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DIRADICAL CYCLIZATION METHODOLOGIES. MODEL STUDIES PROBING THE APPLICATION OF PHOTOINDUCED-ELECTRON TRANSFER PROCESSES IN SYNTHETIC ROUTES TO THE PROTOBERBERINE AND SPIROBENZYL ISOQUINOLINE ALKALOIDS

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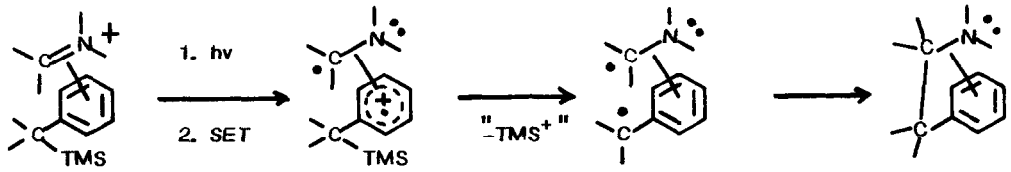
Abstract. Model studies have demonstrated that diradical cyclization processes, promoted by excited state electron transfer-desilylation pathways, serve as novel methods for construction of ring systems found in members of the protoberberine and spirobenzyl isoquinoline alkaloid families.

In previous studies, we have demonstrated how sequential electron transfer-desilylation pathways[1] serve as the basis for photochemical processes used to generate diradical intermediates as part of efficient methods for heterocyclic-ring construction.[2] In more recent efforts, we have uncovered new carbon-carbon bond forming processes, occurring upon irradiation of arene-iminium salt systems which follow this same mechanistic sequence.[3] In these cases, excitation of either the iminium salt or the arene components which contain benzylic trimethylsilyl-substituents initiates the sequential electron transfer-desilylation process outlined in eq. 1. The remarkably high chemical and quantum efficiencies of intramolecular photocyclization reactions promoted in this way suggested that this "diradical cyclization" methodology might be applicable to the construction of key N-heterocyclic and carbocyclic ring systems found in selected natural product families.[4]

A preliminary evaluation of a number of factors suggested that this methodology might be suited to the synthesis of members of the protoberberine and spirobenzyl isoquinoline alkaloid classes which share the respective fused- and spiro-tetracyclic parent ring systems represented by **3** and **4**.[6] In a conceptual sense, the basic ring systems common to these natural product families can be envisaged as being generated through synthetic routes in which the tetrahydroiso-

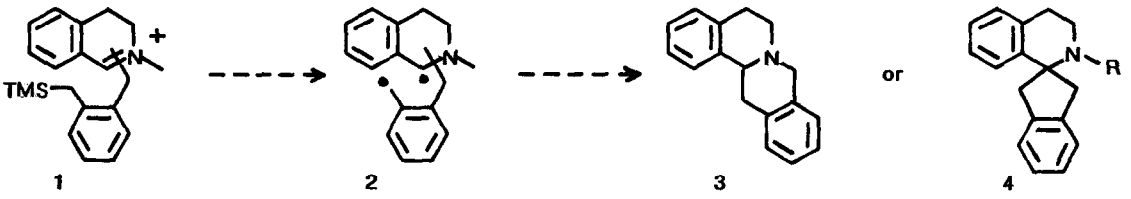


(1)

quinoline and o-xylyl units are joined at appropriate positions by use of C-C and C-N bond forming methods. The initial C-N and C-C bond forming steps employed to unite these fragments in respective protoberberine and spirobenzyl isoquinoline synthetic strategies following these designs should be straightforward owing to the variety of charge affinity patterns indigenous to 3,4-dihydroisoquinoline, o-xylyl halide and related systems. Diradical cyclization methods would then be applied to create the fused-heterocyclic or spiro-carbocyclic C-rings in the target natural product structures.

These concepts are manifested in strategies for protoberberine and spirobenzyl isoquinoline alkaloid ring construction outlined in Scheme 1. Excited state initiated electron transfer-desilylation sequences would be involved in the generation of diradical intermediates **2** from the corresponding dihydroisoquinolinium salts **1** in routes to the respective tetracyclic amines **3** and **4**. The results of recent photochemical investigations with the hydroisoquinolinium perchlorate salts **6**, **10**, and **11** described below indicate that the approaches embodied in this scheme are viable and represent new and potentially efficient methods for isoquinoline alkaloid synthesis.[7]

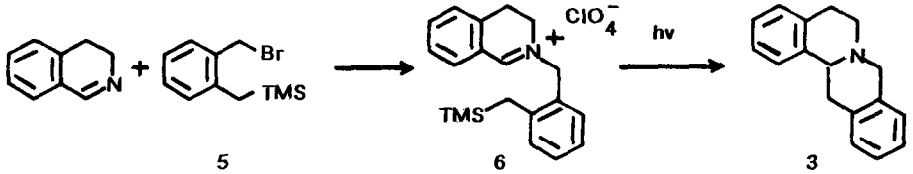
Scheme 1.



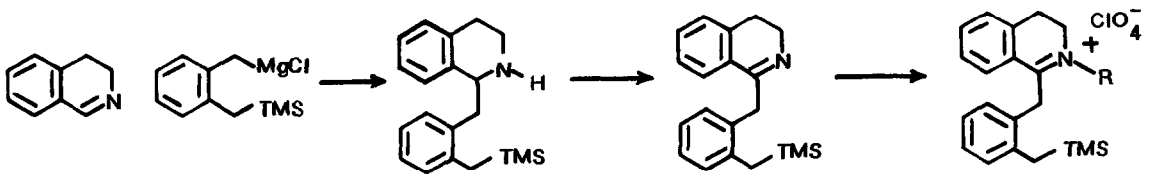
1 **2** **3** **4**

The N-o-xylyldihydroisoquinolinium salt **6** was formed by the silver ion assisted N-alkylation of 3,4-dihydroisoquinoline with o-(trimethylsilylmethyl)benzyl bromide **5** ($AgClO_4$, MeCN, 25°C; recryst MeOH; mp 140-142°C; UV(MeCN) max 285nm; 64%). Irradiation (λ>270nm) of a MeCN solution of this substance followed by aq. $NaHCO_3$ work-up, flash chromatography on silica-gel (25% Et_2O-hexane) and recrystallization (Et_2O) provided the known[9] tetracyclic product, berbine (**3**) (mp 80-82°C, lit[9] mp 85°C) in 80% yield.[10]

The sequence used for preparation of the 1-benzyl-2-methyldihydroisoquinolinium perchlorate **10** began with the addition of o-(trimethylsilylmethyl)benzyl magnesium chloride **7** (from the corresponding chloride)[8] to 3,4-dihydroisoquinoline (Et_2O, 25°C, 75%). The formed tetrahydroisoquinoline **8** was then converted to its dehydro derivative **9** by N-chlorination (NCS, Et_2O) and dehydrochlorination (KOH, MeOH, 88% overall). Silver ion assisted methylation ($AgClO_4$, MeI, MeCN; recryst MeOH, 66%) of **9** provided the desired perchlorate salt **10** (mp 156-158°C; UV(MeOH) max 283

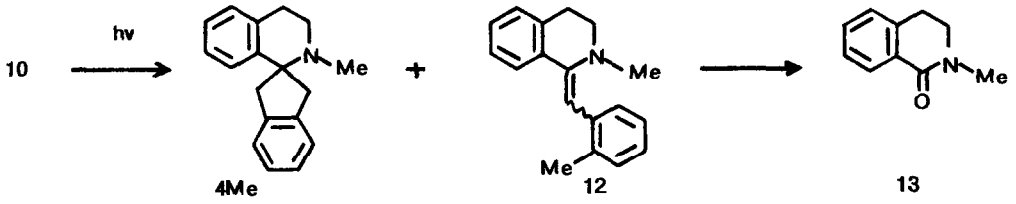


5 **6** **3**



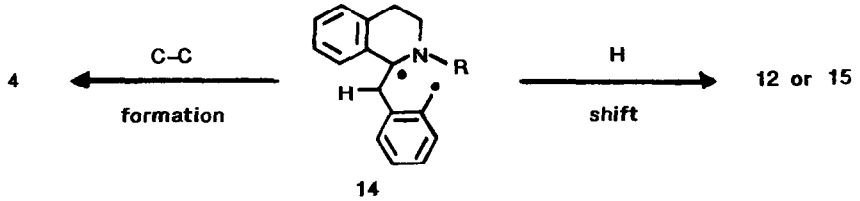
7 8 9 10 (R=Me) 11 (R=H)

nm). In contrast to the high efficiency observed for photoreaction of 6, photocyclization of **10** proved to be an extremely low yielding process. Accordingly, irradiation (λ>270nm) of **10** in MeOH or MeCN followed by aqueous $NaHCO_3$ work-up and silica-gel chromatography (5% MeOH-$CHCl_3$) led to production of the target spirocyclic-amine **4Me**[10] in an 8% yield. The major product (ca. 75%) generated in this process, as detected by ^{1}H-NMR spectroscopic analysis of the crude photolysate,[11] is the unstable desilylated-enamine **12**. This material undergoes oxidative decomposition upon chromatographic purification to provide in trace quantities the tetrahydroisoquinol-1-one derivative **13**.

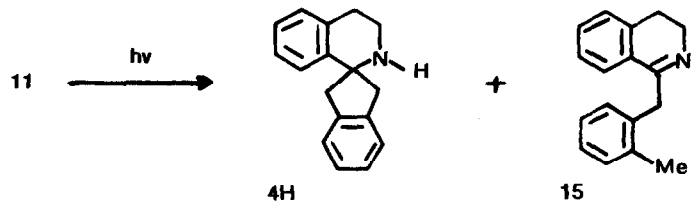


4Me 12 13

A mechanistic analysis of these results has led to a superior procedure for affecting spirobenzyl isoquinoline ring construction. The product ratio obtained from reaction of the N-methyl salt **10** can be understood in terms of a pathway involving partitioning of the diradical **14** (R=Me) by hydrogen shift and C-C bond forming processes. We reasoned that the presence of the N-methyl substituent in **14** might lead to more favorable enamine **12** production through a steric effect causing formation of the adjacent quaternary center to be a high energy route. Thus, a diradical **14** (R=H) which lacks a bulky N-substituent might be more disposed toward cyclization. This proposal was tested through studies with the N-H homolog **11**, which was generated in MeCN solution by treatment of **9** with 4 eq. of $HClO_4$ (UV(MeCN)max 277 nm). Irradiation (λ>270nm, MeCN) of **11** followed by aq. $NaHCO_3$ work-up and flash alumina chromatography[12] ($CHCl_3$) provided the spirocyclic product **4H**[10] (43%) along with the desilylated dihydroisoquinoline **15**[10] (9%). Thus, it appears that the yield of this spirocyclization process is indeed controlled by the nature of the N-substituent.



14



4H 15

The observations reported above suggest that "diradical cyclization" methodologies, promoted by excited state electron transfer-desilylation sequences, represent new and potentially useful strategies for protoberberine and spirobenzyl isoquinoline alkaloid ring construction.

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References and Notes.

(1) Ohga, K.; Yoon, U.C.; Mariano, P.S., J. Org. Chem., **1984**, 49, 213.

(2) Tiner-Harding, T.; Ullrich, J.W.; Chiu, F.T.; Chen, S.F.; Mariano, P.S., J. Org. Chem., **1982**, 47, 3360; Brumfield, M.A.; Quillen, S.L.; Yoon, U.C.; Mariano, P.S., J. Am. Chem. Soc., **1984**, 106, 6855.

(3) Lan, A.J.Y.; Quillen, S.L.; Heuckeroth, R.O.; Mariano, P.S., J. Am. Chem. Soc., **1984**, 106, 6439.

(4) Studies probing the use of this methodology in harringtonine[5a] and erythrina[5b] alkaloid synthesis are currently underway.

(5) a) Chiu, F.T.; Ullrich, J.W.; Mariano, P.S., J. Org. Chem., **1984**, 49, 228; b)Unpublished results of Ahmed-Schofield, R.; and Mariano, P.S.

(6) Shamma, M., "The Isoquinoline Alkaloids", in Organic Chemistry Series, ed. Blomquist, A.T.; Wasserman, H., Vol 25 pp 268-314 and 380-398, Acad. Press, **1972**.

(7) This approach might also be useful as a method for aporphine and proaporphine isoquinoline alkaloid synthesis.

(8) The bromide **5** was prepared by a sequence involving bis-trimethylsilylation of o-methylbenzyl-alcohol (3 eq nBuLi, Et_2O; TMSCl), O-TMS hydrolysis (1M H_2SO_4, THF) and bromination (Ph_3P, CBr_4, Et_2O) in an overall yield of 68%. The intermediate alcohol in this sequence was transformed to the chloride precursor of **7** by reaction with Ph_3P in CCl_4 (90%).

(9) Chakravarti, S.N.; Hayworth, R.D.; Perkin, W.H., J. Chem. Soc., **1972**, 2275.

(10) All of the spectroscopic properties of this substance were in full accord with its assigned structure.

(11) Characteristic ^{1}H-NMR resonances for **12** are δ($CDCl_3$) 2.24 (ArMe), 2.58 (N-Me), 5.95 (C=CH).

(12) Woelm N 32-63 um alumina was used for this purpose.

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