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Photoinduced electron transfer in organic synthesis: Application to alkaloids

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Abstract: An effective, mild and direct route for regioselective iminium cation generation from tertiary amines and alkaloids is developed using a single electron transfer SET photocatalytic process. By modifying the various factors controlling the outcome of this process (sensitizer, solvent, added salt and nucleophile agent) some interesting nucleophilic reactions, particularly intramolecular cyclisation and a regioselective synthesis of 2-cyano-1,2,5,6-tetrahydropyridines, have been found and exploited in indole alkaloid synthesis.

The discovery and development of new photochemical processes has led to a considerable increase in the use of photochemistry for the synthesis of complex molecules. Increasing research activity in single electron transfer (SET) processes has focused not only on mechanism but also in discovering new synthetically useful reactions. Of particular interest is the use of iminium cations which are important electrophiles and are frequently used for preparing biologically active nitrogen heterocycles. In the absence of convenient procedures for generating regiospecific iminium cations for synthetic utilizations, a SET photocatalytic regioselective general procedure for *in situ* generation of iminium cation from ^{1}acceptor*-amine pairs has been developed. The remarkable advantages of this methodology are presented in connection with the synthesis of various biologically active alkaloids. Photoinduced electron transfer (PET) reaction from electron acceptor sensitizer*-amine complexes produces a radical anion and planar amine radical cation (1,2). The overall thermodynamics of the reaction unambiguously and exclusively are in favour of electron transfer for many sensitizer-amine pairs. The rate constants are sensitive to electronic energies and reduction potentials of the sensitizers and oxidation potentials of the amines, as well as the structures of both sensitizers and amines (3). In general, amines with low ionization potentials such as tertiary amines are the most effective electron donors. Among these factors, the reactivity of PET reaction is dependent on solvent polarity (4) and, the question is whether the primary intermediate is a solvent separated ion pair (SSIP) or a contact ion pair (CIP). The SSIP is more stable in polar solvents (5) and in these solvents the highly solvated ion radicals separate to form free radical ion pairs (FRIP) (6). The most general pathways available to these reactive amine radical cation intermediates is probably the fragmentation to ions and neutral radicals. In particular, fragmentation of cation radicals leading to radical and cationic species is a well studied subject (7). A number of studies have demonstrated that amine radical cation undergo efficient

proton loss and carbon-carbon bond cleavage at sites adjacent to nitrogen (8). Proton loss from simple tertiary amines to generate an α-amino alkyl radical is a common feature. Thus, it was envisaged that the SSIP formed between 9,10-dicyanoanthracene (DCA)-tertiary amine pair will dissociate into FRIP in the medium of high polarity such as acetonitrile. In the presence of molecular oxygen, the SET process is a photocatalytic general method for iminium cation generation (Fig. 1).

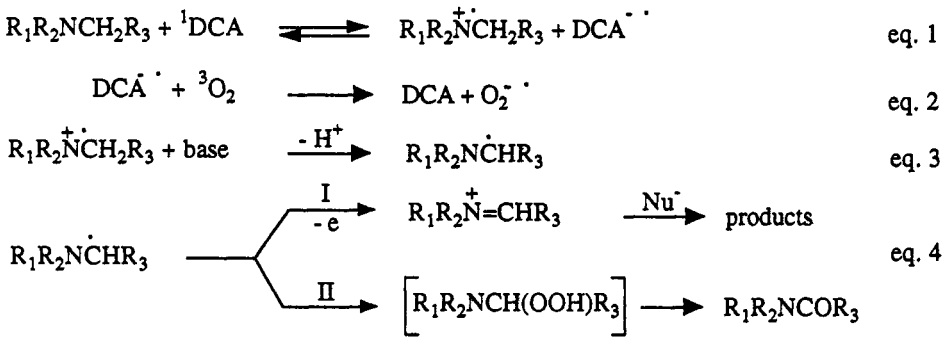


Fig. 1 Mechanism of iminium cation formation.

In acetonitrile, all tertiary amines quench DCA fluorescence at the diffusion controlled rate (9) and the amine radical cation is generated by electron transfer from amine to ^{1}DCA (eq. 1). From the respective reduction potentials of ground state oxygen and DCA (E ($O_2/O_2^{-\cdot}$) = -0.78 V, E (DCA/DCA$^{-\cdot}$) = -0.89 V (10) the cyano arene radical anion transfers an electron to molecular oxygen (eq. 2). This step should reduce the rate of back electron transfer to the amine radical cation and is at the origin of the photocatalytic process as already proposed by Davidson (11) and Foote (12) some time ago. Finally, deprotonation of the amine radical cation, possibly by superoxide anion (13) or cyano arene radical anion, gives rise to an α-amino radical (14) which can react in two ways:

- either by electron loss because of its reduced ionization potential (15), probably due to the cyano arene radical anion, giving an iminium ion which is subsequently trapped with an internal nucleophile allowing the obtention of products (eq. 4, step I).
- or, in the absence of an internal nucleophile, by recombination with an oxygen species (O_2, $O_2^{-\cdot}$ or $HO_2^{\cdot}$) giving a N-carbonyl derivative, probably via an α-hydroperoxy amine (step II).

Therefore, it was anticipated that iminium cation thus generated by this photocatalytic sequence from nonsymmetrical tertiary amines will be highly regiospecific and will depend upon the factors that influence the orientation of α-deprotonation from initially formed amine radical cation. Kinetic acidity which is subject to stereoelectronic factor (16), solvent polarity (17), basicity of oxidizing agents and oxidation potentials of amines are some of the important parameters which may influence the site of deprotonation of nonsymmetrical amine radical cation.

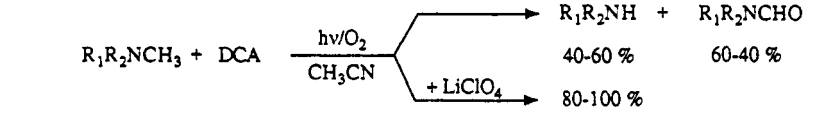
This report summarizes our main results in the alkaloid field through the generation of regioselective iminium cations from tertiary amine radical cations. Particularly, by modifying the various factors controlling the outcome of this process: sensitizer, solvent, added salt and nucleophile agent.

SET Promoted Photo N-Demethylation

Photooxidative N-demethylation of tertiary amines was undertaken because this reaction with chloroformate reagents (18), leads generally to limited yields and the toxicity of the required reagents is a real drawback, although these methods may be in some case efficient. In addition, oxidative N-demethylation of tertiary amines is relevant as an enzymatic model for the cytochrome P-450 specific reaction (19).

We carried out a mild and useful alternative photochemical method for N-demethylation of some alkaloids which leads to important intermediates for the preparation of biologically active analogues (14). This method is based on a very interesting recent finding that added salts can greatly affect PET reactions (17) as reported by Mizuno, Otsuji and coworkers (20) a most striking example being the enhancement of photooxidation of biphenyl derivatives by the addition of $Mg(ClO_4)_2$.

In a similar way, we have shown that the irradiation of an acetonitrile solution of the amine in the presence of a catalytic amount of DCA, under oxygen bubbling, affords both nor and N-formyl derivatives in variable yields. In the presence of an added salt such as $LiClO_4$ or $Mg(ClO_4)_2$, with an optimum of concentration (0.25 to 0.5 equiv.), the nor-derivative is obtained highly efficiently (Fig. 2).



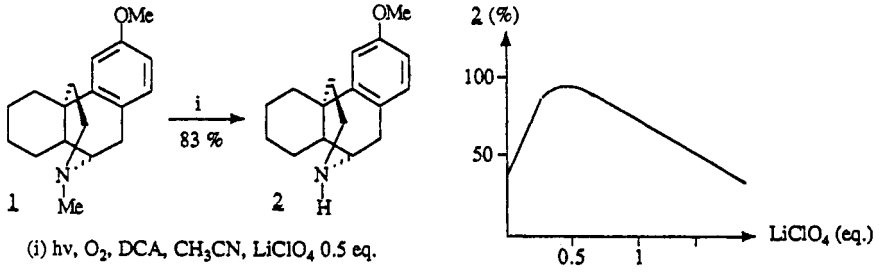


Fig. 2 Salt effects in the photochemical N-demethylation of tertiary amines.

In a typical example, a solution of dextromethorphan 1 (2 mmol) and DCA (0.02 mmol) in acetonitrile (50 ml) with variable amounts of $LiClO_4$ (0.1 to 5 equiv.) is irradiated under oxygen bubbling for 30-90 minutes with a 500 W high-pressure Hg lamp ($\lambda > 420$ nm) at 20°C. After reaction, which is monitored by t.l.c., the products are separated by flash chromatography.

A typical curve (shown in Fig. 2) reveals the salt concentration dependence of nor-dextromethorphan 2 formation and its dramatic increase for 0.5 equiv. salt concentration. A similar effect was observed for several other N-methylated alkaloids such as codeine, tropinone, tropine, atropine, scopolamine, etc...(14). These photochemical N-demethylation reactions are believed to proceed from an initial electron transfer along the general sequence depicted in Fig. 1. The effects of added salts is to increase the overall rate of photooxidation by a factor 2 to 3 and to favour step I over step II (Fig. 1, eq. 4). Acceleration of the reaction appears to be keeping with the results of the literature (21) which have shown that added salts increase both the proportion of a radical ion pair

dissociation, via pair exchange, and the lifetime of radical ions, slowing down the rate of back electron transfer. The more unexpected orientation effect arises probably from the stabilisation of the iminium ion by an ionic association which favours its formation from the neutral α-amino radical.

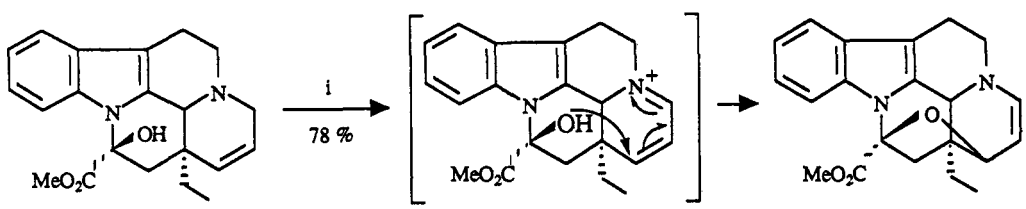
From these results we decided to synthesize a specific sensitizer which could mimic cytochrome P-450 selective reactions: the dication N,N^1-dimethyl-2,7-diazapyrenium (DAP^{2+}, $2BF_4$-).

The dication DAP^{2+}, $2BF_4$- is an electron acceptor ($E(DAP^{2+}/DAP^{+\cdot}) = -0.43$ V) (22) which can be excited by visible light, not absorbed by amines. Thus, the PET oxidation of our N-methylated alkaloids models in the presence of a catalytic amount of DAP^{2+} gave exclusively nor-products in excellent yields (85-95%). The operating conditions of a typical procedure are similar to those of the reaction using DCA and added salts (23). The specificity of this sensitizer is probably connected to both its powerful electron acceptor and being a salt.

The selectivity of these N-demethylations can be explained by stereoelectronic factors. Since the deprotonation step from amine radical cation required the overlap of half vacant hydrogen p-orbital with incipient carbon radical p-orbital (16), the stereoelectronic effect forces the generation of least substituted α-amino radical and thus regioselective iminium cation from these substrates.

SET Photocatalytic Hemisynthesis of criocerine

The solvent can affect PET reactions in a variety of ways and, particularly, solvent effects reveals interesting features in product distributions. This property was used in the hemisynthesis of the alkaloid criocerine from the Δ^{14}-vincine, an analogous of the cerebrovascular vincamine. It was anticipated that the PET reaction will produce a conjugated iminium intermediate and, the presence of hydroxide group as internal nucleophile was expected to trap the iminium ion to give the heterocyclic derivative (Fig. 3).



Δ^{14}-vincine (i) hv, O_2, DAP^{2+}, CH_2Cl_2 criocerine

Fig. 3 Hemisynthesis of the criocerine

Thus, the irradiation of an acetonitrile (ϵ=37.5) solution of Δ^{14}-vincine in the presence of a catalytic amount of DAP^{2+}, under oxygen bubbling, affords a complex mixture of products from which the criocerine was obtained in poor yield (15%). A similar procedure carried out with dichloromethane (ϵ=9) as solvent leads efficiently to the criocerine (78%). This result can arise by a cage intramolecular cyclization between the hydroxide group and the iminium ion formed from a polar exciplex or CIP in non polar solvent. Under these conditions the sensitizer radical anion is potentially much reactive with the amine radical cation (24).

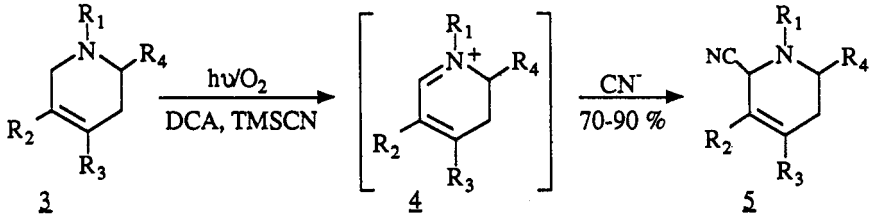
SET Regioselective Photocatalytic Synthesis of 2-Cyano-1,2,5,6-tetrahydropyridines. Applications in indole alkaloids

There is continuous interest in α-aminonitriles mainly because they are intermediates in convenient preparative methods for obtaining nitrogen-containing heterocycles. Specifically, 2-cyano-1,2,5,6-tetrahydropyridines, which are versatile synthetic equivalents of 5,6-dihydropyridinium salts, are potentially powerful synthons for the preparation of functionalized piperidines as one can envisage successive control over three of the ring carbon centres (C-2,3,4). In contrast to the unstable 5,6-dihydropyridinium salts, which can exist only under a very restricted set of conditions (i.e. acidic media), their cyano adducts are readily isolable entities.

The only chemical preparation of these α-amino nitriles make use of the classical modified Polonovski reaction[25], i.e. TFAA treatment of the 1,2,5,6-tetrahydropyridines *N*-oxides followed by cyanide trapping. This potential reactivity has since been exploited in a number of syntheses, particularly in the indole alkaloid area[26]. Nevertheless, the Polonovski protocol suffers from several drawbacks : the necessary acidity of the medium during the formation of the α-amino nitrile is a problem when further *in situ* reactions are envisaged with carbon nucleophiles and other organometallic reagents.

An alternative method to circumvent these drawbacks is the SET photocatalytic reaction which allows the regioselective formation of 2-cyano-1,2,5,6-tetrahydropyridines under mild conditions.

In a typical procedure, irradiation of acetonitrile solution of N-alkyl-3-piperidines 3 and trimethylsilyl cyanide (TMSCN) as cyanating agent, in the presence of a catalytic amount of DCA and under oxygen bubbling, affords the endocyclic α-amino nitriles 5 in fair yields (Fig. 4) (27, 28).



R_1=Me, Bn, $CH(CO_2Me)_2$, tryptophyl R_3=H, Me, tBu

R_2=H, Me, Et, OBn R_4=H, Me

Fig. 4 Regioselective photocatalytic synthesis of 2-cyano-1,2,5,6-tetrahydropyridines.

When N-alkyl substituants are Bn, CH_2CO_2Et or $CH(CO_2Me)_2$, it is noteworthy that these results are in accord with neither a simple steric nor a kinetic acidity effect. In all cases, the SET photocatalytic method generates the thermodynamically favoured endocyclic iminium ions. In addition, our first attempts have shown that TMSCN is a superior trapping agent for iminium intermediates (29) and it also displays a suitable protection towards enamine moieties. Therefore, these results have been extended to regioselective synthesis of 2-cyano-N-tryptophyl-Δ3-piperidines which can be used as synthons for a general approach to the construction of complex alkaloids (30).

A mild and efficient synthesis of some indoloquinolizidine alkaloids through a Pictet-Splenger reaction applied to these α-amino nitriles generated *in situ* has been carried out. Thus, following the

preceding protocol, after complete disappearance of the starting tetrahydropyridine 6, aqueous HCl 1 N is added to the resulting reaction mixture which is stirred for 3 hours at 50-60°C under argon atmosphere. After usual treatment, the tetracyclic indoloquinolizidine 7 is separated by flash chromatography (Fig. 5).

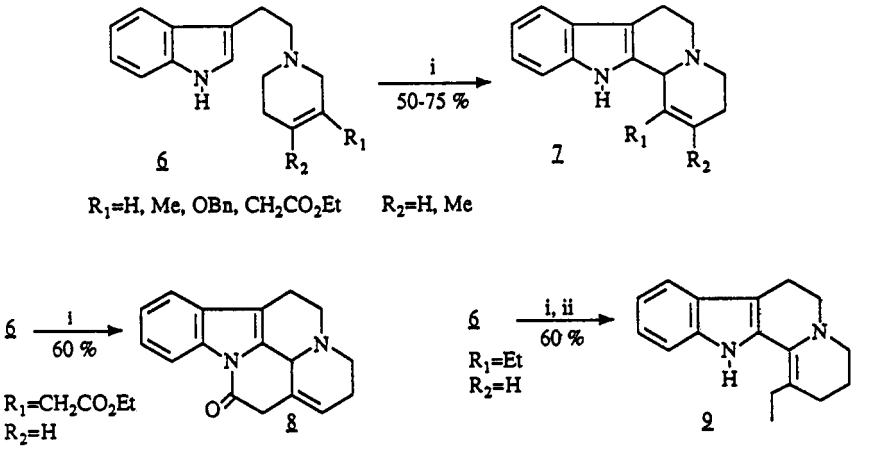


Fig. 5 Synthesis of indoloquinolizidine alkaloids from 2-cyano-1,2,5,6-piperidines.

When the R_1 substituent is CH_2CO_2Et, the α-amino nitrile intermediate leads to the tetracyclic derivative 7, which spontaneously cyclizes to the pentacyclic eburnane type alkaloid 8. When R_1 is an ethyl group, by isomerization of the double bond of the tetracyclic intermediate 7, this procedure constitutes a new practical synthetic entry to the so-called Wenkert's enamine 9 (31) a key intermediate for the preparation of several clinically useful antihypertensive eburnane alkaloids (32).

The results presented in this report demonstrate the development of a new concept for the synthesis of reactive iminium cations, which has proved to be very useful in the synthesis of biologically active alkaloids, photocatalytic process using a SET. Thus, it is expected that these new methodologies will attract much attention in synthetic design of alkaloids and other heterocycles.

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