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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].

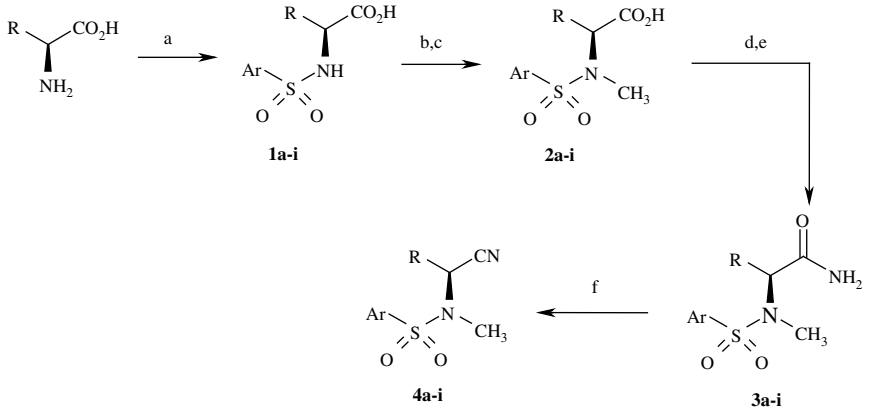
Herein, we report the synthesis of enantiomerically pure *N*-methyl-*N*-arylsulfonyl-α-aminonitriles from the corresponding (L)- and (D)-α-amino acids by means of *N*-methyl-*N*-arylsulfonyl-α-amino amides. These compounds are new and represent the first example of enantiomerically pure *N*,*N*-disubstituted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