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Ring opening of cyclic sulfamidates with bromophenyl metal reagents: complementarity of sulfamidates and aziridines

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ABSTRACT

Bromophenyl magnesium reagents generated via a Knochel type magnesium–halogen exchange of aryl iodides undergo regioselective ring opening of cyclic primary and secondary *N*-Boc sulfamidates in good to excellent yields. With secondary sulfamidates the reaction proceeds with clean inversion of the stereochemistry. This protocol complements the ring opening of aziridines with bromophenyl metal reagents and extends its scope to secondary substrates.

Early papers on the ring opening of cyclic sulfam(id)ates with a variety of nucleophiles made specific mention of the complementarity with aziridines.[1a–c] In a recent paper ring opening reactions of aziridines with *ortho*-bromophenyl metal reagents as a means to access pharmacologically interesting indolines were reported[2] (Scheme 1). The present work allows a comparison of *N*-Boc aziridines and *N*-Boc sulfamidates as electrophiles and provides evidence for the superiority of analogous ring opening reactions of cyclic sulfamidates with respect to regiochemical control and simplicity of the reaction conditions.

During a program directed toward selective $5HT_{2c}$ receptor agonists[3a,b] we were confronted with the problem of introducing a chiral 2-amino-propyl moiety[4] at the 3-position of an indole. Ring opening of aziridines was expected to be a straight forward way to affect the desired transformation. Aryl lithium, aryl magnesium halide, aryl zinc halide and aryl organocuprate reagents have all been used in the ring opening of aziridines.[5a–d] Our attempts to open a variety of differently N-protected aziridines (*N*-tosyl, *N*-Boc, *N*-benzyl) with the indole lithium reagent obtained from iodine metal exchange of an iodoindole were unsuccessful (Scheme 2). Neither addition of copper(I)salts such as copper(I)iodide or copper(I)bromide-dimethylsulfide complex nor addition of Lewis acids such as borontrifluoride etherate improved the conversion.

When *N*-Boc-sulfamidate **2b** was reacted with lithioindole, obtained at −78 °C by iodine lithium exchange, the desired 2-amino-propylated derivative was formed in an excellent 86% yield (Scheme 2).[3a] While this protocol allowed rapid and efficient access to the desired serotoninergic compounds its restriction to primary sulfamidates and the necessity to operate at low temperatures limited practicality and versatility.

Reaction of commercial phenyllithum with sulfamidate **2b** at −78 °C required a ca twofold excess for complete consumption of **2b** and resulted in a 53% yield of the ring opened product accompanied by 32% of the des-Boc analog resulting from competing attack of the lithio species at the Boc carbonyl. With this result we felt encouraged to study ring opening reactions of cyclic sulfamidates with the aim to develop a general practical method for the synthesis of β-phenylethylamines allowing regio and stereocontrolled introduction of substituents both at the 1 and the 2-position. (Scheme 3).

Substituted β-phenylethylamines represent an important class of pharmacologically active compounds.[6] They can also serve as intermediates to a wide variety of equally interesting derivatives such as indolines.[7a–d] *Ortho*-bromophenyl analogs in particular are well established precursors for indolines.[2]

Ring opening of mono substituted *N*-Boc-aziridines works well with *ortho*-bromophenyl lithium at −78 °C in the presence of borontrifluoride etherate and proceeds regioselectivly with attack at the less hindered side. Reactions with phenylzinc, phenylmagnesium chloride or corresponding organocuprate reagents were less satisfactory in terms of reaction times and excess of reagent necessary for full conversion of the employed aziridines.

The ease of preparation and the much higher stability of arylmagnesium halide reagents especially in the presence of

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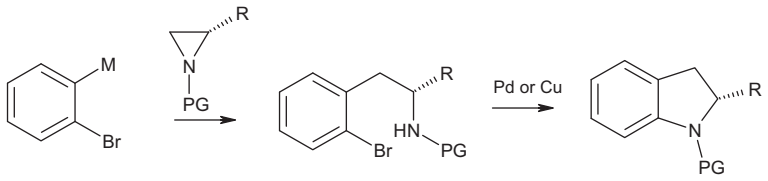
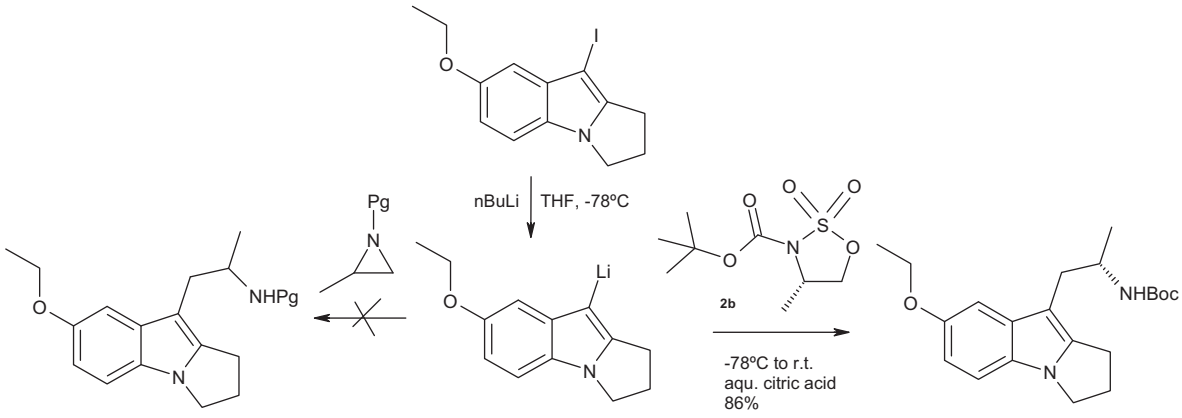
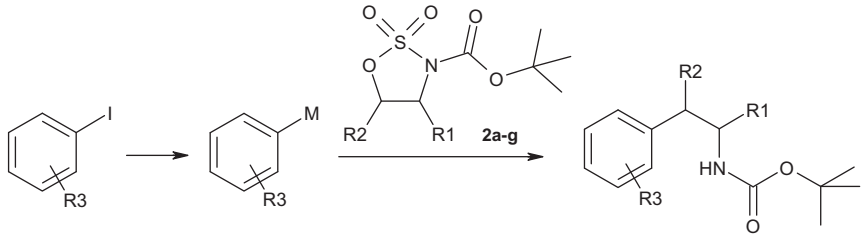


Scheme 1. Synthesis of indolines via ring opening of aziridines.

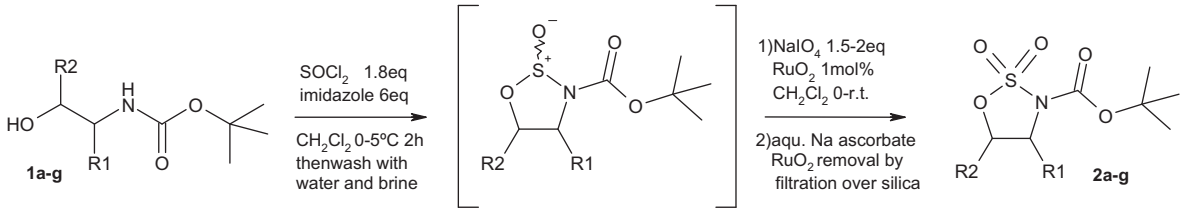


Scheme 2. Reaction of N-protected aziridines and *N*-Boc sulfamidates with 3-lithioindoles.



Scheme 3. General synthesis of 1- or 2-monosubstituted β-phenylethylamines via ring opening of sulfamidates.

Table 1
Yields and selected properties of *N*-Boc sulfamidates



Entry	Chirality	R^1	R^2	Yield (%)	ee[11] (%)	Mp (°C)	Lit.
2a	–	H	H	72	–	117–118	
2b	R	CH_3	H	88	100	121–122	120–121[12]
2c	S	CH_3	H	88	100	122–123	
2d	S	H	CH_3	84	99.2	115–117	
2e	R	H	CH_3	84	99.7	117–118	
2f	S	COOEt	H	71	n.d.		
2g	S	$CH_2OTBDMS$	H	83	n.d.		

ortho-halo substituents, however, would make them the preferred organometal species provided their reactivity being sufficient.

For instance *ortho*-bromophenyl magnesium halides can be generated at −15 °C and undergo copper(I) promoted 1,4-addition to enones at temperatures as high as 0 °C.[8a,b]

For the synthesis of more elaborated β-phenylethylamines especially such as the ones carrying additional bromine substituents we investigated ring opening of cyclic *N*-Boc-sulfamidates by aryl magnesium halides.

The synthesis of cyclic *N*-Boc sulfamidates[9a,b] is well established and involves the reaction of *N*-Boc protected amino alcohols with thionylchloride in the presence of a suitable base followed by Sharpless oxidation of the formed sulfamidites. We have developed a convenient modified protocol which also addresses removal of toxic ruthenium tetroxide produced during Sharpless oxidation[10] (Table 1).

As sulfamidates are well known to undergo ring opening with a variety of nucleophiles including halides we sought to generate the Grignard reagent with the least nuleophilic halide possible. A Knochel[8a] type halogen metal exchange of iodo-bromobenzenes with isopropylmagnesium chloride in diethyl ether proceeded rapidly at −15 °C. When sulfamidate **2b** was added to this mixture it was rapidly consumed predominantly with the formation of the desired ring opened product. Addition of 1 mol % of copper(I) iodide improved the conversion with respect to suppression of unwanted side products resulting from competitive opening of the sulfamidate by the halide counter anion.[13]

Although primary sulfamidates **2a**, **2b** and **2c** reacted even at −78 °C the outcome with respect to yield and stereochemical purity did not differ to reactions carried out at non cryogenic −15 °C. At this temperature all reaction components were freely soluble in diethyl ether in which the reactions looked cleaner than in tetrahydrofuran. After hydrolysis of the reaction mixture with 10% aqueous citric acid the target compounds **3a**, **3b**, **3c**, **4c**, **5c**, and **6c** were obtained by crystallization from heptane or by short path distillation (in case of low melting or oily products) in analytically and optically pure form in yields ranging from 65 to 83% at a 5 mmol scale[14] (Table 2). Similar ring opening reactions of *N*-Boc aziridines provide comparable yields but require the phenyllithium reagent and activation by borontrifluoride etherate, rather than the Grignard reagent, and operation at cryogenic −78 °C.[2]

As the starting iodoaryl compounds as well as their des iodo analogs were easily separable from the reaction mixture by our standard workup procedure we usually used them in a twofold

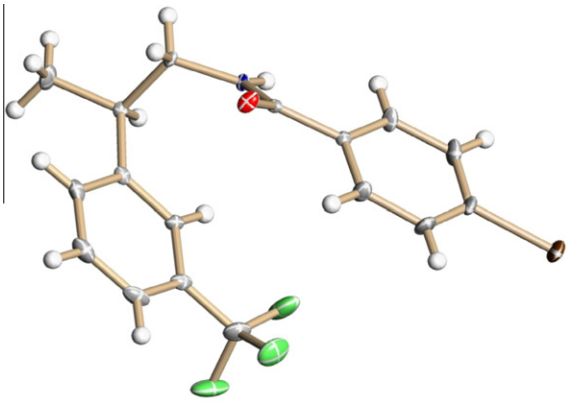
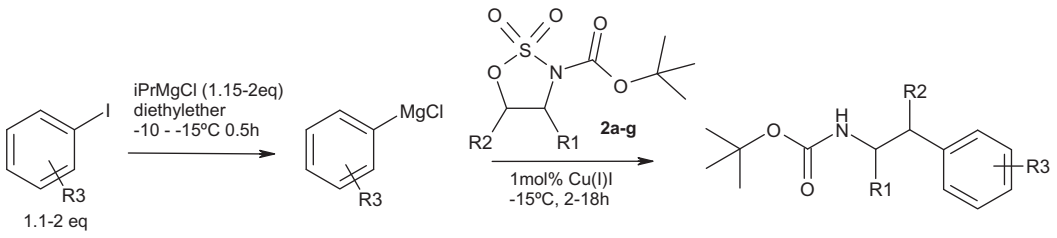


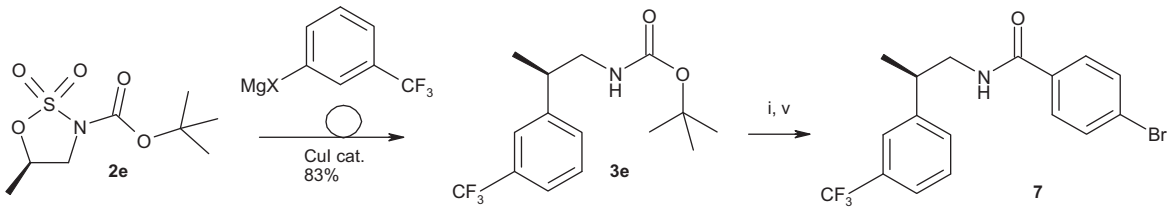
Figure 1. X-ray crystal structure compound **7**.

Table 2
β-Phenylethylamines derived from ring opening of cyclic sulfamidates



Entry	R1	R2	R3	Chirality	Yield (%t)	ee[15] (%)	Mp (°C)
3a	H	H	*m*-CF_3	–	82[b]	–	54–56
3b	CH_3	H	*m*-CF_3	*R*	78[a]	100	84–85
3c	CH_3	H	*m*-CF_3	*S*	75[a]	99.7	84–85
3d	H	CH_3	*m*-CF_3	*S*	87[b]	99.2	39–40
3e	H	CH_3	*m*-CF_3	*R*	85[b]	99.3	40–41
4c	CH_3	H	*o*-Br	*S*	83[a]	100	94–95
4e	H	CH_3	*o*-Br	*R*	75[b]	99.6	Oil
5c	CH_3	H	*m*-Br	*S*	70[a]	100	108–109
5e	H	CH_3	*m*-Br	*R*	62[b]	>97.9	Oil
6c	CH_3	H	*p*-Br	*S*	65[a]	>98.7	98–99
6e	H	CH_3	*p*-Br	*R*	62[a]	>99.6	57–59
6f	COOEt	H	*o*-Br	*S*	43[c]	n.d.	
6g	$CH_2OTBDMS$	H	*o*-Br	*R*	89[c]	n.d.	

[a] Crystallization.
[b] Distillation.
[c] Chromatography.



Scheme 4. Stereochemical course of reactions with secondary sulfamidates. Reagents: (i) 2.26 N hydrochloric acid in ethyl acetate; (v) 4-bromobenzoylchloride, Hünig's base.

excess. However using only slight excess (1.1 equiv) of the iodoaryl starting material did not reduce the yield significantly (Table 2, entry **6g**).

Having access to the isomeric enantiomerically pure secondary sulfamidates **2d** and **2e** from an earlier program we submitted them to the same reaction conditions. Again good conversions (62–87%) this time to β-substituted phenylethylamines **3d**, **3e**, **4e**, **5e**, and **6e** were observed. This substitution pattern has not been accessible by analogous ring opening reactions of *N*-Boc aziridines due to their propensity to open from the less hindered side. In contrast to analogous ring opening reactions of primary sulfamidates no significant conversion was observed below ca. −40 °C.

The ring opening of secondary sulfamidates **2d** and **2e** with nucleophiles such as indoles has been shown to proceed with inversion.[16] Copper(I) mediated ring opening reactions of the secondary cyclic sulfamidates **2d** and **2e** with phenylmagnesium chloride reagents (Table 2, entries **3d**, **3e**, **4e**, **5e**, **6e**) also proceed with inversion as evidenced by the X-ray single crystal analysis (Fig. 1) of a crystalline derivative **7** obtained from phenylethlamine **3e** by *N*-Boc deprotection and acylation with 4-bromobenzoyl chloride (Scheme 4).[17]

Having established conditions for efficient ring opening of simple methyl substituted primary and secondary *N*-Boc sulfamidates we next explored sulfamidates carrying extra functionality such as carboxylate and silyloxymethyl substituents.

Starting from L-serine esters sulfamidates **2f** and **2g** were obtained via, also commercially available, intermediates **1f** and **1g** by a standard sequence of reactions in excellent overall yield as crystalline white powders.

Reaction of ethoxycarbonyl substituted **2f** with *o*-bromophenylmagnesium chloride under the above described conditions provided an unsatisfactory 40% yield of carboxyl substituted *o*-bromophenylethylamine presumably due to competing attack at the ester group (Table 2, entry **6f**). During their elegant synthesis of Reinieramycin Zhu et al. used ring opening of t-butylester substituted *N*-Boc aziridine with an *o*-methoxy stabilized aryl Grignard with good success[18] which suggests that this aziridine might also be better compatible *o*-bromophenylmagnesium chloride than *N*-Boc sulfamidate **2f**. Silyloxymethyl substituted sulfamidate **2g** gave an excellent 89% yield of the desired product (Table 2, entry **6g**) this time after chromatography. Similar ring opening of a corresponding silyloxymethyl substituted aziridine was reported in comparable 79% yield again using a phenyllithium reagent with activation by borontrifluoride etherate at −78 °C.

The extension of this chemistry to heteroaryl metal reagents and secondary silyoxymethyl substituted sulfamidates as well as application to the synthesis of pharmacologically interesting azaindolines[19] will be reported in due course.

In conclusion we have demonstrated that cyclic primary and secondary *N*-Boc-sulfamidates undergo efficient copper(I) promoted ring opening reactions with bromoarylmagnesium chlorides obtained from Knochel type iodo metal exchange at convenient temperatures (−15 °C) thus giving access to optically pure 1- and 2-monosubstituted β-(bromophenyl)-ethylamines in good to excellent yields.

In comparison ring opening reactions with corresponding mono substituted *N*-Boc aziridines require the more reactive but less stable bromoaryllithium reagents in combination with a Lewis acid and are typically carried out at −78 °C. They occur exclusively at the less hindered side and thus provide access exclusively to 2-substituted phenylethylamines. Pyrimidine-2-sulfonyl (pymisyl) protected aziridines have recently been shown to ring open efficiently upon reaction with organocuprates offering benefits over *N*-Boc aziridines with respect to reactivity. While synthetic accessibility of *N*-Boc-aziridines and *N*-Boc-sulfamidates is comparable the latter are superior with respect to regiochemical control as well as reactivity in reactions with aryl Grignard reagents.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.07.123.

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10. *Modified general protocol for the synthesis of N-Boc cyclic sulfamidates*: To a solution of imidazole (41.2 g, 0.60 mol, 6.00 equiv) in dichloromethane (400 mL) was added at 0 °C a solution of thionyl chloride (21.41 g, 0.18 mol, 13.06 ml, 1.8 equiv) in dichloromethane (130 ml) during 15 min. The reaction mixture was then stirred at ambient temperature for 1 h and then cooled to −10 °C. To the resulting suspension was added a solution of *N*-Boc-D-alalinol (17.52 g, 0.10 mol) in 200 ml dichloromethane during 30 min at −10 °C and the mixture was then stirred at ambient temperature for 2 h. To the resulting suspension was added water (800 ml) and the mixture was stirred at ambient temperature for 10 min. The phases were separated and the organic phase was washed with 10% aqueous citric acid (500 ml) and half concentrated brine (500 ml) and dried over magnesium sulfate. The solids were removed by filtration and washed with ca 50 ml dichloromethane. The combined filtrates were mixed with a 10% aqueous sodium meta periodate solution (500 ml) and cooled to 0 °C. To the well stirred mixture was added ruthenium dioxide

hydrate (0.90 g, 0.0060 mol 0.01 equiv) and the mixture was stirred at 0 °C for 2 h and at ambient temperature for 2 h. The phases were separated and the organic phase washed with a 10% aqueous sodium ascorbate solution (100 ml). The phases were separated and the organic phase was filtered over silica gel (300 g). The product was eluted with heptane/ethyl acetate = 2: 1. The product fractions were combined and concentrated until crystallization occurred. The solid was collected by filtration, washed with heptane and dried to constant weight under high vacuum to yield **2b** (20.1 g, 86%) as white crystals melting at 121–122 °C.

11. Chiral LC on a Chiralcel-ODH, 25 cm × 4.6 mm, DB075 mobile phase A: heptan B: heptan+ 5% ethanol+ 5% isopropanol+ 0.01 M NH4Ac
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13. When 10 mol % of copper(I)iodide was employed the yields did not improve and the product of competitive ring opening of the sulfamidate with iodide became detectable.
14. *General protocol for ring opening of sulfamidates with bromophenyl magnesium chlorides*: To a 2 M solution of isopropylmagnesium chloride in diethyl ether (5 ml; 0.010 mol) was added drop wise at −12 °C the corresponding bromo-iodobenzene (2.83 g; 0.010 mol; 2 equiv) and the mixture was stirred at −12 °C for 2 h. To the resulting mixture was added cuprous(I) iodide (0.020 g; 0.10 mmol; 0.01 equiv) and the mixture was stirred at −12 °C for 0.5 h. The resulting mixture was added via syringe to a suspension of the corresponding sulfamidate (**2b** or **2c**) (1.19 g 0.0050 mol; 1 equiv) in 10 ml diethyl ether at −12 °C and the mixture was stirred at this temperature for 2 h. To the resulting solution was added drop wise a 10% aqueous solution of citric acid (10 ml) and the mixture was stirred at room temperature for 2 h. The phases were separated, the organic phase was concentrated under aspirator vacuum and the residue was purified by kugelrohr distillation (0.4 m bar, 105 °C) or by crystallization from heptane to furnish products (Table 2, entries **4**–**6b** and **c**) in 62–83% yield.
15. Chiral LC on a Chiralcel-ODH, 25 cm × 4.6 mm, DB075 mobile phase A: heptan B: heptan+ 5% ethanol+ 5% isopropanol+ 0.01 M NH4Ac
16. Roever, S.; Adams, D. R.; Benardeau, A.; Bentley, J. M.; Bickerdike, M. J.; Bourson, A.; Cliffe, I. A.; Coassolo, P.; Davidson, J. E. P.; Dourish, C. T.; Hebeisen, P.; Kennett, G. A.; Knight, A. R.; Malcolm, C. S.; Mattei, P.; Misra, A.; Mizrahi, J.; Muller, M.; Porter, R. H. P.; Richter, H.; Taylor, S.; Vickers, S. P. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3604–3608.
17. A single crystal of compound **7** (0.8 × 0.03 × 0.03 mm) was mounted in a loop and cooled to 89 K in a nitrogen stream. Data were collected at the swiss light source beamline X10SA using a MAR CCD225 detector with synchrotron radiation (0.7 Å) and data processed with the program XDS. The crystal structure was solved and refined with ShelXTL (Bruker AXS, Karlsruhe). The absolute configuration of the molecule was determined to be R based on refinement of the Flack absolute structure parameter (Flack 1983). The low standard deviation (0.008) of the Flack parameter (0.036) indicated a reliable determination of the absolute structure. Flack, H.D. Acta Crystallogr., Sect. A **1983**, *39*, 876–881.
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