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Approach to Geminally Alkylated Azaphthalans via a Consecutive Double Desilylation–Alkylation Reaction: Application to a Synthesis of Cerpegin

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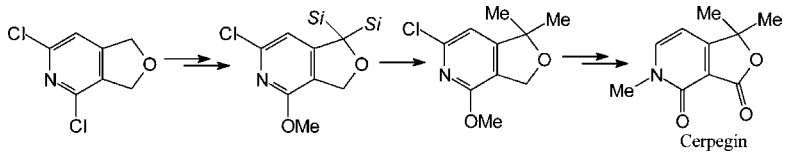
ABSTRACT



A new approach to geminally alkylated azaphthalans and an application of this chemistry to the synthesis of the pyridone alkaloid, cerpegin, is reported.

Although much attention has been paid to the introduction of two organic groups at the 1,3-positions of phthalans,[1−4] practically no report is available for the synthesis of geminally alkylated phthalans and their congeners (azaphthalans) from their parent molecules. Like their 1,3-counterparts that show promising pharmacological profiles,[5] geminally alkylated phthalans and azaphthalans also display significant biological activities, most of which have been reported in the patent literature.[6] Thus, introduction of two organic groups on the same benzylic carbon in phthalans and azaphthalans is an important task in organic synthesis.

Current methods for the direct synthesis of 1-substituted as well as 1,3-disubstituted phthalans and azaphthalans involve deprotonation of the parent compounds or their Cr-$(CO)_3$ complexes at the α-position followed by trapping of the resulting species with a carbon electrophile.[1−4] It should be noted that the choice of base is critical for effective deprotonation of these systems.[4] To date, only *t*-BuLi and *n*-BuLi-lithium 2-(dimethylamino)ethoxide (LiDMAE) are found to be useful bases.[1,4] With other basic reagents such as *n*-BuLi-*t*-BuOK, Li-naphthalene, Li-4,4′-di-*tert*-butylbiphenyl, and *n*-BuLi-THF, ring cleavage was observed,[4,7] and with lithium amide bases such as LDA, the lithiation was poorly selective.[2,4] Herein, we report a route to geminally alkylated azaphthalans based on a consecutive double desilylation−alkylation reaction and an application of this chemistry to the synthesis of the pyridone alkaloid, cerpegin.

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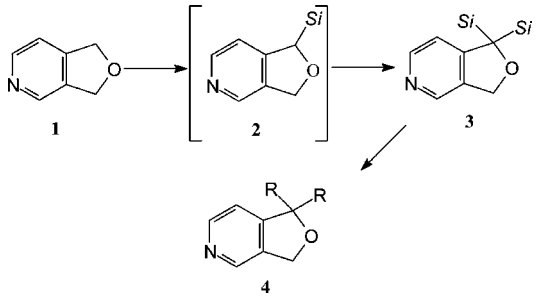
Our strategy toward geminally alkylated azaphthalans, e.g., **4** is outlined in Scheme 1. On the basis of the stabilization

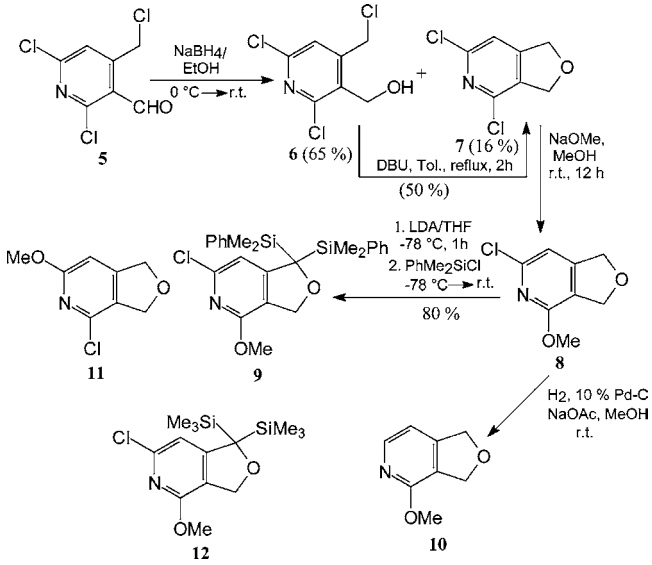
Scheme 1. Synthetic Strategy for Geminally Alkylated Azaphthalans



of a carbanion by an α-silyl group, it was envisaged that lithiation of monosilylated azaphthalan **2** and a followup silylation would lead to the introduction of the new silyl group on the same α-carbon (although it may require some kinetic [steric] balance). The resulting species **3**, upon fluoride ion-promoted cleavage of the two C−Si bonds and alkylation, would provide an efficient route to 1,1-dialkylated azaphthalans, e.g., **4**.

In this context, a model azaphthalan **8** was prepared from the chloro-substituted aldehyde **5**[8] by a standard synthetic protocol (Scheme 2). Thus, reduction of **5** with sodium

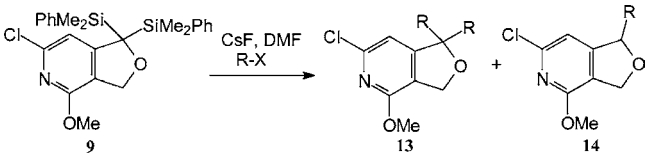
Scheme 2. Synthesis of Bissilylated Azaphthalans



borohydride in ethanol (0 °C → rt) yielded a separable mixture of alcohol **6** (65%) and azaphthalan **7** (16%). For the sake of convenience, the crude product mixture after sodium borohydride reduction was treated with DBU in toluene at reflux for 2 h to give only azaphthalan **7** (mp 75−76 °C). Exposure of **7** to NaOMe in methanol gave a single methoxy-substituted product (mp 59−60 °C) to which structure **8** was assigned on the basis of the following experiments. Reductive removal of chlorine in **8** (H_2, Pd−C, NaOAc, MeOH, rt) afforded **10**. In the ^{1}H NMR of **10** ($CDCl_3$), the appearance of a pair of doublets at δ 6.81 (J = 5.2 Hz) and 8.07 (J = 5.2 Hz) confirmed its structure, thus ruling out the alternative structure **11**. Evidently, selective displacement of one of the chlorine atoms flanking the nitrogen atom of pyridine ring of **7** by a methoxide nucleophile is interesting.[9] Treatment of azaphthalan **8** with 2 equiv of LDA in THF at −78 °C for 1 h and subsequent quenching of the resultant metalated product(s) with chlorodimethylphenylsilane (2.1 equiv) gave a disilylated azaphthalan **9** in one pot as a yellowish oil in 80% yield. The position of the silyl groups in **9** is based on a single-crystal X-ray structure determination[10] of the related bis-trimethylsilyl-substituted azaphthalan **12** (mp 95−96 °C), obtained in a very poor yield from **8** under similar metalation−silylation conditions.

At this stage, sequential introduction of two alkyl groups to **9** was studied using a tandem double desilylation−alkylation strategy (cf. Scheme 1). Thus, the treatment of **9** with 2 equiv of CsF and MeI in DMF at room temperature afforded **13** (R = Me) as the major product contaminated with only a minor amount of **14** (R = Me). In addition, the consecutive double desilylation−alkylation reaction was performed with other electrophiles, and the results are summarized in Table 1. A pure sample of **13** (R = Me) was

Table 1. Consecutive Double Desilylation−Alkylation Reaction



entry	R	yield of **13** + **14** (%)	**13**/**14**
1	Me−	70	75/25
2	CH_2=$CHCH_2$−	68	70/30
3	$PhCH_2$−	61	58/42

obtained by repeated preparative thin-layer chromatographic purification (silica gel, petroleum ether) of the mixture of **13** and **14** (R = Me).

It is pertinent to mention here that most of the references[4,7] cited earlier in this paper describe the difficulty of carbanion generation in the benzylic position(s) in phthalans. Since the presence of a nitrogen atom as in azaphthalans may improve the chances of carbanion generation at the desired site, there is a possibility that, in these cases (cf. **8**), a sequential double alkylation would work and save the need for the desilylative procedure.

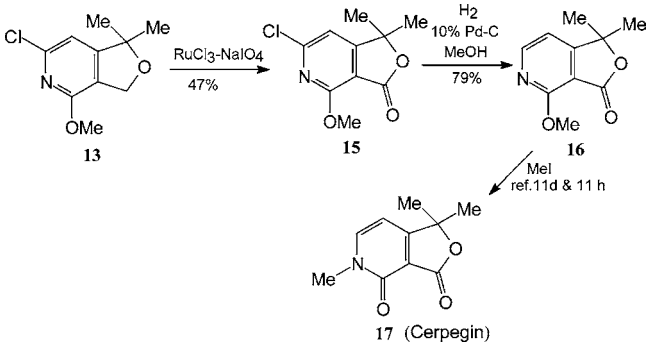
(8) Sarkar, T. K.; Basak, S. Unpublished results.

(9) At this point in time, we have no clear explanation for the regioselective displacement **7** → **8**.

(10) Unpublished work with Professor H.-K. Fun (Penang, Malaysia).

To address this issue, the monomethylated azaphthalan **14** (R = Me), contaminated with **8**, was made via the treatment of **8** with LDA (2 equiv) and subsequent exposure of the lithiated species to MeI. Further exposure of **14** (contaminated with **8**) to LDA and a followup treatment with methyl iodide did not give any dimethylated product. Also, treatment of **8** with sodamide in DMSO at ambient temperature led to uncharacterizable byproducts and no desired product, e.g., **14** (R = Me) was found to form. Moreover, replacement of the base in these reactions by $LiNH_2$ in liquid NH_3 failed to yield any **14** (R = Me) in our hands; instead, the starting material was returned practically quantitatively.

Scheme 3. Application of Geminally Alkylated Azaphthalans



We then realized that the present consecutive double desilylation−alkylation reaction could be applied to the synthesis of cerpegin[11] isolated from *Ceropegia juncea*, a plant used in traditional Indian medicine for its tranquilizer, antiinflammatory, analgesic, and antiulcer properties.[12] Thus, oxidation of geminally methylated azaphthalan **13** under $RuCl_3$−$NaIO_4$ conditions[13] gave **15** (47%) as a white crystalline solid (Scheme 3). Removal of the chlorine atom in **15** with hydrogen in the presence of 10% Pd−C and NaOAc gave **16** (79%), which has been previously[11d,h] converted to cerpegin **17** upon exposure to MeI. Thus, a formal synthesis of cerpegin has been completed.

In conclusion, this is the first report wherein two alkyl groups were introduced on the same α-carbon of azaphthalans in one pot by a consecutive double desilylation−alkylation reaction. Furthermore, this chemistry proved to be useful in a synthesis of the pyridone natural product, cerpegin.

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Supporting Information Available: Spectra for characterization of **6**−**9**, **12**, **13** (R = Me), **13** (R = allyl), and **16** and an X-ray picture of **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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