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Novel use of organosilanes and boranes in natural product synthesis

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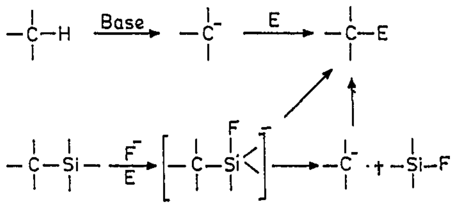
Abstract - Carbanions can be generated through fluorodesilylation which avoids strongly basic conditions of conventional methods. This forms the basis of an effective solution to the long standing problem of coupling phthalides with isoquinolinium salts. α-halogenated silanes afford carbene equivalents which are used for the synthesis of stilbenes, epoxides and cyclopropanes. This approach is especially useful for 2-phenylbenzazepines where the usual ring expansion procedures are not suitable. Similarly, oxoquinodimethane equivalents have been obtained and trapped to get isocoumarins and protoberiberine alkaloids.
Aryne generation has been accomplished, under non-basic and safe conditions, through thermolysis of o-silyl aryl sulphoxides. Finally, use of silicon and related elements for dipole stablised carbanion formation has been investigated and applied to synthesis of natural products.

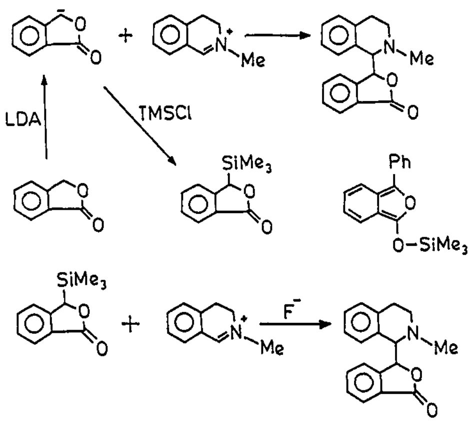
Over the last decade or so organosilanes have become quite important in synthetic practice. One important use is for generation of carbanions, or their pentavalent silyl equivalents, by reaction with strong silaphiles like F^-. The procedure avoids harsh basic conditions and can be used in the presence of sensitive electrophiles, substrates or products (Scheme 1). We have taken advantage of this to couple pthalides with isoquinolinium salts, a reaction which proceeds poorly under conventional carbanion generation conditions. A number of pthalide isoquinoline alkaloids were thus synthesised in good yields. For comparison, the earlier obtained yields are shown in parenthesis. The starting silyl compounds could be obtained in a straightforward manner, without any o-silylation observed with 3-arylpthalides (Schemes 2 and 3).

Fluorodesilylation is specially useful for forming carbanions from substrate having suitably placed leaving groups. In such a case, the loss of the electrofuge from the carbanion leads to diradicaloids, or their equivalents, which can be trapped to obtain a variety of cyclic compounds. The nature of the diradicaloid formed depends upon the original juxtaposition of the silyl group and the electrofuge (Scheme 4).

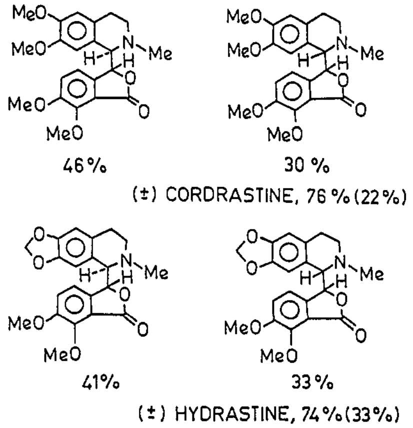
Scheme 1



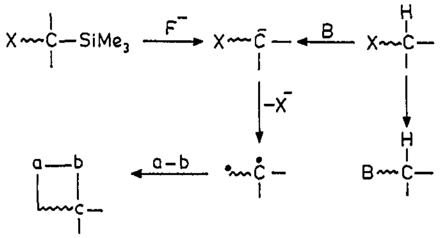
Scheme 2



Scheme 3



Scheme 4



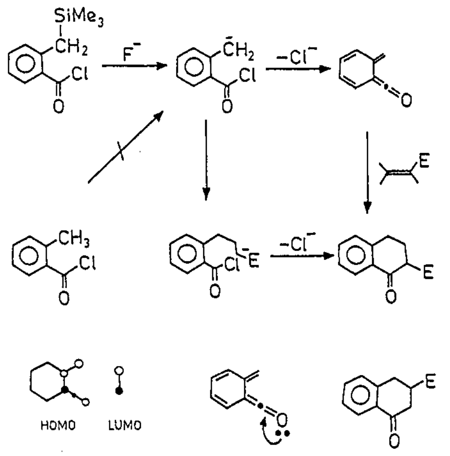
Such a reaction has been used earlier to form quinodimethanes. We were interested to see if the procedure can be extended to keto quinodimethanes to procure additionally functionalised products. Treatment of silyl toluic chlorides 1 with F^- in presence of electron deficient alkenes indeed furnished 2-substituted 1-tetralones. The observed regioselectivity conforms to a stepwise addition or HOMO-LUMO interaction in a $\pi^4 + \pi^2$ addition (Scheme 5).

Reaction with F^- in absence of dienophiles gave two dimeric products suggestive of keto-quinodimethane intermediacy. However, attempted intramolecular trapping failed (Scheme 6).

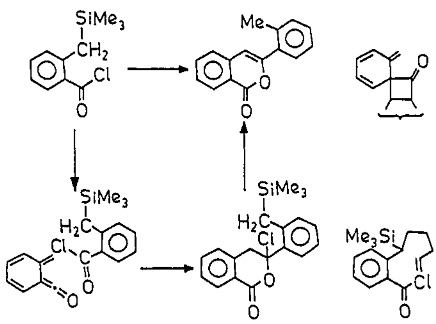
Treatment of 1 with F^- in the presence of carbonyl compounds gave dihydroisocoumarins. Tetrahydroberberine alkaloids were obtained similarly, by using dihydroisoquinolinium salts as the trapping agents (Schemes 7 and 8).

If the silyl and the leaving group are present on adjacent carbons, a double bond could be formed. This is the basis of a method for benzyne generation by thermolysis of 2. Here the sulphoxide serves as an intramolecular silaphile. Some typical benzyne reactions were carried out. Compared to other procedures for forming benzynes under neutral conditions, this method is safe and the starting material is easily accessible through directed metalation of diphenyl sulphide (Scheme 9).

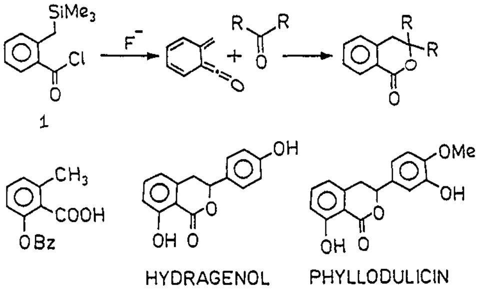
Scheme 5



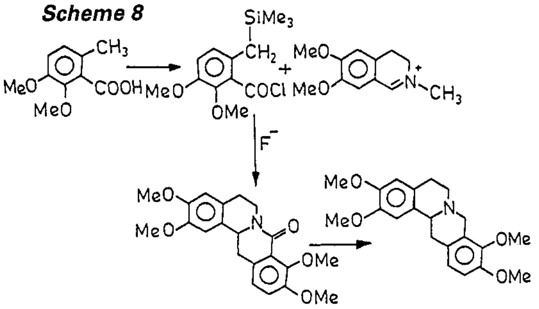
Scheme 6



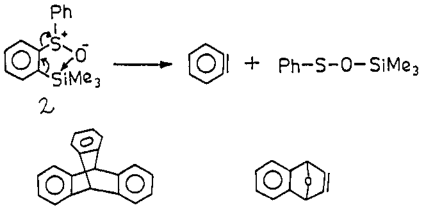
Scheme 7



Scheme 8

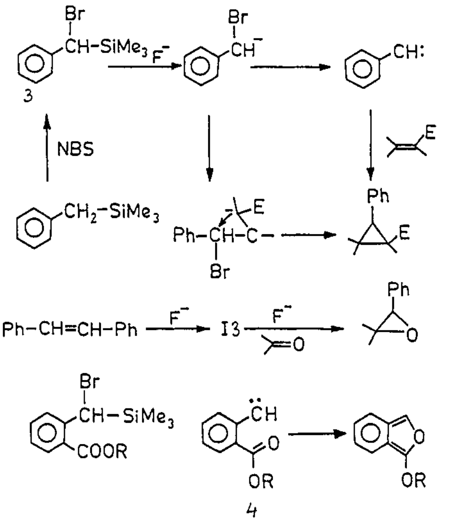


Scheme 9



L. CASTEDO AND E. GUITIAN, STUDIES IN NATURAL PRODUCT CHEMISTRY, VOL. 3, PART B, ED. ATTA-UR-RAHMAN, ELSEVIER, AMSTERDAM, 1989.

Scheme 9



α-Halogenated silanes were found to serve as good precursors of carbenoids. Thus treatment of 3 with F⁻ in presence of electron deficient alkenes and carbonyl compounds afforded cyclopropanes and epoxides respectively. In absence of external traps, stilbenes were formed in excellent yields. For this reaction a two-step mechanism is favoured as the expected carbene capture by the adjoining carbethoxy group was not observed with 4 (Scheme 10).

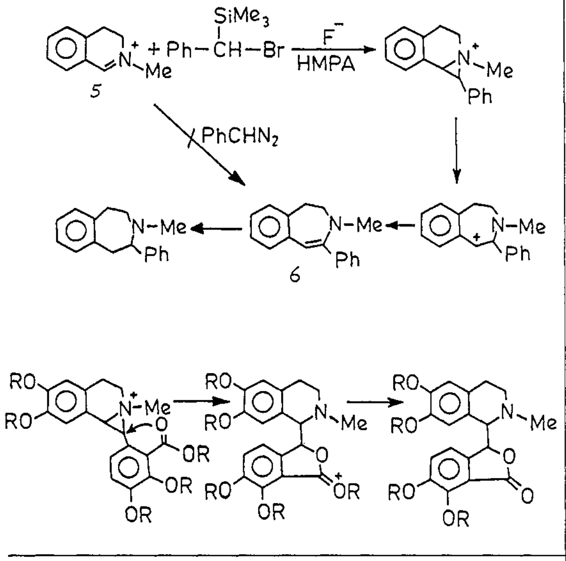
Finally, the procedure was applied for the synthesis of pharmacologically important 3-phenylbenzazepines since ring expansion of 5 with phenyldiazomethane is known to fail. Heating an equimolar mixture of 5 and 3 with a slight excess of CsF in HMPA gave 6 in good yield. The reaction is presumed to proceed through an aziridinium intermediate. If an orthocarbethoxy group is present the reaction adopts a different course to give pthalide isoquinoline alkaloids (Scheme 11).

The above discussed routes to 1-substituted isoquinoline alkaloids entail addition of a nucleophile to 5. An alternate approach envisages reaction of an electrophile with the carbanion 7. However, N-alkyl tetrahydroisoquinolines are known to get deprotonated preferentially at position 4. In fact, direct α-metalation of amines is inefficient generally and an indirect route through stananes was developed. However, the starting materials in the above procedure are not easily accessible (Scheme 12).

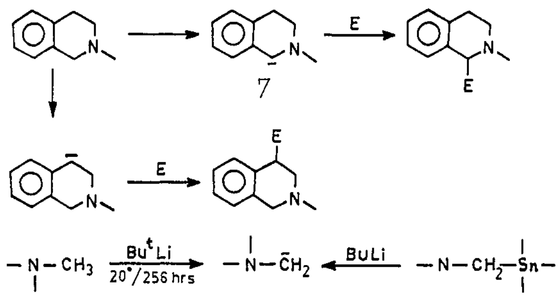
Since elaboration of amines through α-substitution is a matter of wide interest and it can be done most effectively through azacarbanions, numerous methodologies have been developed to facilitate their generation. These are based on temporary attachment of a group (G) which provides anionic stabilisation through chelation or ion-dipole interaction (Scheme 13) (ref. 1 to 5).

We thought of exploiting, for this purpose, the propensity of silicon d orbitals to accept a lone pair from an adjacent nitrogen atom. The dipole thus generated could lead to carbanion stabilisation. However, this approach was not successful, nor was that based on chromium carbonyl complex formation reported by Davies (Scheme 14).

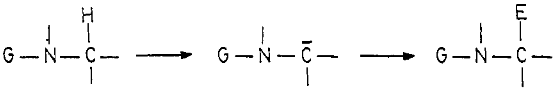
Scheme 11



Scheme 12



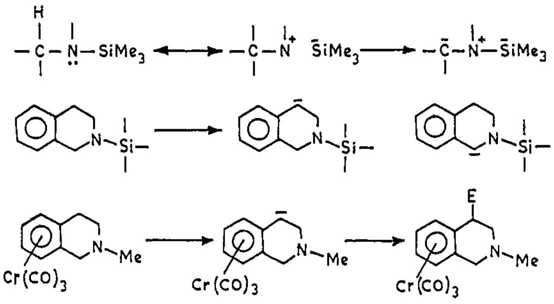
Scheme 13



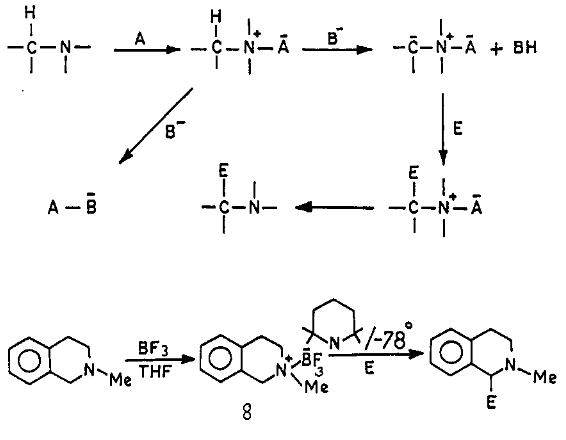
G-N- STABILISES CARBANION BY DELOCALISATION, CHELATION OR ION-DIPOLE INTERACTION.

G = HINDERED AMIDES, CARBAMATES, CABOXYLATES, NITROSOAMINE, FORMAMIDINE, N-OXIDES ETC.

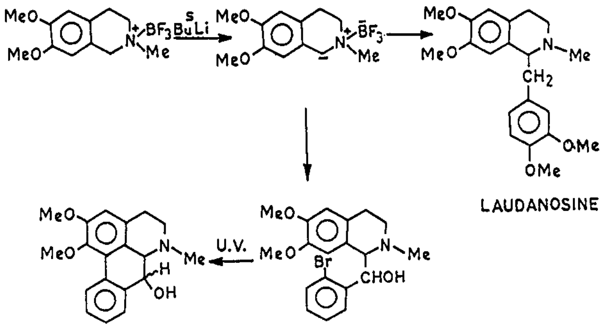
Scheme 14



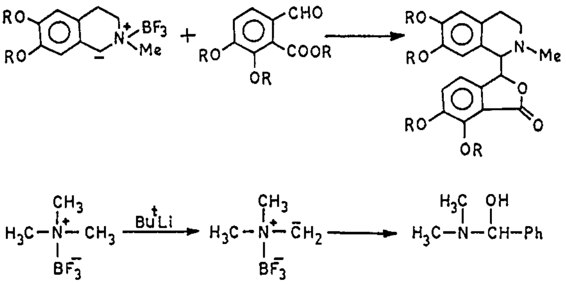
Scheme 15



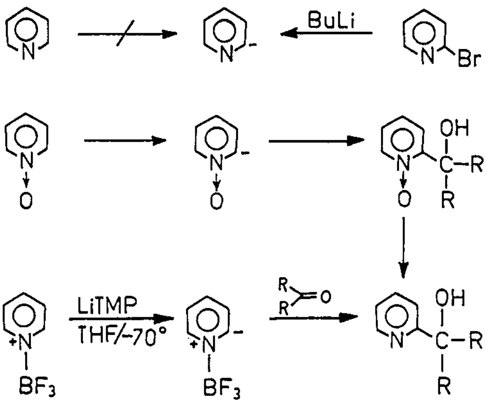
Scheme 16



Scheme 17



Scheme18



At this stage we approached the problem from an altogether different angle. Attachment and removal of groups securely appended at nitrogen involves effort which can be avoided if lewis acid complexation provides the requisite carbanion stabilisation. For the success of this approach it would be necessary to suppress likely reaction of the complex, especially attack of the base at the lewis acid centre or the α-carbon. It was heartening to find that complex 8 on treatment with LiTMP followed by an electrophile gave 1-substituted products in good yields (Scheme 15).

In case of alkoxy substituted quinolines, it was necessary to use a stronger base for metalation, i.e., sec.butyl lithium was needed. Using these conditions, a number of alkaloids were synthesised. Further, azacarbanions devoid of benzylic stabilisation could also be formed with t-butyllithium (Schemes 16 and 17).

α-Metalation of pyridine is known to proceed poorly and bromopyridines are used as precursors. An alternate route involving N-oxide formation-deoxygenation has been devised for α-substitution. We found that treatment of Py.BF_3 with LiTMP followed by carbonyl compounds gives corresponding alcohols in excellent yield (Scheme 18).

The concept of stabilising azacarbanions by lewis acid complexation is simple but, to our knowledge, has not been explicitly formulated earlier. Its scope, including use of chiral lewis acids and generation of 1,3-dipoles from imines, is currently under investigation in our laboratories.

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