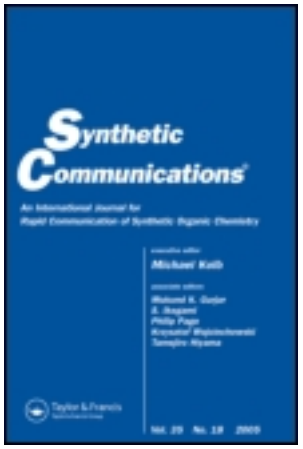

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Accepted author version posted online: 22 Feb 2012.Version of record first published: 13 Nov 2012.

To cite this article: Najeh Tka , Jamil Kraïem & Béchir Ben Hassine (2013): Synthesis of Enantiomerically Enriched α-Bromonitriles from Amino Acids, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 43:5, 735-743

To link to this article: http://dx.doi.org/10.1080/00397911.2011.608142

Synthetic Communications®, 43: 735–743, 2013

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2011.608142

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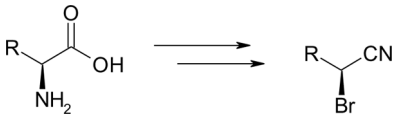
GRAPHICAL ABSTRACT



Abstract *Two methods were investigated for the preparation of six chiral α-bromonitriles with different optic purities. The nitrous deamination of amino acids gives α-bromoacids, which react with chlorosulfonyl isocyanate followed by triethylamine to afford α-bromonitriles with moderate enantiomeric excess. However, the dehydration of corresponding α-bromoamids using thionyl chloride gives α-bromonitriles with good enantiomeric excess up to 94%. The use of phosphoryl chloride instead of thionyl chloride results in more than 30% racemization as determined by high-performance liquid chromatograpic analysis.*

Keywords α-Bromoamids dehydration; chiral α-bromoacids; enantiomerically enriched α-bromonitriles

INTRODUCTION

Bromonitriles are potentially useful intermediates used for the synthesis of biologically active compounds.[1–2] Recently, the addition of Grignard reagents to bromonitriles was found to be an efficient route to prepare heterocyclic systems in particular functionalized cyclic imines used for alkaloid natural product synthesis.[3–5] Although they have shown important synthetic utilities, bromonitriles have not been well studied. Furthermore, the described methods often afford products in unsatisfactory way. Methods based on radical processes lead to a mixture of isomers,[6–8] and most of methods based on nucleophilic substitution of the hydroxyl group give poor yields or are time-consuming multistage processes.[9,10]

Somewhat frustratingly, the literature is bereft of reports concerning the preparation of α-bromonitriles in an enantiomerically enriched form. To our knowledge, only two examples have been described in the literature with no indication of the

Received March 31, 2011.
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products' optical purity. Recently, Matveeva et al.[11] used the 2,4,4,6-tetrabromocyclohexa-2,5-dienone complex with triphenylphosphine for the synthesis of bromonitriles by nucleophilic substitution of optically active cyanodrins. The second described method is the dehydration of optically active amide which affords α-bromonitriles with moderate yields.[12–14] Therefore, there is further scope to explore more efficient synthetic methods, giving α-bromonitriles in the combined terms of quantitative yields and enantiomeric purity.

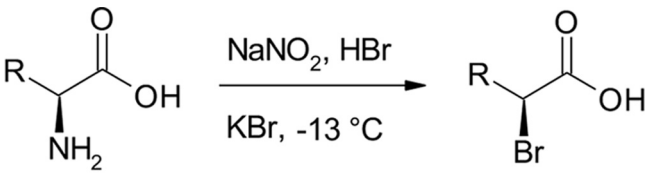
As part of our work aimed at the synthesis of new enantiomerically pure nitriles from amino acids[15] and investigation of the synthesis of new biologically active heterocyclic compounds,[16–18] herein we report the synthesis of new optically active α-bromonitriles using inexpensive and readily available (L)-amino acids following two methods, leading to products with different enantiomeric excesses and chemical yields.

RESULTS AND DISCUSSION

Larchevêque and Petit[19] have described the enantiospecific transformation of (L)-serine to the corresponding 2-bromo-3-hydroxypropanoïc acid. The reaction occurred with retention of the configuration, which can be explained by the formation of lactone as intermediate. Following the some procedure, we have prepared α-bromoacids **1a–f** by nitrous deamination of commercially available (L)-amino acids (Scheme 1). The reaction occurred with high stereospecificity as determined by high-performance liquid chromatography (HPLC) using a chiral column. Operatiing conditions were adjusted by injecting racemic α-bromoacids prepared from (*D, L*)-amino acids.

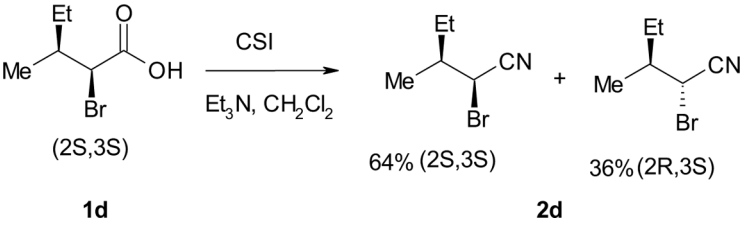
Desired α-bromoacids were obtained with excellent chemical yields ranging from 84% to 93% and were used as key products. We decided to use the (2S,3S)-2-bromo-3-methylpentanoic acid **1d** first to measure easily using ^{1}H NMR the epimerization of the asymmetric carbon C2, giving two diastereoisomers (2S,3S) and (2 R,3S) (Scheme 2).

The first synthetic method is the most economical and allows direct access to α-bromonitrile **2d**. The (2S,3S)-2-bromo-3-methylpentanoic acid **1d** react's with chlorosulfonyl isocyanate to give the *N*-chlorosulfonylamides, which can be converted by equivalent amounts of triethylamine to their corresponding nitriles **2d**. This method[20] provides α-bromonitrile **2d** in one step but with poor chemical yield



1a-f

Scheme 1. Synthesis of enantiomerically pure α-bromoacids **1a**–**f** from the corresponding natural α-amino acids. **a:** R = Me; **b:** R = i-Pr; **c:** R = i-Bu; **d:** R = *sec*-Bu; **e:** R = Bn; **f:** R = Ph.



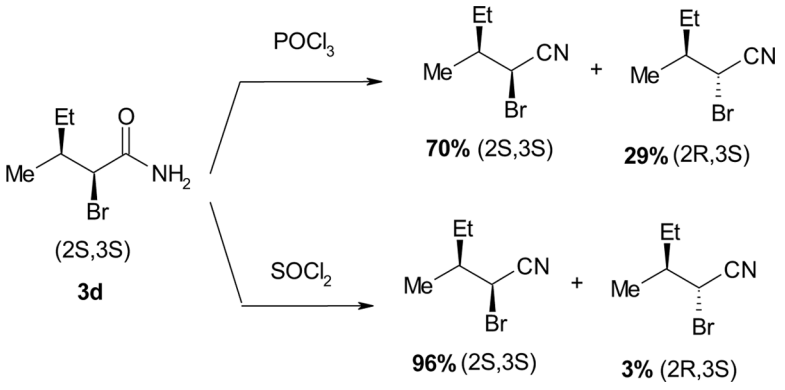
Scheme 2. Synthesis of α-bromonitrile **2d** from (2S,3S)-2-bromo-3-methylpentanoïc acid **1d**.

and epimerization exceeding 36% as detected by ^{1}H NMR of compound **2d** and confirmed by gas-phase chromatography (GPC).

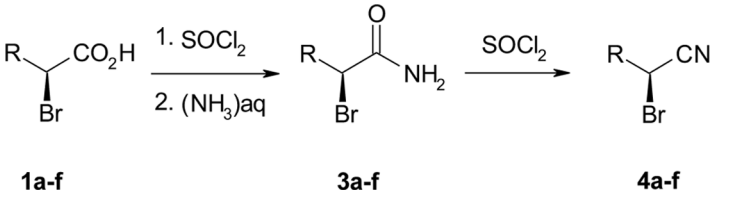
This result prompted us to try another approach to obtain nonracemic α-bromonitriles. Perhaps the most efficient described method is the dehydration of amids with different agents in particular phosphorus pentoxide.[21–23] Chiral α-bromoamids **3a–f** were prepared in good yields by simple treatment of α-bromoacids **1a–f** with thionyl chloride followed by ammonia.

According to the HPLC studies, chiral α-bromoamids **3a–f** were formed without significant racemization. Operatory conditions were adjusted by injecting racemic α-bromoamids prepared from (*D, L*)-amino acids. The (2S,3S)-2-bromo-3-methylpentane amide **3d** containing two asymmetric carbons was first dehydrated by phosphoryl chloride. Dehydration occurred using $POCl_3$ as solvent and reagent at a temperature of 40 °C for 3 h (Scheme 3). Chemical yield of obtained 2-bromo-3-methylpentane nitrile **4d** was acceptable; however, an important epimerization around 30% has been detected.

This epimerization was measured by ^{1}H NMR according to the signal relative to the proton linked to the asymmetric carbon bearing the nitrile group, which resonates in different positions for each pair of diasteromers. As shown in Fig. 1, the signal of this proton appeared as two doublets: a first doublet at 4.44 ppm ($J = 4.8$ Hz) corresponding to the diastereomer (2S,3S) and a second doublet at 4.45 ppm ($J = 4.2$ Hz) corresponding to the diastereomer (3S,2 R) relative to the partial epimerization of carbon C2. This eventual epimerization can be explained by the



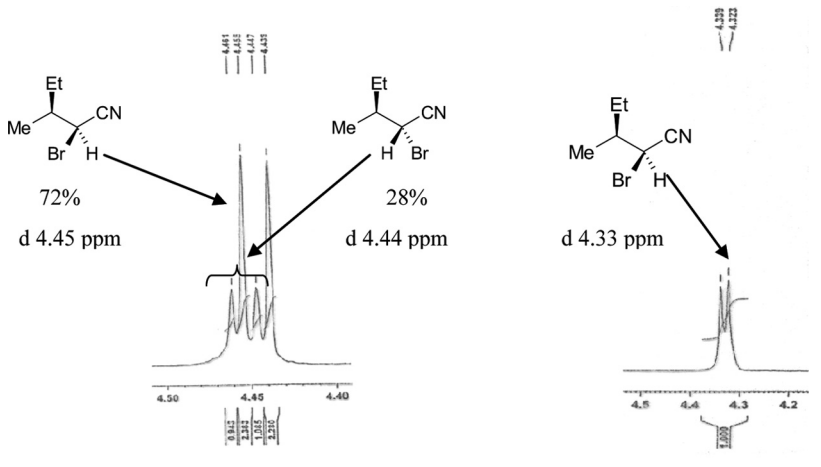
Scheme 3. Dehydration of α-bromoamids **3d** using $POCl_3$ and $SOCl_2$.



Scheme 4. Synthesis of α-bromonitriles **4a–f** from the corresponding α-bromoamids **3a–f**. **a:** R = Me; **b:** R = i-Pr; **c:** R = i-Bu; **d:** R = *sec*-Bu; **e:** R = Bn; **f:** R = Ph; **g:** R = i-Pr (racemic).

electron-withdrawing effect of the cyano group which makes the proton of the asymmetric carbon somewhat acidic. $POCl_3$ frees $POCl_2$ (OH) during the reaction and, then the presence of such a basic site would catalyze the racemization process by interaction with the acidic proton. We decided then to use thionyl chloride as dehydrating agent, which was expected to give better results (Scheme 3). Unlike $POCl_3$, by-products from the dehydration by $SOCl_2$ are HCl (g) and SO_2 (g), which is convenient to avoid the racemization, because there is no possible acid–base interaction between the acidic proton of α-bromonitrile. As expected, the dehydration of (2S,3S)-2-bromo-3-methylpentane amide **3d** is accompanied by only a slight epimerization, which was not detected by ^{1}H NMR (see Fig. 1). This unavoidable epimerization was measured by GPC and did not exceed 4% (see Fig. 2).

We applied thionyl chloride to dehydrate the other α-bromoamides **3a–f** leading to the corresponding α-bromonitriles **4a–f** with good yields (Scheme 4). Enantiomeric ratios were measured by HPLC using a chiral Chirobiotic V column and did not change significally for the series of compounds. As shown in Table 1, partial racemization was still evident in all cases. This eventual racemization is the result of heating the mixture of α-bromoamide and thionyl chloride for 2 h at 79 °C. We note that α-bromonitrile **4a–f**



(a) (b)

Figure 1. Signal of the C*-H proton of α-bromonitrile **4d** dehydrated with phosphoryl chloride (a) and thionyl chloride (b).

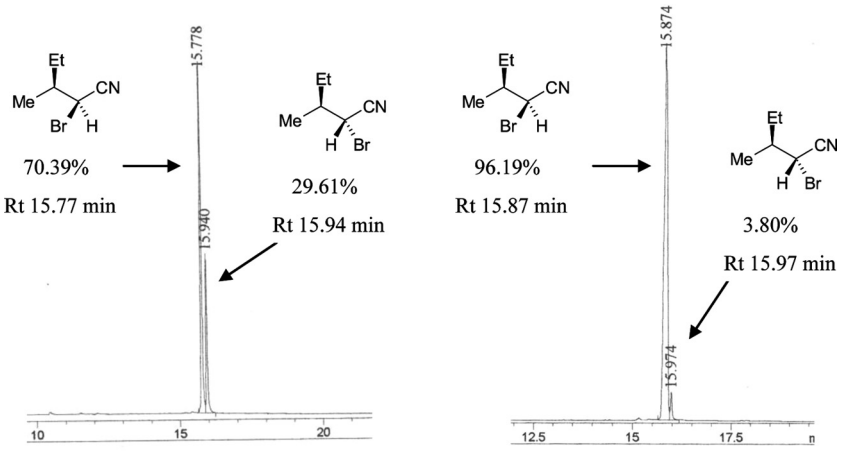


Figure 2. GPC of α-bromonitrile **4d** dehydrated by phosphoryl chloride (a) and thionyl chloride (b).

Table 1. Synthesis of α-bromonitriles **4a–f** from the corresponding α-bromoamids **3a–f** using thionyl chloride

Amino acids	α-Bromonitriles	R	Yields (%)	*Ee* (%)
Alanine	**4a**	Me	90	94
Valine	**4b**	i-Pr	88	93
Leucine	**4c**	i-Bu	92	91
Isoleucine	**4d**	sec-Bu	90	92
Phenylalanine	**4e**	Bn	86	90
Phenylglycine	**4f**	Ph	77	88

are colorless liquids and could be chromatographed on a flash neutral alumina-gel column with no detectable changes in enantiomeric enrichment.

CONCLUSION

To conclude, the preparation of enantiomerically enriched α-bromonitriles from their corresponding amino acids has been achieved for the first time by investigating two synthetic methods. Dehydration of chiral α-bromoamides using thionyl chloride gave the best results in the combined terms of quantitative yields and enantiomeric purity. The study of the synthetic features of these products to prepare new chiral biologically active heterocyclic compounds is under investigation in our laboratory.

EXPERIMENTAL

Typical Procedure for the Preparation of α-Bromonitrile from Corresponding α-Bromoacid

α-Bromo acid (5 mmol) was dissolved in 40 mL of anhydrous dichloromethane, and then chlorosulfonyl isocyanate (CSI) (5 mmol) was added dropwise. The mixture

was stirred for 1 h at room temperature and then refluxed for 2 h until the end of carbon dioxide evolution. The mixture was cooled in an ice bath (0 °C) and 5 mmol of freshly distilled triethylamine was added dropwise. The mixture is stirred again for 1 h at room temperature until the end of HCl evolution and then washed once with 50 mL of saturated $NaHO_3$ and twice with 100 mL of water. The aqueous phase were then extracted with 2×100 mL of dichloromethane. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue obtained was purified by column chromatography on neutral alumina [cyclohexane–ethylacetate (80:20)].

Typical Procedure for the Preparation of α-Bromoamides

A mixture of α-bromoacid (5 mmol), $SOCl_2$ (20 mmol), and three drops of dry DMF in anhydrous dichloromethane was stirred overnight at room temperature. 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 α-bromoamides **3a–f** were collected.

(2S)-2-Bromopropanamide 3a. Yield 82%; mp 63–65 °C; $[\alpha]_D$ −20.0 (c 0.33%, $CHCl_3$): ee > 99.5% [HPLC analysis using a Chirobiotic V column (4.6 mm × 250 mm) under the following conditions: heptane/isopropanol as mobile phase, rt, (=254 nm, flow rate = 0.6 mL/min, retention time: 30.88 min]; IR (cm^{-1}): $\nu_{CO} = 1716$; $\nu_{N\text{-}H} = 3432$; ^1H NMR (300 MHz, $CDCl_3$): δ 1.88 (d, 3H, $J = 6.9$ Hz), 3.79 (q, 1H, $J = 6.9$ Hz), 6.14 (s, 1H), 6.44 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$), δ 21.47, 39.52, 175.71 (CO). Anal. calcd. for C_3H_6BrNO, 151.99: C, 23.71, H, 3.98, N, 9.22. Found: C, 23.76; H, 4.02; N, 9.25.

(2S)-2-Bromo-3-methylbutanamide 3b. Yield = 88%; mp 92–94 °C; $[\alpha]_D$ −25.0 (c 0.33%, $CHCl_3$): ee > 99.5% [HPLC analysis using a Chirobiotic V column (4.6 mm × 250 mm) under the following conditions: heptane/isopropanol as mobile phase, rt, λ=254 nm, flow rate = 0.6 mL/min, retention time: 32.96 min]; IR (cm^{-1}): $\nu_{CO} = 1712$, $\nu_{N\text{-}H} = 3435$; ^1H NMR (300 MHz, $CDCl_3$): δ 1.07 (d, 3H, $J = 6.6$ Hz), 1.12 (d, 3H, $J = 6.9$ Hz), 2.26 (m, 1H), 4.08 (d, 1H, $J = 7.5$ Hz), 6.22 (s, 1H); 6.52(s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$); δ19.77, 20.14, 32.15, 54.11, 173.01 (CO). Anal. calcd. for $C_5H_{10}BrNO$, 180.05: C, 33.36; H, 5.60; N, 7.78. Found: C, 33.39; H, 5.64; N, 7.81.

(2S)-2-Bromo-4-methylpentanamide 3c. Yield = 82%; mp 73–75 °C; $[\alpha]_D$ −30.0 (c 0.33%, $CHCl_3$): IR (cm^{-1}): $\nu_{CO} = 1719$, $\nu_{N\text{-}H} = 3439$; ^1H NMR (300 MHz, $CDCl_3$): δ 0.90 (d, 3H, $J = 6.3$ Hz), 0.96 (d, 3H, $J = 6.3$ Hz), 1.90 (m, 3H), 4.37 (dd, 1H, $J_1 = 5.7$ Hz, $J_2 = 5.7$ Hz), 6.20(s, 1H), 6.32 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$), δ 21.02, 22.71, 26.35, 44.50, 49.13, 172.08 (CO).

(2S,3S)-2-Bromo-3-methylpentanamide 3d. Yield = 90%; mp 83–85 °C; $[\alpha]_D$ −35.0 (c 0.33%, $CHCl_3$): IR (cm^{-1}): $\nu_{CO} = 1724$, $\nu_{N\text{-}H} = 3430$; ^1H NMR (300 MHz, $CDCl_3$): δ 0.94 (t, 3H, $J = 7.2$ Hz), 1.11 (d, 3H, $J = 6.6$ Hz), 1.32 (m,

1H), 1.81 (m, 1H), 2.09 (m, 1H), 4.18 (d, 1H, $J = 8.1$ Hz), 6.04 (s, 1H), 6.44 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$), δ11.01, 16.64, 26.58, 38.46, 52.91, 170.96 (CO). Anal. calcd. for $C_6H_{12}BrNO$, 194.07: C, 37.13; H, 6.23; N, 7.22. Found: C, 37.17; H, 6.26; N, 7.26.

(2S)-2-Bromo-3-phenylpropanamide 3e. Yield = 85%; mp 103–105 °C; $[\alpha]_D$ −40.0 (c 0.33%, $CHCl_3$); IR (cm^{-1}): $\nu_{CO} = 1714$, $\nu_{N\text{-}H} = 3432$; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.54 (d, 1H), 3.41 (d, 1H), 4.52 (t, 1H), 6.22 (s, 1H), 6.52 (s, 1H), 7.07–7.65 (m, 5H), ^{13}C NMR (75 MHz, $CDCl_3$), δ 33.58, 60.09, 126.62, 127.22, 128.31, 129.16, 129.75, 35.53, 137.35, 143.68, 177.98. Anal. calcd. for $C_9H_{10}BrNO$, 228.09: C, 47.39; H, 4.42; N, 6.14. Found: C, 47.42; H, 4.47; N, 6.19.

(2S)-2-Bromo-2-phenylethanamide 3f. Yield = 79%; $[\alpha]_D$ −45.0 (c 0.33%, $CHCl_3$); IR (cm^{-1}): ee > 99.5% [HPLC analysis using a Chirobiotic V column (4.6 mm × 250 mm) under the following conditions: heptane/isopropanol as mobile phase, rt, λ=254 nm, flow rate = 0.6 mL/min, retention time: 28.52 min]; $\nu_{CO} = 1711$, $\nu_{N\text{-}H} = 3433$; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.25 (s, 3H), 6.02 (s, 1H), 6.32 (s, 1H), 7.18–7.71 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$), δ 40.47, 128.74, 129.55, 130.16, 134.75, 171.13 (CO).

Typical Procedure for the Dehydration of α-Bromoamides

The α-bromoamide (4 mmol) was dissolved in 20 mL of freshly distilled thionyl chloride. The mixture was refluxed for 2 h until the amide was consumed (as monitored by thin-layer chromatography, 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 a neutral alumina gel, using [cyclohexane–ethylacetate (8:2)], to afford pure α-bromonitriles **4a–f**.

(2S)-2-Bromopropanenitrile 4a. Yield = 90%; $[\alpha]_D$ −50.0 (c 0.25%, $CHCl_3$); HRMS-ESI calcd. for C_3H_4BrN 132.95274; found 132.95279; ee ∼94% [HPLC analysis using a Chirobiotic V column (4.6 mm × 250 mm) under the following conditions: heptane/isopropanol as mobile phase, rt, λ=254 nm, flow rate = 0.6 mL/min, retention time: 15.25 min, 17.94 min]; IR (cm^{-1}): $\nu_{CN} = 2249$; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.97 (d, 3H, $J = 7.2$ Hz), 4.38 (q, 1H, $J = 6.9$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$), δ 21.21, 23.91, 118.26 (CN).

(2S)-2-Bromo-3-methylbutanenitrile 4b. Yield = 88%; $[\alpha]_D$ −55.0 (c 0.25%, $CHCl_3$); HRMS-ESI calcd. for C_5H_8BrN 160.98403; found 160.98408; ee ∼93% [HPLC analysis using a Chirobiotic V column (4.6 mm × 250 mm) under the following conditions: heptane/isopropanol as mobile phase, rt, λ=254 nm, flow rate = 0.6 mL/min, retention time: 17.66 min, 19.54 min]; IR (cm^{-1}); $\nu_{CN} = 2239$; ^{1}H NMR (300 MHz, $CDCl_3$): δ1.15 (d, 3H, $J = 2.4$ Hz), 1.18 (d, 3H, $J = 2.4$ Hz), 2.16 (m, 1H), 4.24 (d, 1H, $J = 5.1$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$), δ 19.09, 19.59, 33.89, 35.75, 116.60 (CN).

(2S)-2-Bromo-4-methylpentanenitrile 4c. Yield = 92%; $[\alpha]_D$ −60.0 (c 0.25%, $CHCl_3$); HRMS-ESI calcd. for $C_6H_{10}BrN$ 174.99969; found 174.99972; ee ~91% [HPLC analysis using a Chirobiotic V column (4.6 mm × 250 mm) under the following conditions: heptane/isopropanol as mobile phase, rt, λ=254 nm, flow rate = 0.6 mL/min, retention time: 19.01 min, 22.66 min]; IR (cm^{-1}): ν_{CN} = 2242; ^1H NMR (300 MHz, $CDCl_3$): δ 0.93 (m, 6H), 1.87–2.02 (m, 3H), 4.29 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$), δ 21.64, 25.66, 26.63, 45.17, 52.65, 117.66 (CN).

(2S,3S)-2-Bromo-3-methylpentanenitrile 4d. Yield = 90%; $[\alpha]_D$ −65.0 (c 0.25%, $CHCl_3$); HRMS-ESI calcd. for $C_6H_{10}BrN$ 174.99969; found 174.99974; ee ~92% [HPLC analysis using a Chirobiotic V column (4.6 mm × 250 mm) under the following conditions: heptane/isopropanol as mobile phase, rt, λ=254 nm, flow rate = 0.6 mL/min, retention time: 21.81 min, 23.27 min]; IR (cm^{-1}), ν_{CN} = 2240; ^1H NMR (300 MHz, $CDCl_3$): δ 0.97 (t, 3H, J = 7.5 Hz), 1.17 (d, 3H, J = 6.6 Hz), 1.48 (m, 1H), 1.69 (m, 1H), 1.97 (m, 1H), 4.33 (d, 1H, J = 4.8 Hz), ^{13}C NMR (75 MHz, $CDCl_3$), δ11.38, 16.03, 26.98, 34.22, 40.39, 116.43 (CN).

(2 s)-2-Bromo-3-phenylpropanenitrile 4e. Yield = 86%; $[\alpha]_D$ −70.0 (c 0.25%, $CHCl_3$); ee ~90% [HPLC analysis using a Chirobiotic V column (4.6 mm × 250 mm) under the following conditions: heptane/isopropanol as mobile phase, rt, λ=254 nm, flow rate = 0.6 mL/min, retention time: 22.65 min, 25.33 min]; IR (cm^{-1}); ν_{CN} = 2245; ^1H NMR (300 MHz, $CDCl_3$): δ 3.38 (d, 1H), 3.42 (d, 1H), 4.43 (dd, 1H, J_1 = 7.2 Hz, J_2 = 7.5 Hz), 7.28–7.45 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$), δ 27.75, 43.07, 117.35 (CN), 128.71, 129.41, 129.74, 135.00.

(2S)-2-Bromo-2-phenylethanenitrile 4f. Yield = 77%; $[\alpha]_D$ −45.0 (c 0.33%, $CHCl_3$); ee ~88% [HPLC analysis using a Chirobiotic V column (4.6 mm × 250 mm) under the following conditions: heptane/isopropanol as mobile phase, rt, λ=254 nm, flow rate = 0.6 mL/min, retention time: 20.64 min, 22.87 min]; IR (cm^{-1}); ν_{CN} = 2238; ^1H NMR (300 MHz, $CDCl_3$): δ 4.25 (s, 1H), 7.18–7.61 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$), δ 40.47, 118.11 (CN), 128.74, 129.55, 130.16, 134.75.

ACKNOWLEDGMENT

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

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