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Synthesis and synthetic applications of 2-amino-3-halo-1-oxypropanes

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Contents

1. Introduction

β-Halo amines comprise an extensive class of reactive organic compounds with plentiful applications, mainly as synthons in organic chemistry[1] and as anticancer agents in medical chemistry.[2] In addition, 1,2,3-triheteroatom-substituted propane derivatives ('C3-units') are well known in pharmaceutical science due to the pronounced bioactivities ascribed to many representatives, e.g., β-blockers.[3] The combination of a β-halo amine and a 'C3-unit' in one framework results in a special structural entity, featuring beneficial effects arising from both these moieties. 2-Amino-3-halo-1-oxypropanes **1** (Fig. 1) comprise an interesting subclass of the latter compounds, exhibiting a pronounced reactivity due to the β-halo amine moiety and suitable for the synthesis of a variety of functionalised target compounds due to the presence of both a nitrogen and an oxygen atom. In contrast with their isomeric counterparts, i.e., 3-amino-1-halo-2-oxypropanes **2**, the chemistry of 2-amino-3-halo-1-oxypropanes **1** is less well known to organic chemists, despite there being several useful reports on the (asymmetric) synthetic applicability of these β-halo amines. In the present review, the synthesis and use of 2-amino-3-halo-1-oxypropanes **1** will be discussed in detail by means of a comprehensive literature overview. *C*-Substituted 2-amino-3-halo-1-oxypropanes fall outside the scope of this review and will not be dealt with here.

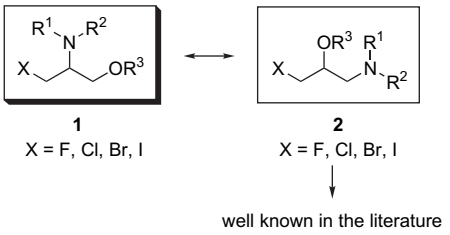

Figure 1.

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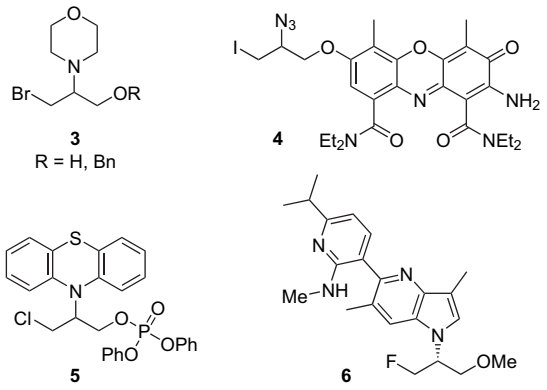


Figure 2.

2. Biological relevance

Whereas the majority of literature reports on 2-amino-3-halo-1-oxypropanes are dealing with synthetic applications, several examples are available describing different bioactivities. In this section, four selected examples of compounds with (potential) biological activity will be presented, all of them bearing a different halo atom (Fig. 2). The morpholines **3** (β-bromo amines) have been studied as antimicrobial and antioxidative lubricant additives,[4] and phenoxazin-3-one **4** (β-iodo amine derivative) has been described as an actinomycin D analogue.[5] Furthermore, phenothiazine **5** (β-chloro amine) has been studied as an anthelmintic agent in mice infected with *Nippostrongylus braziliensis*,[6] and the fused pyridine **6** (β-fluoro amine derivative) has been reported as a CFR-1 receptor ligand useful for the treatment of central nervous system and peripheral disorders (stress, anxiety, depression, cardiovascular disorders and eating disorders).[7]

Other types of biological activities and applications of 2-amino-3-halo-1-oxypropanes have also been mentioned briefly, including herbicidal activity,[8] and their use as brain protective agents[9] and as agonists of the adenosine A1 receptor.[10]

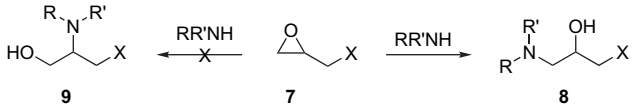
Due to the reactive nature of β-halo amines, which are prone to form highly electrophilic aziridinium species, these compounds are frequently reported in the literature as substrates for further elaboration towards all kinds of target compounds. In the following section, the synthesis and reactivity of 2-amino-3-halo-1-oxypropanes will be discussed in detail.

3. Synthesis and synthetic applications of 2-amino-3-halo-1-oxypropanes

In this section, the literature reports will be organised according to the underlying synthetic approach. In general, methods towards the synthesis of 2-amino-3-halo-1-oxypropanes can be divided into three categories: ring opening of epichlorohydrin, ring opening of aziridine derivatives and, as the major method, the use of the amino acid, L-serine, as starting material. The common element in these approaches comprises the use of a three-carbon unit.

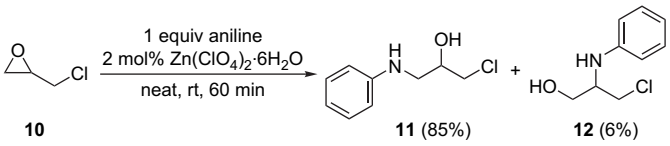
3.1. Synthesis and synthetic applications of 2-amino-3-halo-1-oxypropanes prepared from epichlorohydrin

The synthesis of 3-amino-1-halo-2-propanols **8** can be very easily achieved upon treatment of epihalohydrin **7** (X=Cl, Br) with a nucleophilic amine through ring opening of the epoxide at the less hindered position (Scheme 1).[11] On the contrary, the synthesis of the other regioisomers, i.e., 2-amino-3-halo-1-propanols **9**, requires ring opening of the epoxide **7** by an amine at the more hindered position, which is unfavoured and is thus rarely observed.



Scheme 1.

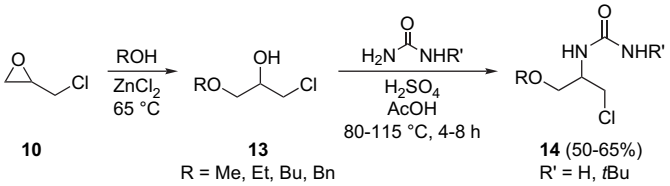
In some cases, the attack at the substituted position has been reported as a side reaction to afford the corresponding amino alcohol as the minor constituent. For example, zinc(II) perchlorate hexahydrate has been presented as a new and efficient catalyst for the ring opening of epichlorohydrin **10** with aniline in the presence of 2 mol % of $Zn(ClO_4)_2 \cdot 6H_2O$, resulting in γ-chloro amine **11** as the major compound (85%), besides a minor amount of the β-chloro amine **12** (6%) (Scheme 2).[12]



Scheme 2.

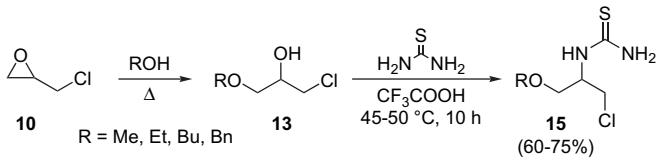
In a different approach, the ring opening of epichlorohydrin by an alcohol has been used for the synthesis of the corresponding 2-propanols, followed by displacement of the hydroxyl group by urea or thiourea. In this respect, chlorohydrins **13** have been prepared by reaction of the appropriate alcohols with epichlorohydrin **10** in the presence of $ZnCl_2$, which were subsequently treated with urea or *N*-*tert*-butylurea in the presence of H_2SO_4 and acetic acid to afford the substituted ureas **14** after 4–8 h at elevated temperatures (Scheme 3).[13,14] Ureas **14** showed a pronounced antimicrobial effect when present in low concentrations (0.5–1%) in motor oils.

Analogously, the reaction of epichlorohydrin **10** with different alcohols afforded 2-propanols **13**, which were treated



Scheme 3.

with thiourea in the presence of CF_3COOH to give the *N*-substituted ureas **15** in good yields (Scheme 4).[15] Remarkably, N-alkylation of thiourea was reported instead of S-alkylation, although the latter is commonly observed in organic chemistry.[16]



Scheme 4.

Despite the well-suited molecular structure of epichlorohydrin for the synthesis of 2-amino-3-halo-1-propanols, the inherent reactivity of the epoxide moiety has hampered the elaboration of convenient synthetic approaches towards the title compounds, as the direct introduction of a nitrogen nucleophile results in 3-amino-1-halo-2-propanols instead. To date, the only alternative consists of ring opening of the epoxide by an alcohol, followed by displacement of the 2-hydroxyl group by a nitrogen nucleophile such as a urea or thiourea. In the following section, the ring opening of the aza analogues of epoxides, i.e., aziridines, will be dealt with.

3.2. Synthesis and synthetic applications of 2-amino-3-halo-1-oxypropanes prepared from aziridine derivatives

An old and straightforward reaction in organic synthesis involves the ring opening of aziridines by means of hydrogen halides. For example, aziridine ester **16** has been reduced with $LiAlH_4$ in refluxing diethyl ether to give the corresponding 2-(hydroxymethyl)aziridine **17**, followed by ring opening of the latter aziridine **17** with hydrogen chloride (2 M), affording the β-chloro amine **19** (Scheme 5).[17] This reaction proceeds through the formation of an intermediate 1-alkylaziridinium salt **18**, which undergoes regiospecific ring opening by chloride at the less hindered position.

Furthermore, the ring opening of 1,1-dialkylaziridinium salts has also been studied. 2-(Alkanoyloxymethyl)aziridines **20**, prepared from the corresponding 1-arylmethyl-2-(bromomethyl)aziridines,[18] upon treatment with potassium 2-methylpropanoate or potassium 2-methylbutyrate in DMSO, underwent regioselective ring opening to form the *N*-(2-bromo-3-alkanoyloxypropyl)amines **22** using allyl bromide or an arylmethyl bromide in acetonitrile. Treatment of the latter β-bromo amines **22** with tetrabutylammonium fluoride in acetonitrile afforded 2-amino-1-fluoropropanes **23** as the major compounds (72–86%), besides the isomeric 1-amino-2-fluoropropanes **24** in minor quantities (14–28%) (Scheme 6). The ring opening of the intermediate aziridinium salts **21** by bromide and fluoride in acetonitrile resulted in a different regioselectivity with a preferential attack of bromide at the more hindered carbon atom and of fluoride at the less hindered carbon atom of the aziridinium ion.[19] Fluorinated amino acids (such as 3-fluoro-D-alanine) and other fluoro amines have received a lot of attention, due to their interesting biological activities.[20] Moreover, the incorporation of a β-fluoro amine moiety into a 1,2,3-triheteroatom-substituted propane skeleton (as in fluoro amines **23** and **24**) has led to the discovery of a new class of powerful antimicrobial agents, with florfenicol[21] as a well known example.

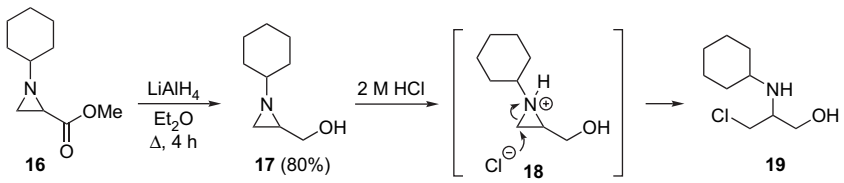
In the previous examples, the ring opening of 2-(oxymethyl)-aziridines by means of halides was employed for the synthesis of 2-amino-3-halo-1-oxypropanes. Alternatively, the ring opening of 2-(halomethyl)aziridines by means of an alcohol can be envisaged. Boiling *N*,*N*-dichlorosulfonamide **25** with allyl chloride in CCl_4 gave the dichloride **26**, which was subsequently treated with a base, affording 2-(chloromethyl)aziridine **27** in 72% yield. Ring opening of the latter aziridine **27** by means of water, methanol or phenol furnished the β-chloro amines **28**, due to nucleophilic attack at the less hindered position (Scheme 7).[22]

In a final example, 2-amino-3-chloro-1-oxypropanes were obtained unintentionally. 1-*tert*-Butoxycarbonyl-2(*R*)-(benzyloxymethyl)aziridine **29** was treated with 3 equiv of 3-methyl-1-butanol in the presence of 2 equiv of zinc chloride in order to obtain the corresponding β-amino ether via ring opening of the intermediate aziridinium salt by the alcohol. Instead, (*S*)-β-chloro amine **30** was isolated as the major compound through ring opening by the nucleophilic chloride anion at the less hindered position, besides a minor amount of the other regioisomer (*S*)-**31** formed via attack at the more hindered aziridine carbon atom (Scheme 8). If other Lewis acids were used ($BF_3 \cdot Et_2O$ or $Zn(OTf)_2$), the contemplated amino ethers were obtained as mixtures of isomers.[23]

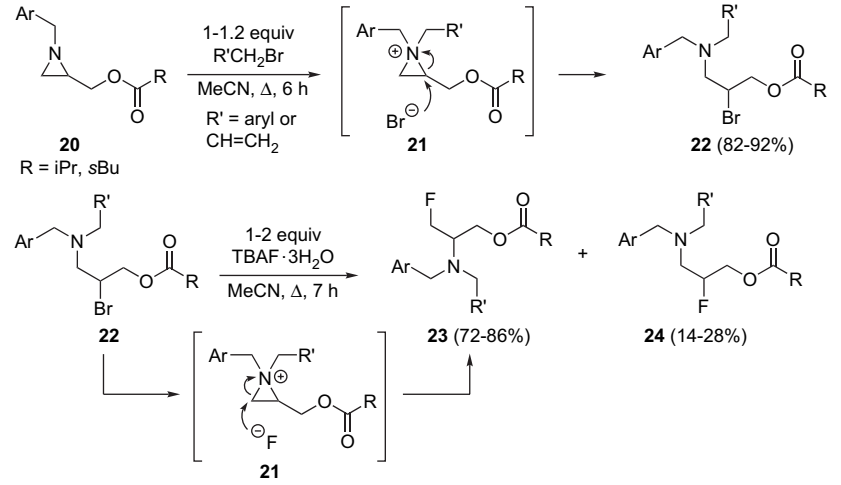
The most logical protocol for the synthesis of 2-amino-3-halo-1-oxypropanes from aziridine derivatives comprises the ring opening of 2-(hydroxymethyl)- or 2-(alkoxymethyl)aziridines by means of hydrogen halides via intermediate aziridinium salts. Despite the synthetic potential of this methodology, it has only been applied very rarely in organic synthesis and deserves further elaboration.

3.3. Synthesis and synthetic applications of 2-amino-3-halo-1-oxypropanes prepared from L-serine

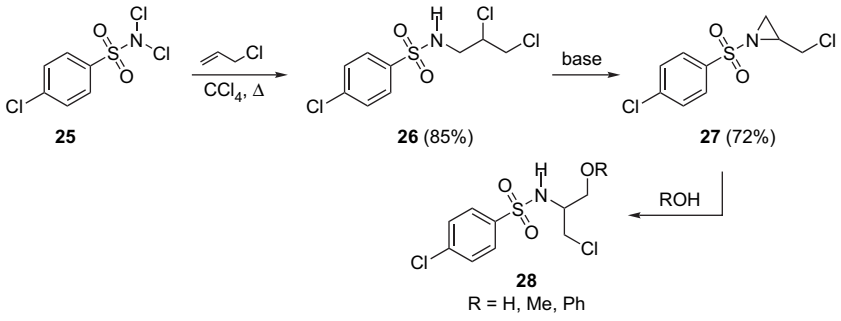
The major part of the literature reports comprises the synthesis of chiral 2-amino-3-halo-1-oxypropanes, starting from the naturally occurring amino acid, L-serine.



Scheme 5.



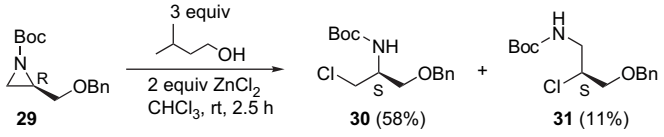
Scheme 6.



Scheme 7.

In some cases, the latter amino acid is first transformed into an *N*,*O*-five-membered heterocyclic ring (an oxazolidine, an oxazoline or an oxazolidinone), which is then cleaved to afford the title compounds. For example, 3-iodo-1-propanol **34** has been prepared from (*S*)-serine **32** via oxazolidine **33** and was used as an intermediate in the synthesis of compound **35**, an optically active tricyclic intermediate for the preparation of manzamines (Scheme 9).[24] The latter compounds are complex alkaloids isolated from marine sponges. In an analogous approach, a functionalised tricyclic intermediate was prepared and referred to as the 'tricyclic heart' of manzamine A.[25]

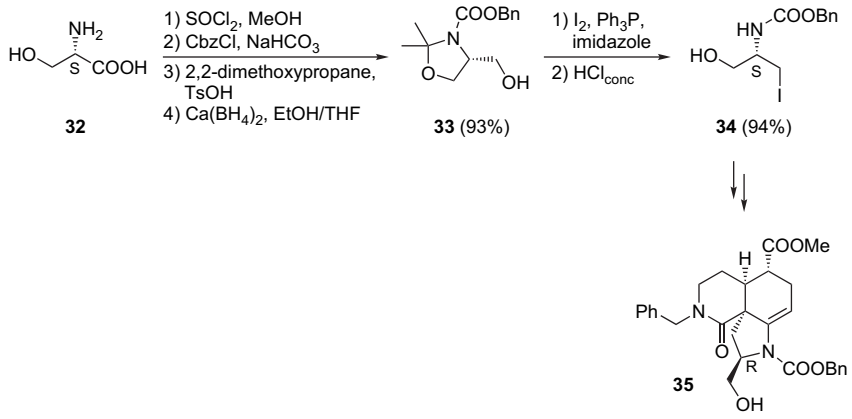
The chiral 4-(hydroxymethyl)oxazolidine **36** was prepared from L-serine in a four-step procedure,[26] and treated with a 3-substituted phenol in the presence of triphenylphosphine and diethyl azodicarboxylate in toluene to afford the ethers **37**. Cleavage of the oxazolidine ring with *p*-toluenesulfonic acid (PTSA) in methanol resulted in the β-amino alcohols **38**, and the primary hydroxyl group was subsequently replaced by a halogen atom to give the β-halo amines **39** upon treatment with triphenylphosphine, iodine and imidazole (for the iodo derivatives) or with Ph_3P and tetrachloromethane (for the chloro derivatives). β-Halo amines **39** then served as substrates for a radical cyclisation with either Bu_3SnH and AIBN in benzene or $(Me_3Si)_3SiH$ and AIBN in toluene, affording a mixture of chiral 3-aminochromanes **40** and **41** and the non-cyclised amines **42** (Scheme 10).[27]



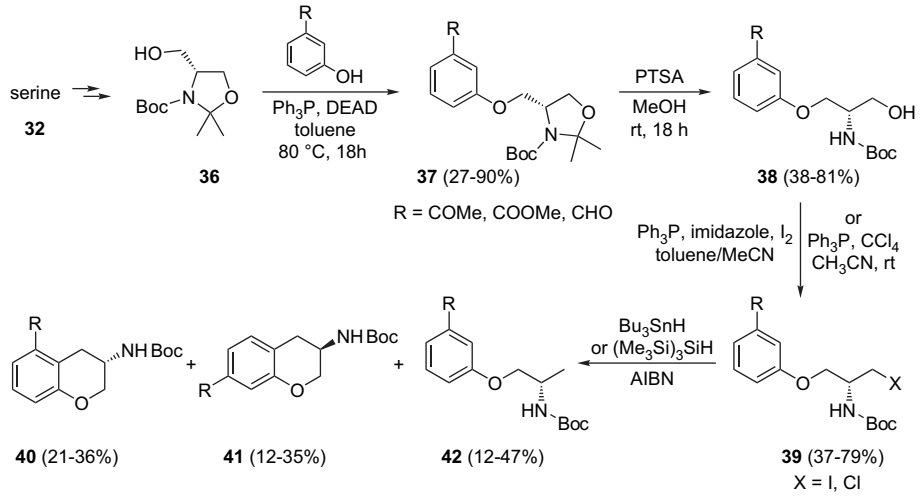
Scheme 8.

2-Amino-3-chloro-1-propanol **45** has been prepared starting from serine via an intermediate oxazoline **43**, which was reduced and ring opened to the dichloride **44** upon consecutive treatment with sodium borohydride and thionyl chloride, followed by treatment with hydrogen chloride (Scheme 11).[28] The amine **45** and analogous compounds have been tested as orally active male antifertility agents.[29]

Novel bis(oxazoline) ligands **50** have been prepared for the palladium-catalysed asymmetric allylic alkylation of 1,3-diphenyl-2-propenyl acetate, starting from L-serine methyl ester **46**. Condensation of the latter with ethyl benzimidate in the presence of Et_3N afforded 2-phenyloxazoline **47**,[30] which was subsequently transformed into the diamide **48** via a three-step procedure involving reduction of the ester, oxazoline cleavage and condensation with 2,2-dimethylpropanedioyl



Scheme 9.

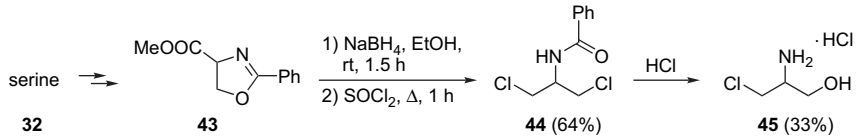


Scheme 10.

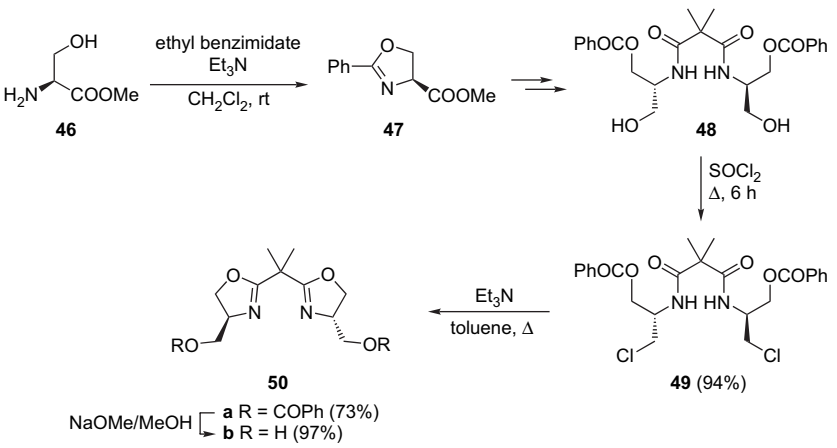
dichloride. Treatment of diol **48** with an excess of thionyl chloride afforded the corresponding dichloride **49** in excellent yield, which was cyclised into bis(oxazoline) **50a** (R=COPh) upon reflux in toluene (Scheme 12). Saponification of **50a** (R=COPh) with NaOH in MeOH resulted in the corresponding diol **50b** (R=H).[31]

4-(Iodomethyl)oxazolidin-2-one **51** has been synthesised from L-serine **32** in a six-step procedure. Treatment of this oxazolidin-2-one **51** with caesium carbonate in methanol resulted in cleavage of the heterocyclic moiety to give the amino alcohol **52** in quantitative yield (Scheme 13). The latter β-iodo amine **52** served as a substrate for the synthesis of *S*-oxo-[(methylthio)methyl]cysteinol **53** via a four-step approach.[32] The interest in *S*-oxo-[(methylthio)methyl]cysteinol **53** is due to its biological relevance, e.g., as part of the natural product, sparsomycin.

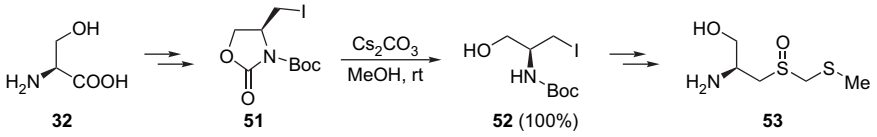
Another strategy consists of the direct replacement of the hydroxyl group of serine by a halo atom through activation of the alcohol and subsequent nucleophilic displacement by a halide. Esterification and *N*-Boc-protection of L-serine **32** afforded the methyl ester **54**, which was converted into the β-chloro amine **55** by consecutive treatment with (i) hexachloroethane and Ph_3P and (ii) lithium borohydride in THF.[33] After O-protection, chloroalkane **56** was transformed into a dianionic organolithium species **57** by means of a butyllithium/lithium naphthalenide (LiNp) combination in order to minimise the possibility of β-elimination. Quenching of this dianion **57** with different electrophiles resulted in the



Scheme 11.



Scheme 12.



Scheme 13.

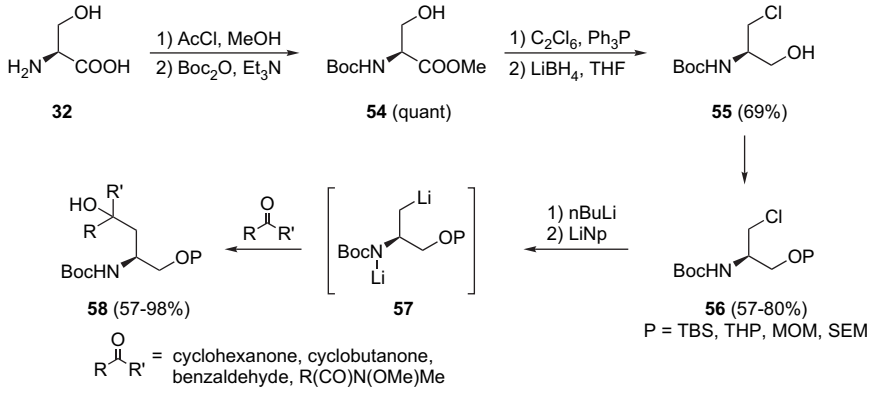
isolation of a variety of novel enantiomerically pure adducts **58** (Scheme 14).[34,35] These adducts were further converted into the corresponding amino alcohols and amino acids. Quenching of the organolithium reagents **57** with triisopropyl borate and hydrolysis of the intermediate boronic esters afforded the corresponding boronic acids, which were used successfully for the Suzuki cross-coupling with a variety of aryl halides.[36]

The (*S*)-serine derivative **59** has been transformed into the iodo amine **60** upon treatment with methyltriphenoxyphosphonium iodide in DMF, followed by reduction with sodium borohydride to the corresponding alcohol **61** (Scheme 15). Reaction of the latter **61** with 2,2-dimethoxypropane afforded 4-(iodomethyl)oxazolidine **62**, which served as a substrate in radical addition reactions with, for example, 2-aminoacrylates in the presence of a Zn/Cu-couple to form the corresponding addition products **63**.[37]

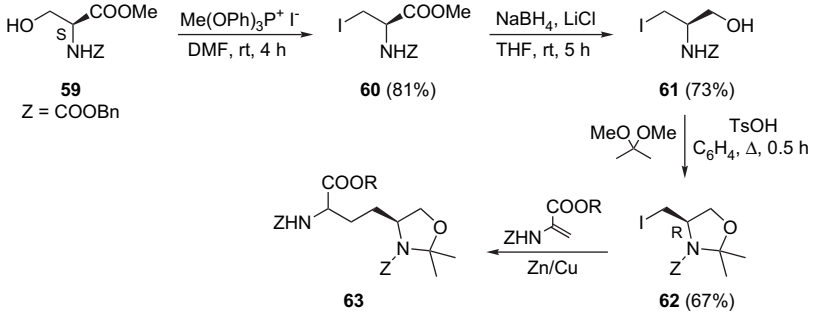
C_2-Symmetrical 2,6-bis(oxazolyl)pyridine **65** bearing hydroxymethyl groups on the oxazoline rings has been synthesised as a water-soluble ligand from L-serine methyl ester hydrochloride **46** and pyridine-2,6-dicarboxylic acid chloride in four steps and in an overall yield of 54%. The final step in this synthesis comprised the O-cyclisation of amide **64** in an alkaline medium (Scheme 16).[38]

The carbamate **67** has been prepared, starting from the protected serine derivative **66**,[39] followed by conversion of the alcohol into iodide **68** upon tosylation and subsequent nucleophilic displacement by iodide. The β-iodo amine **68** was used for the synthesis of 2-alkenylazetidines (such as **69**) and 2-alkenylaziridines by Pd-catalysed intramolecular amination of the intermediate amino allenes (Scheme 17).[40]

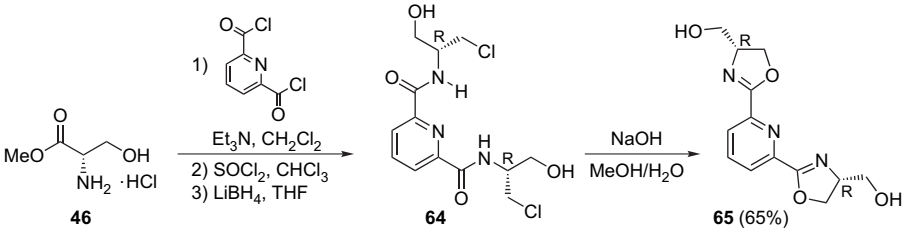
L-Serine has been used frequently as a chiral substrate for the asymmetric synthesis of 2-amino-3-halo-1-oxypropanes which, in turn, were used for further elaboration towards



Scheme 14.



Scheme 15.



Scheme 16.

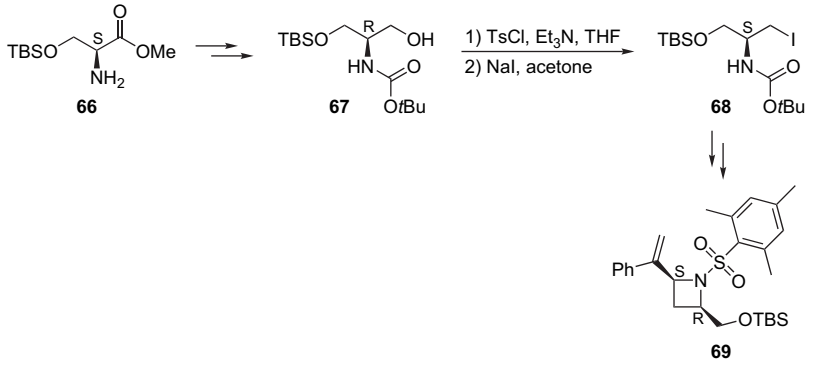
relevant target compounds such as manzamine derivatives, 3-aminochromanes, bis(oxazoline) ligands, cysteinol derivatives and 2-(1-alkenyl)aziridines and -azetidines.

3.4. Miscellaneous

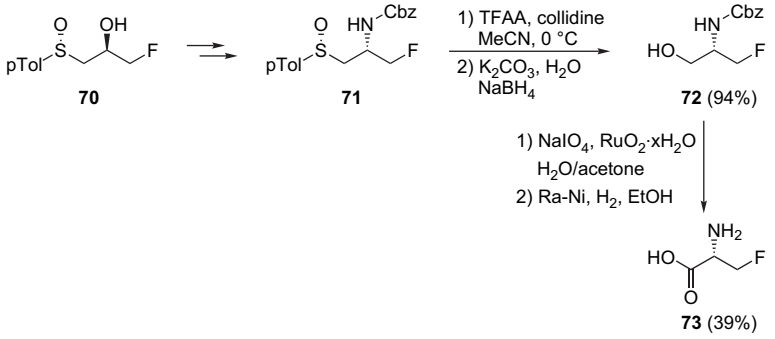
Apart from the above-mentioned protocols, a few other methodologies towards 2-amino-3-halo-1-oxypropanes can be mentioned. β-Aminosulfoxide **71** has been prepared from γ-fluoro-β-hydroxysulfoxide **70** in a three-step approach involving substitution of the hydroxyl group by azide, reduction of the azide to the corresponding amine and N-protection with benzyl chloroformate. The carbamate **71** was then subjected to a non-oxidative Pummerer rearrangement upon treatment with trifluoroacetic acid (TFAA) and *sym*-collidine in acetonitrile at 0 °C towards an intermediate trifluoroacetoxy sulfenamide, which was treated with aqueous K_2CO_3 and then $NaBH_4$ to afford β-fluoro amino derivative **72** in excellent yield (Scheme 18). In the final stage, oxidation of the hydroxymethyl group by $NaIO_4/RuO_2$ and hydrogenolysis of the *N*-Cbz protective group resulted in the desired (*S*)-3-fluoroalanine **73**, which is known to be useful as a broad-spectrum antibacterial agent.[41]

β-Iodo amine **76** has been prepared via an iodine-induced cyclofunctionalisation/hydrolysis protocol, starting from benzimidate **74** upon treatment with iodine in chloroform at room temperature. This transformation is assumed to proceed via a dihydro-oxazolium intermediate **75**, which undergoes hydrolysis to the ester **76** in 60% yield (Scheme 19).[42]

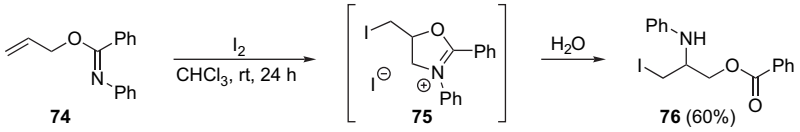
Tetrafluorobenzoylacetate **77** has been transformed into the oxetane derivative **78** via a three-step procedure, and this was then ring opened by means of a 20% solution of hydrogen chloride in ethanol to give the β-chloro amine **79** (X=Cl) in almost quantitative yield or, alternatively, by means of 70%



Scheme 17.



Scheme 18.



Scheme 19.

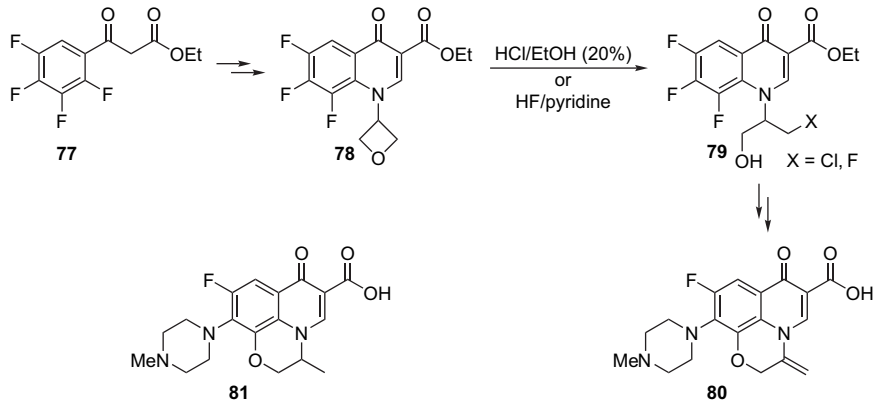
HF–pyridine to form the β-fluoro amine **79** (X=F) in 35% yield (Scheme 20). The β-halo amines **79** were further used for the synthesis of the tricyclic quinolonecarboxylic acid **80** as an analogue of the quinolone antibacterial agent, ofloxacin **81**.[43]

Benzothienooxazolopyrimidinium salts **83** have been prepared by an electrophile-induced cyclisation of allyl ether **82** upon treatment with bromine in acetic acid, either with 2 equiv of bromine towards the monobromide **83** (n=1) or with 4 equiv of bromine towards the tribromide **83** (n=3). The reaction of these pyrimidinium salts **83** with an excess of sodium acetate in DMF or DMSO afforded β-bromo amine **84** in good yields (Scheme 21).[44]

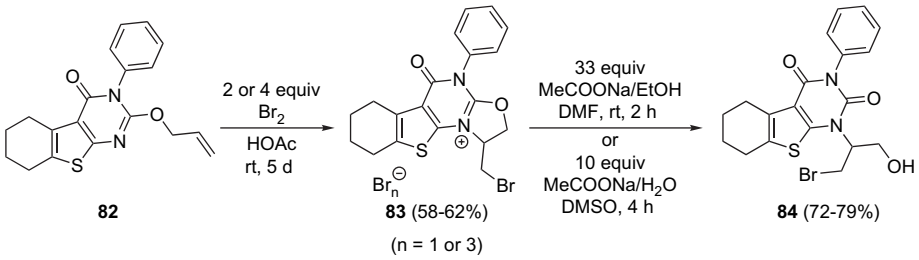
3-Azido-2-iodopropyl ether **86** has been prepared in 73% yield by azido-iodination of allyl ether **85** upon treatment with iodine monochloride and sodium azide in acetonitrile. Reduction of the azide **86** with lithium aluminium hydride and subsequent acetylation with benzoyl chloride afforded the aziridine **87**. Finally, ring enlargement of the *N*-acyl aziridine **87** using iodide as the nucleophilic promoter and acetone as the solvent ('Dewar's conditions') furnished oxazoline **88** with complete regioselectivity (Scheme 22).[45]

The addition of bromine fluoride, generated from hydrogen fluoride and *N*-bromoacetamide, to allyl alcohol **89** (R=H) or allyl ether **89** (R=Bn) afforded a mixture of two adducts, which was subsequently, and as such, treated with sodium azide in DMF to give the corresponding azido fluorides **90** and **91** in a 6:1 ratio (Scheme 23). The azides **90** were further used for the synthesis of 5-fluorocyclophosphamides **92** as potential antitumour agents.[46]

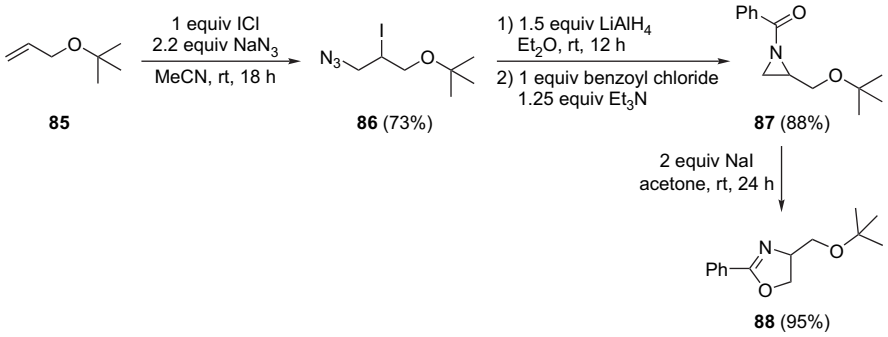
Finally, 2-amino-3-halo-1-oxypropanes have been briefly mentioned in several other reports, sometimes related to the synthesis of potential bioactive target compounds. For example, 1-(2-halo-1-hydroxymethylethyl)pyridinium nitrates have been evaluated as electrophiles for addition to unsaturated systems,[47] substituted phenylalanylamides have been prepared as rooting stimulators of rice via intermediate 2-amido-3-bromo-1-benzyloxypropanes[48] and a 2-amido-3-iodo-1-propanol



Scheme 20.

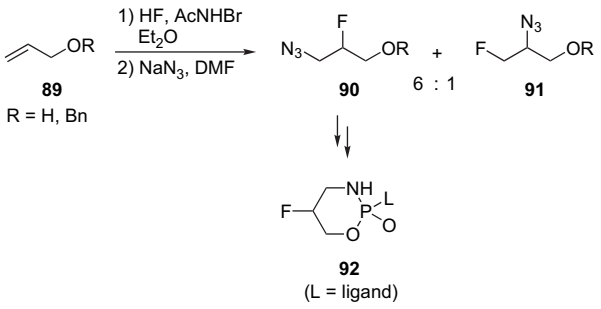


Scheme 21.



Scheme 22.

derivative has been described as an intermediate in the synthesis of aminodiols and 2-(hydroxymethyl)aziridines using acetate and carbonate ions on a polymeric support.[49] The reaction of perfluoro-(2,4-dimethyl-3-oxa-2,4-diazapentane) with allyl chloride has been found to afford a minor amount (11%) of a 2-amino-3-chloro-1-oxypropane derivative.[50] Analogously, treatment of allyl halides with dinitrogen trioxide has been reported to give amine oxides.[51] Furthermore, 1-aryloxy-3-chloro-2-(*N*-isopropylamino)propanes have been described as precursors for the corresponding propanols[52] or aziridines[53] related to β-adrenergic blocking agents, and 2-amino-3-fluoro-1-propanol has been used for the synthesis of complex pyridonecarboxylic acids as antibacterial agents.[54] The kinetics of a drug–receptor (muscarinic and nicotinic cholinoreceptor) interaction have been studied by means of alkylating agents such as 3-chloro-2-(dimethylamino)propyl hydroxydiphenylacetate.[55]



Scheme 23.

4. Conclusions

As compared to 3-amino-1-halo-2-oxypropanes, the 2-amino-3-halo-1-oxypropanes have received less attention in the literature, due to the limited number of protocols available for their preparation. Although 2-(oxymethyl)aziridines comprise suitable substrates for the synthesis of 3-amino-1-halo-2-oxypropanes through ring opening of the intermediate aziridinium salts by halides, very few efforts have been made in this direction. On the other hand, chiral 2-amino-3-halo-1-oxypropanes, prepared from the amino acid, L-serine, have become key intermediates in the asymmetric synthesis of interesting target compounds. The challenge for prospective research lies in the development of novel convenient regio- and stereoselective approaches towards 2-amino-3-halo-1-oxypropanes, starting from diverse starting materials in order to explore new transformations en route to different biologically relevant compounds.

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Biographical sketch

Matthias D'hooghe was born in Kortrijk, Belgium, in 1978. He received his master's diploma in Bioscience Engineering—Chemistry from Ghent University (Belgium) in 2001, where he carried out research under the guidance of Professor N. De Kimpe studying new entries towards 1-azabicyclo[*m.n.*0]alkanes. Subsequently, he enrolled in a PhD program with Professor N. De Kimpe as a promoter at the Department of Organic Chemistry, Faculty of Bioscience Engineering, Ghent University (Belgium), studying the synthesis and reactivity of 2-(bromomethyl)aziridines and he obtained the PhD degree in 2006. He was a laureate of the DSM Science and Technology Awards 2007 for outstanding PhD research. At present, he is working as an assistant professor in the group of Professor N. De Kimpe. His main research interests include the chemistry of small-ring azaheterocycles, with a special focus on aziridines, azetidines and β-lactams. He is the author of 32 publications in international peer-reviewed SCI-journals.

Norbert De Kimpe obtained the diploma of chemical agricultural engineer in 1971, the PhD degree in 1975 and the habilitation degree in 1985, all from Ghent University, Ghent (Belgium). He performed postdoctoral research work at the University of Massachusetts, Harbor Campus, at Boston (USA) (1979) and at the Centre National de Recherche Scientifique (CNRS) in Thiais, Paris (France) (1983), where he worked on unstable nitrogen-substituted sulfenyl derivatives and electron-deficient carbenium ions, respectively. He made his scientific career at the Belgian National Fund for Scientific Research, where he went through all stages up to the position of Research Director. During this career, he was affiliated with the Department of Organic Chemistry, Faculty of Agricultural and Applied Biological Sciences at Ghent University, where he took up teaching positions since 1987. He is now full professor in organic chemistry at the latter institution. He was a guest professor at the Centre Universitaire de Recherche sur la Pharmacopée et la Médecine Traditionelle in Butare (Rwanda, Central Africa), and at the Universities of Perpignan (France), Helsinki (Finland), Leuven (Belgium), Siena (Italy), Barcelona (Spain), Sofia (Bulgaria), Buenos Aires (Argentina) and Pretoria (South Africa). He was awarded the degree of Doctor honoris causa from the Russian Academy of Sciences in Novosibirsk (Russia) in 1998 and from the University of Szeged in Szeged (Hungary) in 2007. He received the Medal of Honour of Sofia University (Bulgaria) in 2006. He is the author of 435 articles in international peer-reviewed SCI-journals. His research interests include (1) the synthesis of heterocyclic compounds, with focus on agrochemicals, pharmaceuticals and natural products, (2) flavour chemistry and (3) the bioassay-guided isolation of physiologically active natural products from medicinal plants.