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REGIOSPECIFIC SYNTHESIS OF ISOQUINOLINE ALKALOIDS. USE OF ARYLSILANES IN DIRECTED PICTET-SPENGLER CYCLIZATIONS

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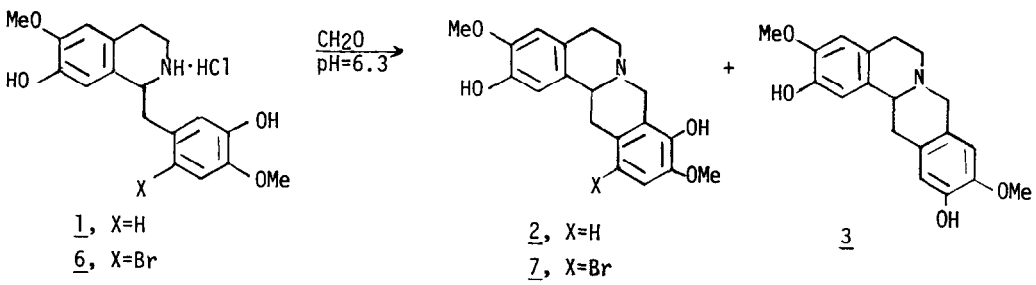
Abstract. The trimethylsilyl group has been shown to be effective as an activating group for *ipso* attack in the Pictet-Spengler reaction to control the regiochemistry in tetrahydroisoquinoline synthesis. In this manner, 2-(2-trimethylsilyl-3-methoxyphenyl)ethylamine was cyclized and N-methylated to give regiospecifically 8-methoxy-N-methyl-1,2,3,4-tetrahydroisoquinoline while the non-silylated compound gave only the 6-methoxy isomer.

The Pictet-Spengler reaction[1] is commonly used in alkaloid synthesis for the construction of a tetrahydroisoquinoline moiety. One problem which arises in the application of this reaction is regiochemical control when there is more than one site for cyclization. Thus, in the cyclization of norreticuline hydrochloride (1) a mixture of scoulerine (2) and coreximine (3) is obtained under physiological conditions.[2]

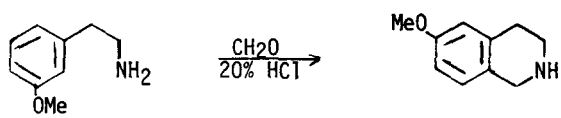


1, X=H
6, X=Br

2, X=H
7, X=Br

3

In other cases, especially when a hydroxy group is absent, the cyclization shows a strong preference for cyclization *para* to the activating group. Thus, when 2-(3-methoxy)phenethylamine (4) is reacted with formaldehyde and 20% hydrochloric acid, only 6-methoxy-1,2,3,4-tetrahydroisoquinoline (5) is obtained (80% isolated yield).[3]



4 5

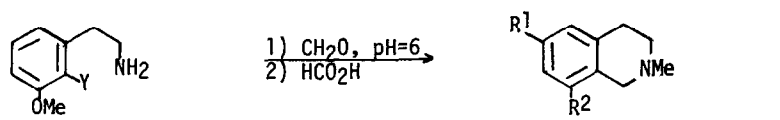
One solution to this regiochemical problem has been to use a blocking group, such as bromine, to prevent cyclization at the *para* position and then to later remove the blocking

group. Kametani has efficiently used this approach to regiospecifically synthesize scoulerine from the norreticuline derivative 6; Pictet-Spengler reaction gave only the brominated scoulerine 7.[4]

An alternate approach would be to use an activating group to bias the attack at the desired position. Although such groups as a *para*-amino group[5] have been used in this connection, the necessity to remove the activating group is a potential problem. Therefore, we set out to investigate the use of an activating group that can undergo *ipso* attack and thus directly replace the activating group by the desired new carbon-carbon bond. We chose the trimethylsilyl group for this purpose.

In this paper we describe the comparison of the silylated phenethylamine 8 with that of 4 under Pictet-Spengler cyclization/N-methylation conditions, see Scheme I. However, three

Scheme I

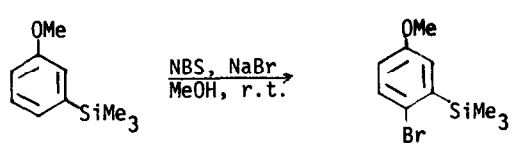


4 : Y = H
8 : Y = $SiMe_3$

15 : R^1 = OMe, R^2 = H
16 : R^1 = H, R^2 = OMe

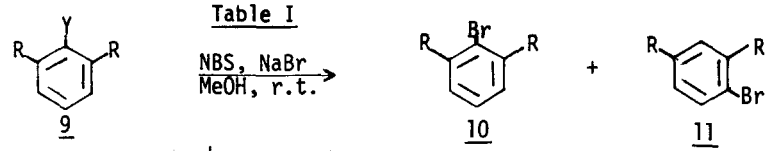
questions needed to be answered before proceeding. First, what are the limitations on the trimethylsilyl group acting in an *ipso* fashion in electrophilic aromatic substitution? Second, does steric congestion, such as 1,2,3-substitution, alter the regiochemical course of the reaction? Third, are silylated compounds such as 8 readily prepared?

From the studies of many workers[6,7] and our own[8], it has been clearly demonstrated that the trimethylsilyl group undergoes *ipso* substitution with a variety of electrophiles. The limitations seem to be that the *ipso* attack must be faster than competing protodesilation and that a strongly activating group, such as hydroxy or methoxy, is not present at a site *meta* to the trimethylsilyl group. The protodesilation problem in most cases can be avoided by careful choice of reaction conditions and electrophilic reagents. In the situation where a strongly activating group is *meta* to the trimethylsilyl group, the product(s) often still retains the silyl group:[7,8]



To investigate the steric congestion question, we studied the bromination of 2,6-dimethoxybenzene 9 (R = OMe, Y = $SiMe_3$) and 2,6-dimethylbenzene 9 (R = Me, Y = $SiMe_3$), see Table I. Under these mild bromination conditions, the trimethylsilyl compounds gave

Table I



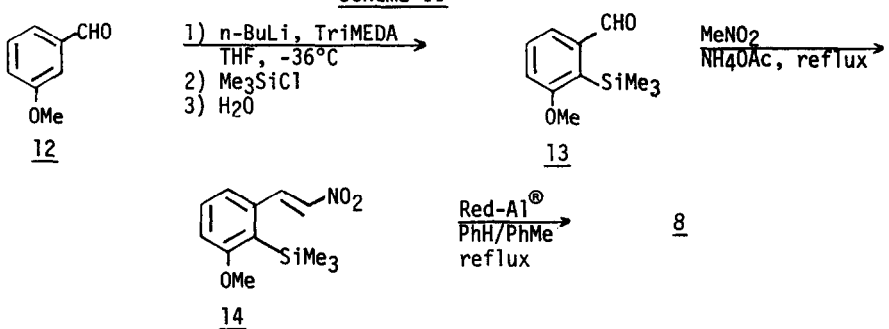
R	Y	10 : 11
MeO	H	4 : 96
MeO	$SiMe_3$	100 : ___
Me	H	4 : 96[a]
Me	$SiMe_3$	100 : ___

a) $Br_2CH_2Cl_2$

exclusively the 1,2,3-products 10 while the non-silylated compounds (9, Y = H) gave mainly the 1,2,4-products 11. It should be noted that m-xylene itself does not react under these mild conditions and requires bromine in methylene chloride. This suggests that the trimethylsilyl group activates the aromatic ring toward electrophilic substitution.[9]

As to the preparation of compounds such as 8, this was readily achieved as shown in Scheme II. The trimethylsilyl was regiospecifically introduced by selective metallation[10] of

Scheme II



the aminal from m-methoxybenzaldehyde (12) followed by reaction with chlorotrimethylsilane to give crystalline 13[11] in 86% yield. Nitrostyrene 14[11] was isolated as a yellow solid in 97% yield by reaction of 13 with nitromethane in the presence of ammonium acetate. Reduction of 14 with Red-Al® gave the desired silylated phenethylamine 8[11] in 68% yield following Kugelrohr distillation.

With 8 now in hand, we compared the Pictet-Spengler reactions depicted in Scheme I. The reaction conditions (refluxing for 8 hours in aqueous ethanol at pH=6) were chosen to minimize protodesilation and the crude reaction mixture was heated with formic acid to carry out Erstweiler-Clark N-methylation. When 4 was subjected to these conditions, the only isolable product was 6-methoxy-N-methyl-1,2,3,4-tetrahydroisoquinoline (15)[11] which was isolated in 22% yield. However, when 8 was reacted in a similar manner the only product isolated was the 8-methoxy isomer 16[11] in 72% yield.

In conclusion, we have demonstrated that the trimethylsilyl group can be used effectively as an activating group for *ipso* attack in the Pictet-Spengler reaction to control the regiochemistry in tetrahydroisoquinoline synthesis.

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11. Satisfactory nmr and ir spectra and analytical data were obtained for this compound.

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