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A General, Regioselective Approach to the Synthesis of Ortho Allylanilines

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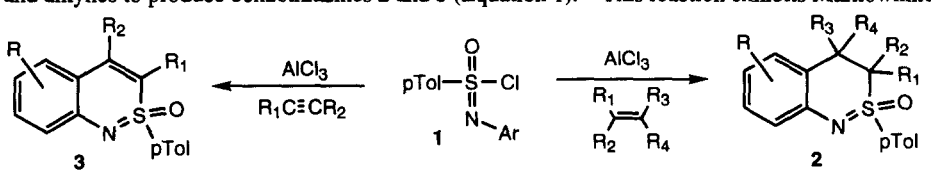
Summary: Readily available 2,1-benzothiazines can be alkylated via deprotonation with butyllithium followed by treatment with iodomethyltrimethylsilane. Subsequent treatment with fluoride and hydrolysis leads to ortho allyl anilines in high yield. The reaction is general and regioselective by virtue of these characteristics being present in the Lewis acid mediated reaction of alkenes and sulfonimidoyl chlorides, the reaction which leads to the 2,1-benzothiazines used as starting materials.

Ortho allylanilines are useful precursors to indole and quinoline compounds. The palladium catalyzed cyclization of allylanilines to indoles render the former indole equivalents.[1] A protocol involving ozonolysis and subsequent intramolecular condensation has also been used to realize this equivalence.[2] Similarly, palladium or other electrophile mediated cyclization have lead to the formation of quinoline derivatives.[3] The importance of such heterocyclic ring systems, especially indoles, in organic chemistry cannot be overstated. A continuing effort exists to develop new routes to indoles in the context of natural products synthesis and the development of new pharmaceuticals.[4] Allyl anilines have also been shown to exhibit a unique photochemistry which has been used in a stereoselective synthesis of 2-indanols.[5] In this report we document a new, general route to allyl anilines which should be of utility in organic synthesis in the context of heterocyclic synthesis and elsewhere.

The synthesis of ortho allylanilines has been approached principally by two methods: amino-Claisen rearrangement of N-allyl anilines and the coupling of nickel allyls with 2-bromoanilines.[1,6] The former method generally requires Lewis or protic acid catalysis and elevated temperatures. The latter method is general but requires the availability of the appropriate 2-bromoanilines and the preparation of allyl nickel species, at least one preparation of which requires the use of the toxic nickel carbonyl.[7] Other routes to allylanilines have also been reported.[5,8]

We have been engaged in the study of the Lewis acid mediated reaction of sulfonimidoyl chlorides with alkenes and alkynes to produce benzothiazines **2** and **3** (Equation 1).[9] This reaction exhibits Markownikov

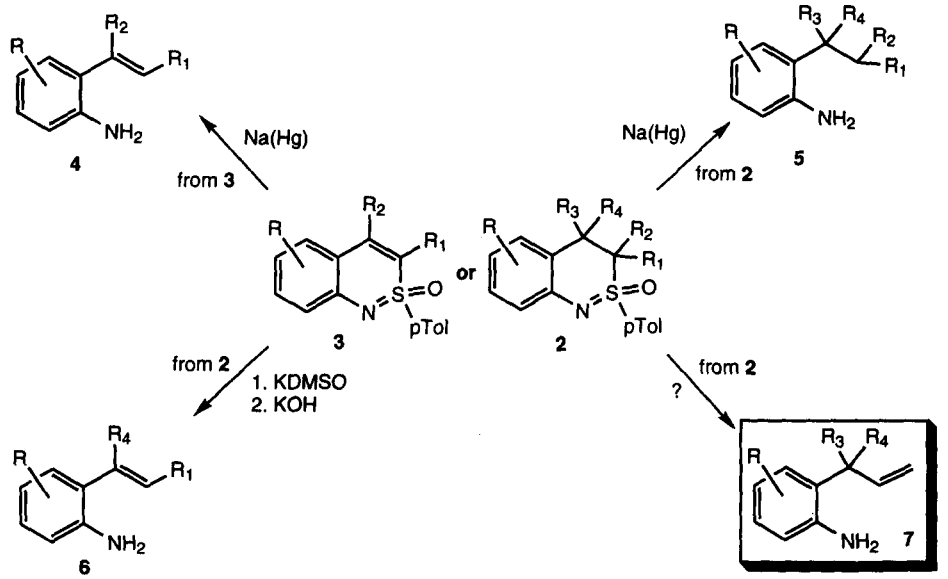


Equation 1

regioselectivity and is quite general. We are interested in using these benzothiazines as useful synthons in a variety of ways. Included among our approaches is reductive and oxidative desulfurization. We have developed methods for the conversion of these heterocycles to 2-alkylanilines and have developed two complementary procedures for the preparation of 2-alkenylanilines (Scheme 1).[10] Further, we have demonstrated the direct conversion of certain benzothiazines to indoles.[10c]

The benzothiazines **2** and **3** are nothing more than cyclic sulfoximines.[11] It occurred to us that a synthetic sequence similar to that developed for the synthesis of alkenes from sulfones would be applicable here.[12] Deprotonation of benzothiazine **2** at carbon 3 followed by alkylation with iodomethyltrimethylsilane and

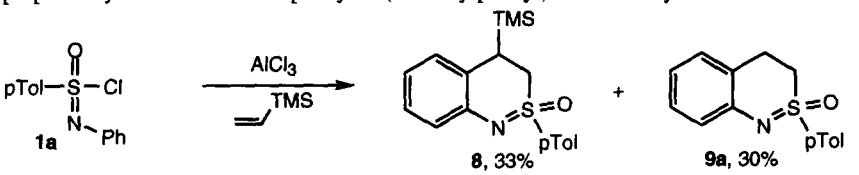
desilylation should provide a direct route to 2-allylanilines. Regioselectivity and generality would be assured by



Scheme 1

these characteristics being present in the reaction leading to the formation of benzothiazines themselves.[9]

The benzothiazines used in this process were prepared according to our published procedure.[9] The "parent" system was prepared by the reaction of N-phenyl-S-(4-methylphenyl)sulfonimidoyl chloride **1a** with



Equation 2

vinyltrimethylsilane. Benzothiazine **9a** was produced directly in 30% yield along with **8**. Though the mechanism of formation of **9a** has not been established, it is interesting to note that **8** could not be converted to **9a** under a variety of acidic conditions.

The alkylation of the benzothiazines used in this preliminary study occurred in high yield and stereoselectively.[13] Treatment of a THF solution of **9a** with n-BuLi at -78 °C and quenching with iodotrimethysilane gave alkylation product **10a** in 90% yield as a 2.3:1 mixture of diastereomers. The stereochemistry of these isomers was not determined. Other benzothiazines were alkylated in a similar fashion and the results are shown in Table 1. Only in the case of **9g** and **9h** was the alkylation stereochemistry determined. X-ray analysis of each of the major diastereomers from the alkylation showed that the trimethylsilyl group is syn to the sulfur-oxygen bond.[14] It is assumed at this time that all the major diastereomers of **10** have this stereochemical feature.

The conversion of benzothiazines **10** to ortho allylanilines consisted of a two step procedure involving fluoride-induced ring opening and subsequent hydrolysis of the resulting sulfinamides.[15] The results are shown in Table 2. Yields are good to excellent. The only difficulty arose in the reaction of **10f**. Under the basic conditions used for sulfinamide hydrolysis, isomerization occurred to produce **12** to the exclusion of any of the

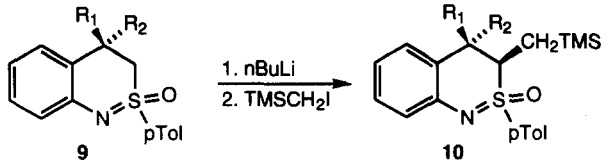


Table 1. Benzothiazine Alkylation with Iodomethyltrimethylsilane

Entry	Educt	R_1	R_2	Product	Ratio	Yield (%)[h]
1	**9a**	H	H	**10a**	2.3:1[f]	90
2	**9b**[a]	nPr	H	**10b**	b	92
3	**9c**[a]	nBu	H	**10c**	b	80
4	**9d**[b]	nPent	H	**10d**	b	84
5	**9e**[c]	tBu	H	**10e**	b	70
6	**9f**[d]	Ph	H	**10f**	b	90
7	**9g**[e]	$-CH_2Ph$	H	**10g**	4.6:1[g]	82
8	**9h**[e]	H	$-CH_2Ph$	**10h**	30.3:1[g]	95
9	**9i**	$-(CH_2)_2-$		**10i**	4.4:1[g]	86
10	**9j**	Et	Et	**10j**	47.4:1[g]	55

[a] Diastereomer ratio (DR)=1.6:1. [b]DR not determined. [c]DR=4.1:1. [d]DR=1.4:1. [e]Single diastereomer. [f]Determined by capillary GC. [g]Determined by HPLC. [h]Isolated yields after chromatographic purification.

allylic isomer. No attempt was made to circumvent this problem.

In summary, we have developed a convenient, regioselective route to ortho allylanilines. The conversion of benzothiazines to other generally useful organic compounds and their use as chiral templates are under study and results will be reported in due course.[16]

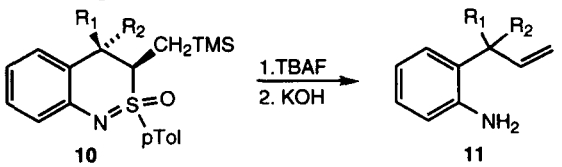
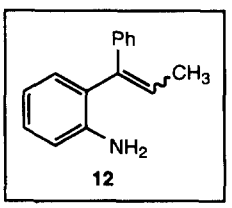


Table 2. Conversion of Benzothiazines 10 to Anilines

Entry	Educt	R_1	R_2	Product	Yield (%)[a]
1	**10a**	H	H	**11a**	69
2	**10b**	nPr	H	**11b**	77
3	**10c**	nBu	H	**11c**	84
4	**10d**	nPent	H	**11d**	76
5	**10e**	tBu	H	**11e**	86
6	**10f**	Ph	H	**12**	87
7	**10g**	$-CH_2Ph$	H	**11g**	85
8	**10h**	H	$-CH_2Ph$	**11h**	84
9	**10i**	$-(CH_2)_2-$		**11i**	71
10	**10j**	Et	Et	**11j**	76

[a]Isolated yields after chromatographic purification.



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13. General alkylation procedure: A flame dried round-bottomed flask equipped with a stirring bar, septum, and N_2 balloon was charged with benzothiazine **9** and sufficient THF to give a ca. 0.2 M solution. The solution was cooled to -78 ^{o}C and allowed to stir for 10 min. n-BuLi (ca. 2 M in hexanes, 1.1 eq.) was added dropwise via syringe and the resulting bright yellow solution was allowed to stir for 15 min. Iodomethyltrimethylsilane (1.2 eq.) was added via syringe over a 30 s period and the resulting solution was allowed to warm slowly to room temperature. The reaction was monitored by TLC and upon completion (ca. 1 h) it was quenched by addition of water. The mixture was extracted with diethyl ether and the organic phase washed with water and brine. The organic phase was dried, the solvent removed in vacuo and the product purified by chromatography.
14. A discussion of the alkylation stereochemistry and X-ray data will appear elsewhere.
15. General procedure for allyl aniline formation: A flame dried round-bottomed equipped with a stirring bar, septum and N_2 balloon was charged with benzothiazine **10** and sufficient THF to give a ca. 0.2 M solution. Tetra-n-butylammonium fluoride in THF (1.1 eq) was then added via syringe and the reaction monitored by TLC. Upon completion the reaction was quenched by the addition of water. Standard work-up gave crude sulfinylanilide which was dissolved in sufficient methanol to give a ca. 0.2 M solution. Potassium hydroxide (3-5 eq) was added and the solution was heated to reflux for 18 h. The reaction mixture was cooled, diluted with water and extracted with diethyl ether. The organic phase was washed with water and brine and dried (Na_2SO_4). The solvent was removed in vacuo and the product **11** purified by chromatography.
16. All new compounds exhibited satisfactory ^{1}H and ^{13}C NMR and IR spectral data as well as satisfactory combustion analysis or exact mass data.

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