Tetrahedron Letters 54 (2013) 545–548

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of ^{15}N-labeled vicinal diamines through N-activated chiral aziridines: tools for the NMR study of platinum-based anticancer compounds

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ARTICLE INFO

Article history:
Received 11 October 2012
Revised 15 November 2012
Accepted 20 November 2012
Available online 29 November 2012

Keywords:
Chiral diamines
Aziridines
^{15}N NMR
Platinum-based anticancer compounds

ABSTRACT

A new method for the synthesis of ^{15}N-labeled chiral β-diamines from a common precursor, either optically pure amino acids or *anti*-β-amino alcohols, is reported. The two diastereomeric series of vicinal diamines are produced through the nucleophilic ring opening of activated chiral aziridines. ^{15}N was introduced by means of [^{15}N]-benzylamine, prepared from $^{15}NH_4Cl$. The final compounds are highly valuable because [^{1}H–^{15}N] NMR is considered a powerful tool for studying the chemical properties of platinum-based complexes.

The β-diamine (or 1,2-diamine) moiety is of great importance in medicinal chemistry, especially in its chiral form. This structure is particularly well represented in anticancer platinum(II) complexes.[1] Since the discovery of *cis*-diamminedichloroplatinum(II) (Cisplatin) by Rosenberg et al. in the late 1960s,[2] the continuous search for new compounds is driven, on the one hand, by the limitations of current platinum-containing drugs (acute toxicity, resistance, limited activity spectrum, and poor pharmacokinetics)[3] and, on the other hand, by the high efficacy of these drugs against various cancers.[4] The biological activity and the chemical properties of Pt compounds (i.e., hydrolysis kinetics, dissociation constants, reactivity with bionucleophiles, proteins, nucleic acids) are closely related. Therefore, tailoring these structure-dependent chemical properties is the basis for the rational design of platinum drugs and is essential to provide new leads with better profiles. Moreover, the importance of chirality to the biological properties of these complexes has largely been demonstrated.[5]

Nuclear Magnetic Resonance (NMR) methods, especially ^{195}Pt and ^{15}N spectroscopy, have proven to be highly useful for the characterization of platinum compounds.[6] The introduction of [^{1}H,^{15}N] NMR techniques, in which the sensitivity is enhanced through polarization transfer,[7] allowed fine studies on the behavior of platinum anticancer derivatives in aqueous solution.[8,5f] However, sensitivity remains a major issue at natural abundance of ^{15}N (0.365%). The possibility of synthesizing ^{15}N-enriched optically pure vicinal diamines is therefore crucial for the understanding of the structure–activity relationships of platinum coordination complexes. Only quite simple complexes were studied until now by ^{15}N NMR and few publications actually mention the preparation of ^{15}N-enriched diamines. Indeed, reported achiral ligands are: alkyl amine derivatives,[9] polynuclear complexes,[10] diethylenetriamine compounds,[11] dipyridine coordinates,[12] diimines,[13] and nitroimidazole compounds.[14] A platinum(IV) chiral compound, using propane-1,2-diamine as the ligand, was reported by Drahoňovský et al.[15a]

Based on their biological and structural properties, seven previously synthesized platinum compounds[5b–d] were selected for ^{15}N labeling prior to a comprehensive NMR study of their chemical properties. A new synthetic method was developed for the introduction of ^{15}N in the target compounds.

Commercially available, optically pure α-amino acids, were used as starting compounds. β-amino alcohols **5** are first produced as described by Reetz et al.[16] and then converted into vicinal diamines with the introduction of ^{15}N (Scheme 1). Alternative synthetic methods, as the organometallic addition to imines derived from **4**[17] and the diastereoselective reduction of 1,2-diimines[18] were assayed but delivered unsatisfactory results. Because the choice of reagents is considerably limited by the need for isotopically enriched compounds, various pathways were considered for the conversion of amino alcohols **5** into diamines. The few publications about ^{15}N-enriched chiral diamines recommended CH_3–$^{15}NH_2$ to open a chiral aziridinium ion obtained from ephedrine or ^{15}N-enriched amino acids, which are very expensive.[15] Asymmetric synthesis through aziridines was demonstrated to be

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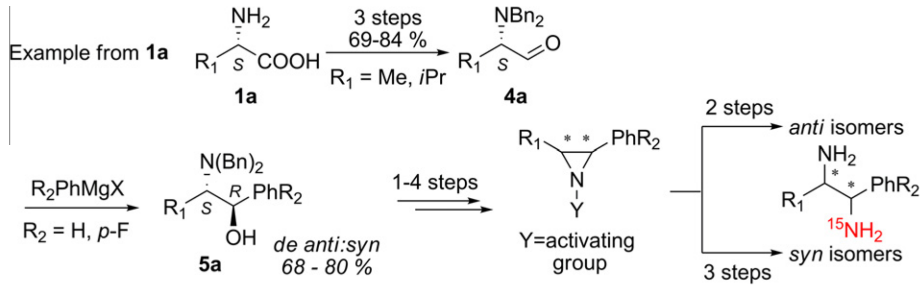
http://dx.doi.org/10.1016/j.tetlet.2012.11.079

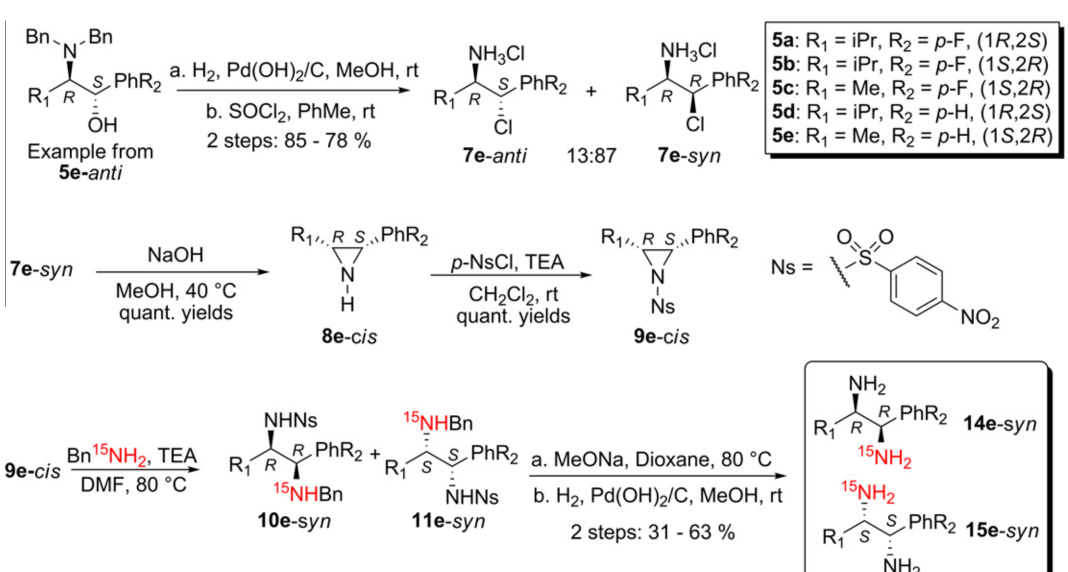


Scheme 1. Overall scheme for the production of ^{15}N-labeled diamines from α-amino acids.

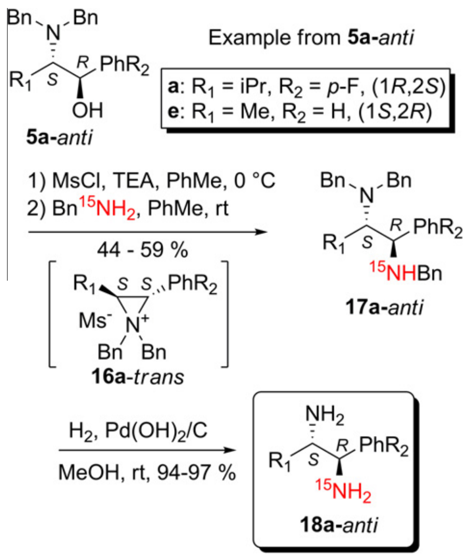
highly efficient for the preparation of nitrogen-containing molecules and, among these, the vicinal diamine moiety is readily obtained.[19] The stereo- and regio-controlled opening of chiral aziridines was thus finally selected and two distinct pathways were used to produce *syn*- and *anti*-configured diamines.

Syn-diamines were obtained from the nosyl-activated aziridines **9**, which were produced from amino alcohols **5** in a four step synthesis (Scheme 2). Nosyl groups allow the very efficient activation of aziridines, comparable to that of aziridiniums with nucleophiles.[20] Other activation methods, especially the use of Lewis acids,[21] were not successful. Simple protonation of the aziridine was not possible, as aziridines are far less basic than benzylamine.[22] Amino alcohols **5** were first debenzylated by treatment with $Pd(OH)_2/C$ under H_2 atmosphere (1 atm), leading to unprotected β-amino alcohols. In the second step, their chlorination using thionyl chloride afforded the amino chlorides **7** (as the hydrochloride salts) with a diastereomeric excess of the *syn* compound; this reagent is indeed known to produce an inversion of configuration in the case of *anti*-configured β-amino alcohols.[23] This diastereomeric mixture was either purified by recrystallization or engaged in the next step.[24] Chlorinated compounds **7** were then cyclized to aziridines **8** under basic conditions, by deprotonation of the hydrochloride salt. After reacting with nosyl chloride to produce nosyl-azirdines **9**, these were easily converted into ^{15}N-labeled *syn*-diamines through nucleophilic ring-opening by reaction with [^{15}N]-benzylamine (prepared from $^{15}NH_4Cl$).[25] This procedure stereospecifically afforded the *syn* isomers as the reactions proceeded exclusively through a S_N2 mechanism, but produced both regioisomers in the case of Me substituted aziridines. Indeed, if benzyl substituted aziridines are known to be regioselectively opened at the benzylic position,[26] in the case of nosyl-activated aziridines **9c** and **9e** (Me substituted aziridines), the preferred position for nucleophilic opening was shifted to the alkyl-substituted carbon C_3 affording both the regioisomers **10** (C_2 opening) and **11** (C_3 opening) in a 35:65 ratio. However, compounds **10** were the only regioisomers obtained upon opening of the bulkier *i*-Pr substituted aziridines **9a**, **9b**, and **9d**, possibly indicating a kinetically unfavorable attack on C_3, due to steric hindrance. All regioisomeric products were separated and identified by the mean of [^{1}H ^{13}C] 2D-NMR experiments.[27] Sulfonamide cleavage upon MeONa treatment[28] and catalytic hydrogenation resulted in the final labeled β-diamines. Thiolated nucleophiles (PhSH, thioglycolic acid, mercaptoethanol), better known for their nosyl cleavage ability,[20a,29] gave unsatisfactory results (i.e., poor yields and/or sluggish reaction rates).

anti-Diamines were synthesized from **5** through a chiral dibenzylaziridinium intermediate (**16**), [5a,19b] which was regiospecifically opened at the benzylic position by [^{15}N]-benzylamine to give **18** after hydrogenation (Scheme 3). Indeed, aziridinium **16** showed a clear preference for nucleophilic attack at the benzylic position, and diamines **17** were the only stereo- and regio-isomeric observed products. Anyway, the presence of a by-product resulting from the opening of dibenzylaziridinium **16** by chloride ions needed products **17** to be purified by flash chromatography prior to catalytic hydrogenation. For pharmacological reasons (i.e., much less active platinum(II) complexes), only two compounds of the



Scheme 2. Conversion of **5** to ^{15}N-labeled *syn*-β-diamines.



Scheme 3. Conversion of **5** to ^{15}N-labeled *anti*-β-diamines

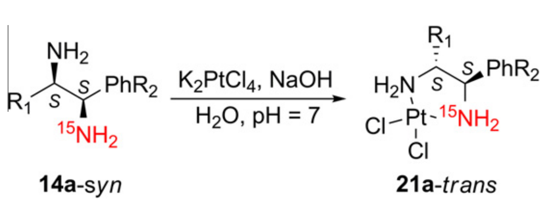
anti series were synthesized to compare their physico-chemical properties with those of their diastereomeric most active analogs.

Finally, the ^{15}N-enriched vicinal diamines were transformed into their platinum-based anticancer analogs by reaction with K_2PtCl_4 in water, the pH being kept constant over the course of the reaction (Scheme 4).

In an attempt to explain the observed ring opening regioselectivity and its unexpected change for the nosyl aziridines, the atomic charges on both the C_2 and C_3 electrophilic positions of **9a–e**, **16a**, and **16e** were calculated by DFT at the B3LYP/6-311G++(2d,2p) level of theory (see Supplementary data).[30] Because Mulliken Population Analysis (MPA)[31] is considered inaccurate and strongly base dependent,[32] Natural Population Analysis (NPA)[33] was used. The NPA atomic charges calculated for the optimized geometry do not discriminate the C_2 and C_3 positions, suggesting that a simple electrostatic picture of the interaction between the electrophilic carbons of the aziridines and the nucleophile cannot account for the observed regiochemistry. Therefore, other electronic effects, especially the localization of lowest unoccupied molecular orbitals and Fukui functions are currently under investigation to deliver a rationale to this surprising loss of regioselectivity. Frontier molecular orbital theory and conceptual DFT have proven to be a successful approach to describe local reactivity in organic molecules and moreover, for the regioselective opening of aziridines.[34]

In conclusion, a convenient synthesis of ^{15}N-labeled chiral vicinal diamines suitable for the production of platinum anticancer derivatives was developed. The present study reports the first diastereo- and enantioselective synthesis of two diastereomeric series of chiral ^{15}N-enriched diamines from a common chiral precursor, which can be either an amino acid or an *anti*-β-amino alcohol, with a controlled stereochemistry on both the amino groups. In addition, an unexpected loss of regioselectivity upon nosyl activation was demonstrated, when it is largely accepted that benzyl aziridiniums are preferentially opened at the aryl substituted carbon. *anti*-Configured diamines were produced from their amino alcohol precursor with an overall yield of 41 to 57%. Yield is significantly decreased (15–33%) for the *syn* isomers as more steps were needed. No separation of regioisomers nor diastereomers were needed to produce enantiopure *anti*-diamines. Nevertheless, production of *syn* isomers was a little trickier. Firstly, as the chlorination steps did not proceed through a stereospecific mechanism (but with good stereoselectivity), either the aminochloride **7** or the aziridine **8** had to be purified and secondly, regioisomers resulting from the opening of nosylaziridines **9** had to be separated through flash chromatography.

The use of chiral aziridines as synthetic intermediates again supports the importance of this three-membered ring in modern organic chemistry.



Scheme 4. Example of production of platinum-based anticancer compounds from vicinal diamines.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.11.079.

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