar = Ph; **f** : R = Ph, Ar = Ph; **g** : R = Me, Ar = p-tolyl; **h** : R = i - Bu, Ar = p-tolyl; **i** : R = *sec*- Bu, Ar = p-tolyl

Scheme 1. Synthesis of *N*-methyl-*N*-arylsulfonyl-α-aminonitriles from the corresponding amino acids. Reaction conditions: (a) $ArSO_2Cl$/NaOH/$EtN(i\text{-}Pr)_2$; (b) $(CH_2)_n$/*p*-toluene sulfonic acid; (c) Et_3SiH/CF_3CO_2H; (d) $SOCl_2$; (e) aq. NH_3; (f) $SOCl_2$ reflux, 2 h.



j: Ar = Ph; **k** : Ar = p -tolyl

Scheme 2. Synthesis of the substituted α-aminonitrile from (L)-proline.

3. Conclusion

To conclude, the preparation of a single-stereocentre series of enantiomerically pure *N*-methyl-*N*-arylsulfonyl-α-aminonitriles from their corresponding α-amino acids has been achieved for the first time in the combined terms of quantitative yields and enantiomeric purity. We analyzed the enantiomeric *ratio* of compounds **4a**–**k** by chiral HPLC analysis. The study of the synthetic features of these products to prepare new chiral heterocyclic compounds is under investigation in our laboratory.

4. Experimental section

TLC was performed on Merck 60F-254 silica gel plates (layer thickness 0.25 mm). Column chromatography was performed on silica gel (70e230 mesh) using ethylacetate and cyclohexane mixture as eluents. CH_2Cl_2 was distilled over CaH_2. Melting points were determined on a Electrothermal 9002 apparatus and are uncorrected. NMR spectra were recorded on Bruker AC-300 apparatus (^1H at 300 MHz and ^{13}C at 75 MHz). All chemical shifts are reported as δ values (ppm) relative to internal tetramethylsilane. IR spectra were recorded on BIO-RAD FTS-6000 apparatus. Mass spectra (EI) were recorded on Hewlett Packard 5897. Elemental analyses were carried out by 'Service de microanalyse' of 'Institut national de recherche et d'analyse physico-chimique de Tunis'. HPLC analyses were conducted on a heptane/isopropanol system with a UV detector at 254 nm, using a Chirobiotic V column (250 × 46 mm) and a flow rate of 0.5 mL/min. Compounds **2a**–**i** were prepared as described [25,26].

4.1. Typical procedure for the preparation of N-methyl-N-arylsulfonyl-2-amino amides

A mixture of *N*-methyl-*N*-sulfonyl-2-amino acid (10 mmol), $SOCl_2$ (40 mmol) and three drops of dry DMF in anhydrous dichloromethane was stirred overnight at room temperature under N_2. After removal of the excess of $SOCl_2$ under vacuum, the residue was added slowly to a cold solution of aqueous ammonium hydroxide and was allowed to warm slowly to room temperature with stirring. The mixture was filtered and the resultant solid was dissolved in boiling ethanol. The solution was, then, filtered while hot and water was added dropwise to the cloud point. After cooling, the pure *N*-methyl-*N*-arylsulfonyl-2-amino amide was collected.

*4.1.1. (2S)-N-methyl-N-phenylsulfonyl-2-amino-propanamide **3a***

Yield = 88%; mp 144–143 °C; IR (cm^{-1}): $\nu_{CO} = 1716$, $\nu_{NH} = 3435$; ^1H NMR (300 MHz, $CDCl_3$): δ: 0.92 (d, 3H, $J = 7.2$ Hz), 2.76 (s, 3H), 4.46 (q, 1H, $J = 7.2$ Hz), 5.83 (1H, NH), 6.51 (1H, NH), 7.61–7.99 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ: 11.96, 30.47, 55.90,127.71, 130.08, 135.65, 144.46, 173.40 (CO). Anal. Calcd for $C_{10}H_{14}N_2O_3S$, 242.30: C 49.57, H 5.82, N 11.56. Found: C 50.05, H 5.78, N 11.85.

*4.1.2. (2S)-N-Methyl-N-phenylsulfonyl-2-amino-3-methylbutaneamide **3b***

Yield = 87%; mp 122–123 °C; IR (cm^{-1}): $\nu_{CO} = 1715$, $\nu_{NH} = 3438$; ^1H NMR (300 MHz, $CDCl_3$): δ: 0.86 (d, 3H, $J = 6.9$ Hz), 0.93 (d, 3H, $J = 6.9$ Hz), 2.09 (m, 1H), 2.83 (s, 3H), 4.78 (d, 1H, $J = 10.5$ Hz), 5.72 (1H, NH), 6.48 (1H, NH), 7.62–7.78 (m, 3H), 7.88 (d, 2H, $J = 7.2$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ: 19.24, 19.34, 26.93, 29.89, 64.70, 127.66, 129.04, 133.14, 136.14, 174.67 (CO).

*4.1.3. (2S)-N-Methyl-N-phenylsulfonyl-2-amino-4-methylpentaneamide **3c***

Yield = 89%; mp 137–138 °C; IR (cm^{-1}): $\nu_{CO} = 1717$, $\nu_{NH} = 3432$; ^1H NMR (300 MHz, $CDCl_3$) δ: 0.90 (d, 6H $J = 5.4$ Hz), 1.57 (m, 3H), 2.78 (s, 3H), 4.65 (dd, 1H $J = 8.7$ Hz, $J = 7.0$ Hz), 5.80 (1H, NH), 6.49 (1H, NH), 7.48–7.75 (m, 3H), 7.78 (d, 2H, $J = 7.2$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.10, 21.53, 24.46, 29.67, 39.67, 55.03, 128.33, 129.03, 134.17, 136.75, 172.28 (CO).

*4.1.4. (2S,3S)N-Methyl-N-phenylsulfonyl-2-amino-3-methylpentaneamide **3d***

Yield = 90%; mp 127–128 °C; IR (cm^{-1}): $\nu_{CO} = 1719$, $\nu_{NH} = 3437$; ^1H NMR (300 MHz, $CDCl_3$): δ: 0.99 (t, 3H $J = 7.5$ Hz); 1.18 (d, 3H $J = 6.6$ Hz); 1.24–1.85 (m, 3H); 2.77 (s, 3H); 4.19 (d, 1H $J = 10.5$ Hz); 5.77 (1H, NH), 6.55 (1H, NH), 7.52–7.70 (m, 3H); 7.88 (d, 2H $J = 7.2$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ: 10.85, 15.70, 25.40, 30.37, 34.81, 58.59, 127.78, 129.81, 133.61; 136.19, 173.28 (CO).

*4.1.5. (2S)-N-Methyl-N-phenylsulfonyl-2-amino-3-phenylpropaneamide **3e***

Yield = 85%; mp 157–158 °C; IR (cm^{-1}): $\nu_{CO} = 1715$, $\nu_{NH} = 3433$; ^1H NMR (300 MHz, $CDCl_3$): δ: 2.60 (m, 1H); 2.83 (s, 3H); 3.25 (m, 1H); 4.75 (t, 1H, $J = 7.2$ Hz); 6.13 (1H, NH), 6.45 (1H, NH), 7.09–7.31 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 29.33, 33.86, 60.89, 126.62, 127.22, 128.31, 129.16, 129.75, 135.53, 137.35, 143.68, 171.98.

*4.1.6. (2R)-N-Methyl-N-phenylsulfonyl-2-amino-2-phenylethaneamide **3f***

Yield = 84%; mp 165–166 °C; IR (cm^{-1}): $\nu_{CO} = 1712$, $\nu_{NH} = 3431$; ^1H NMR (300 MHz, $CDCl_3$): δ: 2.79 (s, 3H); 4.65 (s, 1H); 6.09 (1H, NH), 6.37 (1H, NH), 7.13–7.38 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 28.66, 95.77, 126.22, 127.32, 129.05, 130.16, 131.65, 134.23, 136.15, 142.88, 172.09.

*4.1.7. (2S)-N-Methyl-N-tolylsulfonyl-2-aminopropaneamide **3g***

Yield = 89%; mp 133–134 °C; IR (cm^{-1}): $\nu_{CO} = 1717$, $\nu_{NH} = 3431$; ^1H NMR (300 MHz, $CDCl_3$): δ: 0.97 (d, 3H, $J = 7.2$ Hz), 2.37 (s, 3H), 2.79 (s, 3H), 4.44 (q, 1H, $J = 7.2$ Hz), 5.77 (1H, NH), 6.41 (1H, NH), 7.65 (d, 2H $J = 8.1$ Hz), 7.96 (d, 2H, $J = 8.1$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ: 12.56, 23.78, 30.42, 56.20,126.71, 129.11, 135.45, 143.45, 172.54 (CO).

*4.1.8. (2S)-N-Methyl-N-tolylsulfonyl-2-amino-4-methylpentaneamide **3h***

Yield = 90%; mp 140–141 °C; IR (cm^{-1}): $\nu_{CO} = 1714$, $\nu_{NH} = 3437$; ^1H NMR (300 MHz, $CDCl_3$) δ: 0.98 (d, 6H $J = 5.4$ Hz), 1.74 (m, 3H), 2.35 (s, 3H), 2.83 (s, 3H), 4.54 (dd, 1H $J = 8.6$ Hz, $J = 6.9$ Hz), 5.76 (1H, NH), 6.29 (1H, NH), 7.32 (d, 2H $J = 8.1$ Hz), 7.81 (d, 2H, $J = 8.1$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.01, 21.84, 22.68, 24.68, 29.61, 39.17, 54.82, 127.45, 130.58, 135.85, 142.15, 172.83 (CO).

*4.1.9. (2S,3S)-N-Methyl-N-tolylsulfonyl-2-amino-3-methylpentaneamide **3i***

Yield = 88%; mp 147–148 °C; IR (cm^{-1}): $\nu_{CO} = 1715$, $\nu_{NH} = 3433$; ^1H NMR (300 MHz, $CDCl_3$): δ: 0.92 (t, 3H $J = 7.4$ Hz); 1.34 (d, 3H $J = 6.9$ Hz); 1.33–1.95 (m, 3H), 2.38 (s, 3H), 2.71 (s, 3H); 4.22 (d, 1H $J = 9.9$ Hz); 5.82 (1H, NH), 6.35 (1H, NH), 7.64 (d, 2H $J = 8.1$ Hz), 7.72 (d, 2H, $J = 8.1$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ: 11.48, 17.45, 22.25, 25.65, 31.35, 35.01, 59.29, 127.78, 129.81, 136.19, 143.86, 173.28 (CO).

*4.1.10. (2S)-N-Phenylsulfonyl-2-carbamoylpyrrolidine **3j***

Yield = 86%; mp = 150–151 °C; IR (cm^{-1}): $\nu_{CO} = 1716$, $\nu_{NH} = 3437$; ^1H NMR (300 MHz, $CDCl_3$): δ: 1.98–2.19 (m, 4H); 3.33 (m, 2H); 4.58 (dd, 1H, $J = 6.9$ Hz, $J = 2.7$ Hz), 5.77 (1H, NH), 6.11 (1H, NH), 7.43–7.81 (m, 3H); 7.91 (d, 2H, $J = 7.2$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ: 23.41, 31.87, 45.72, 49.58, 127.5, 129.42, 134.9, 137.38, 172.18 (CO).

*4.1.11. (2S)-N-Tolylsulfonyl-2-carbamoylpyrrolidine **3k***

Yield = 91%; mp = 160–161 °C; IR (cm^{-1}): $\nu_{CO} = 1714$, $\nu_{NH} = 3435$; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.95–2.17 (m, 4H), 2.36 (s, 3H), 3.39 (m, 2H), 4.51 (dd, 1H, $J = 7.5$ Hz, $J = 2.55$ Hz), 5.66 (1H, NH), 6.21 (1H, NH), 7.22 (d, 2H, $J = 8.1$ Hz), 7.79 (d, 2H, $J = 8.1$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 22.9, 25.03, 32.30, 47.93, 48.99, 127.95, 12.35, 134.61, 142.86, 172.33 (CO).

4.2. Typical procedure for the dehydration of N-methyl-N-arylsulfonyl-2-amino amides

N-methyl-*N*-arylsulfonyl-2-amino amide (8 mmol) was dissolved in 5 mL of freshly distilled thionyl chloride. The mixture was refluxed for 2 h until the amide was consumed (TLC). The excess of thionyl chloride was removed under vacuum using a rotary evaporator, and the reaction residue was, then, mixed with crushed ice and extracted with ethylacetate (3×50 mL). The organic layers were combined, washed sequentially with a saturated aqueous $NaHCO_3$ solution and water and dried with anhydrous $MgSO_4$. After that, the solvent was removed under vacuum and the crude product was purified by column chromatography on silica gel, using [cyclohexane:ethylacetate (8:2)], to afford pure *N*-methyl-*N*-arylsulfonyl-2-aminonitrile **4a–k**.

4.2.1. (2S)-N-Methyl-N-phenylsulfonyl-2-amino-propanenitrile ***4a***

Yield = 93%; mp: 78–79 °C; $[\alpha]_D$ −120, (*c*0.5, $CHCl_3$); ee > 99.5% [HPLC analysis using a Chirobiotic V column 4.6 mm × 250 mm under the following conditions: heptane/isopropanol (95:5) as mobile phase, rt, $\lambda = 254$ nm, flow rate = 0.5 mL/min. Retention times: (*S*)-**4a**, 10.45 min; (*R*)-**4a**, 12.86 min]; IR (cm^{-1}): $\nu_{CN} = 2245$; ^1H NMR (300 MHz, $CDCl_3$): δ: 1.57 (d, 3H, $J = 7.2$ Hz), 2.84 (s, 3H), 5.04 (q, 1H, $J = 7.2$ Hz), 7.56-7.83 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$), δ: 18.52, 30.25, 44.70, 116.1 (CN), 127.61, 129.54, 133.79, 136.35; MS/EI $m/z = 224$ ($M^{+\bullet}$); Anal. Calcd for $C_{10}H_{12}N_2O_2S$, 224.24: C 53.55, H 5.39, N 12.49. Found: C 53.43, H 5.22, N 12.31.

4.2.2. (2S)-N-Methyl-N-phenylsulfonyl-2-amino-3-methylbutanenitrile ***4b***

Yield = 94%; mp 75–77 °C; $[\alpha]_D$ −80, (*c* 0.5, $CHCl_3$); ee > 99.5% [HPLC analysis using a Chirobiotic V column 4.6 mm × 250 mm under the following conditions: heptane/isopropanol (95:5) as mobile phase, rt, $\lambda = 254$ nm, flow rate = 0.6 mL/min. Retention times: (*S*)-**4b**, 25.95 min; (R)-**4b**, 31.97 min]; IR (cm^{-1}): $\nu_{CN} = 2246$; ^1H NMR (300 MHz, $CDCl_3$): δ: 0.90 (d, 3H, $J = 6.6$ Hz), 0.96 (d, 3H, $J = 6.6$ Hz), 2.04 (m, 1H), 2.83 (s, 3H), 4.88 (d, 1H, $J = 10.5$ Hz), 7.66–7.83 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ: 19.52, 19.62, 26.93, 30.15, 51.70, 117.4 (CN), 127.5, 129.25, 135.81, 139.84; MS/EI $m/z = 252$ ($M^{+\bullet}$); Anal. Calcd for $C_{12}H_{16}N_2O_2S$, 252.34: C 57.12, H 6.39, N 11.10. Found: C 56.98, H 6.27, N 11.03.

4.2.3. (2S)-N-Methyl-N-phenylsulfonyl-2-amino-4-methylpentanenitrile ***4c***

Yield = 95%; mp = 73–75 °C; $[\alpha]_D$ −70 (*c* 0.5, $CHCl_3$); ee > 99.5% [HPLC analysis using a Chirobiotic V column 4.6 mm × 250 mm under the following conditions: heptane/isopropanol (95:5) as mobile phase, rt, $\lambda = 254$ nm, flow rate = 0.6 mL/min. Retention times: (*S*)-**4c**, 15.43 min; (R)-**4c**, 19.58 min]; IR (cm^{-1}): $\nu_{CN} = 2244$; ^1H NMR (300 MHz, $CDCl_3$) δ: 0.91 (d, 6H $J = 5.4$ Hz), 1.52–1.77 (m, 3H), 2.73 (s, 3H), 4.84 (dd, 1H, $J = 8.7$ Hz, $J = 7.0$ Hz), 7.48–7.78 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.84, 22.62, 24.63, 30.74, 40.67, 48.03, 116.15(CN), 128.00, 129.83, 134.07, 136.75; MS/EI $m/z = 266$ ($M^{+\bullet}$).

4.2.4. (2S,3S)N-Methyl-N-phenylsulfonyl-2-amino-3-methylpentanenitrile ***4d***

Yield = 95%; mp = 81–83 °C; $[\alpha]_D$ −110, (*c* 0.5, $CHCl_3$); IR (cm^{-1}): $\nu_{CN} = 2245$ (CN); ^1H NMR (300 MHz, $CDCl_3$): δ: 0.92 (t, 3H $J = 7.5$ Hz), 1.13 (d, 3H $J = 6.6$ Hz), 1.18–1.27 (m, 1H), 1.69–1.85 (m, 2H), 2.79 (s, 3H), 4.47 (d, 1H $J = 10.5$ Hz), 7.55–7.81 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ: 10.17, 15.75, 24.53, 30.91, 35.81, 54.89, 115.37 (CN), 127.59, 129.49, 133.71, 136.42, MS/EI $m/z = 266$ ($M^{+\bullet}$).

4.2.5. (2S)-N-Methyl-N-phenylsulfonyl-2-amino-3-phenylpropanenitrile ***4e***

Yield = 93%; mp = 97–99 °C; $[\alpha]_D$ −30, (*c* 0.5, $CHCl_3$); IR (cm^{-1}): $\nu_{CN} = 2241$ (CN); ^1H NMR (300 MHz, $CDCl_3$): δ: 2.81 (s, 3H), 3.06 (m, 2H), 4.99 (m, 1H), 7.17–7.69 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 31.33, 39.03, 51.59, 115.60 (CN), 127.90, 128.41, 129.44, 129.67, 129.83, 134.05, 136.95, 136.95, MS/EI $m/z = 300$ ($M^{+\bullet}$). Anal. Calcd for $C_{16}H_{16}N_2O_2S$, 300.38: C 63.98, H 5.37, N 9.33. Found: C 63.86, H 5.35, N 9.40.

4.2.6. (2R)-N-Methyl-N-phenylsulfonyl-2-amino-2-phenylethanenitrile ***4f***

Yield = 94%; mp = 86–88 °C; $[\alpha]_D$ +90; (*c* 0.5, $CHCl_3$); ee > 99.5% [HPLC analysis using a Chirobiotic V column 4.6 mm × 250 mm under the following conditions: heptane/isopropanol (95:5) as mobile phase, rt, $\lambda = 254$ nm, flow rate = 0.5 mL/min. Retention times: (*R*)-**4f**, 14.54 min; (*S*)-**4f**, 19.73 min]; IR (cm^{-1}): $\nu_{CN} = 2242$ (CN); ^1H NMR (300 MHz, $CDCl_3$): δ: 2.60 (s, 3H), 5.86 (s, 1H), 7.18–7.33 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): δ: 31.19, 62.77, 117.56 (CN), 127.68, 128.35, 128.99, 129.45, 130.01, 130.78, 132.25, 132.85; MS/EI $m/z = 286$ ($M^{+\bullet}$).

4.2.7. (2S)-N-Methyl-N-tolylsulfonyl-2-amino-propanenitrile ***4g***

Yield = 92%; mp = 85–87 °C; $[\alpha]_D$ −130, (*c* 0.5, $CHCl_3$); IR (cm^{-1}): $\nu_{CN} = 2246$; ^1H NMR (300 MHz, $CDCl_3$): δ: 1.35 (d, 6H, $J = 7.2$ Hz), 2.37 (s, 3H), 2.75 (s, 3H), 4.94 (h, 1H, $J = 7.2$ Hz), 7.28 (d, 2H $J = 8.1$ Hz), 7.64 (d, 2H, $J = 8.1$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 18.89, 27.30, 30.53, 45.00, 116.54 (CN), 128.013, 130.45, 133.79, 145.05, MS/EI $m/z = 238$ ($M^{+\bullet}$); Anal. Calcd for $C_{11}H_{14}N_2O_2S$, 238.31: C 55.44, H 5.92, N 11.67. Found: C 55.34, H 5.81, N 11.49.

4.2.8. (2S)-N-Methyl-N-tolylsulfonyl-2-amino-4-methylpentanenitrile ***4h***

Yield = 93%; mp = 83–85 °C; $[\alpha]_D$ −60 (*c* 0.5, $CHCl_3$); IR (cm^{-1}): $\nu_{CN} = 2243$; ^1H NMR (300 MHz, $CDCl_3$) δ: 0.91 (d, 6H $J = 5.6$ Hz), 1.59–1.83 (m, 3H), 2.43 (s, 3H), 2.78 (s, 3H), 4.90 (dd, 1H $J = 8.4$ Hz,

$J = 6.75$ Hz), 7.36 (d, 2H $J = 8.1$ Hz), 7.78 (d, 2H, $J = 8.1$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.48, 21.69, 22.28, 24.28, 30.36, 40.34, 47.65, 115.91 (CN), 127.71, 130.09, 133.38, 144.67; MS/EI $m/z = 280$ ($M^{+\bullet}$).

4.2.9. (2S,3S)-N-Methyl-N-tolylsulfonyl-2-amino-3-methylpentanenitrile ***4i***

Yield = 91%; mp = 78–80 °C; $[\alpha]_D$ −100, (*c* 0.5, $CHCl_3$); IR (cm^{-1}): $\nu_{CN} = 2243$ (CN); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.95(t, 3H $J = 7.4$ Hz), 1.18 (d, 3H $J = 6.9$ Hz), 1.21–1.84 (m, 3H), 2.44 (s, 3H), 2.78 (s, 3H), 4.47 (d, 1H $J = 10.4$ Hz), 7.35 (d, 2H, $J = 8.4$ Hz), 7.81 (d, 2H, $J = 8.4$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 10.19, 15.76, 21.69, 24.57, 30.88, 35.90, 54,88, 115.47 (CN), 127.64, 130.08, 133.49, 144.61; MS/EI $m/z = 280$ ($M^{+\bullet}$).

4.2.10. (2S)-N-Phenylsulfonyl-2-cyanopyrrolidine ***4j***

Yield = 96%; mp = 99–101 °C; $[\alpha]_D$ −1040; (*c* 0.5, $CHCl_3$); IR (cm^{-1}): $\nu_{CN} = 2236$ (CN); ^{1}H NMR (300 MHz, $CDCl_3$): δ: 2.02–2.19 (m, 4H), 3.33 (m, 2H), 4.58 (dd, 1H, $J = 6.9$ Hz, $J = 2.7$ Hz), 7.53–7.88(m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ: 24.73, 31.97, 47.58, 48.66, 118.03 (CN), 127.55, 129.42, 133.59, 137.29, MS/EI $m/z = 236$ ($M^{+\bullet}$). Anal. Calcd for $C_{11}H_{12}N_2O_2S$, 236.29: C 55.91, H 5.12, N 11.86. Found: C 56.13, H 4.99, N 11.75.

4.2.11. (2S)-N-Tolylsulfonyl-2-cyanopyrrolidine ***4k***

Yield = 94%; mp = 92–94 °C; $[\alpha]_D$ −980, (*c* 0.5, $CHCl_3$); IR (cm^{-1}): $\nu_{CN} = 2235$ (CN); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.95–2,17 (m, 4H), 2.36 (s, 3H), 3.39 (m, 2H), 4.51 (dd, 1H, $J = 7.5$ Hz, $J = 2.55$ Hz), 7.27 (d, 2H, $J = 8.1$ Hz), 7.72 (d, 2H, $J = 8.1$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.99, 25.03, 32.30, 47.93, 48.99, 118.50 (CN), 127.95, 130.35, 134.61, 144.86; MS/EI $m/z = 250$ ($M^{+\bullet}$).

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