PHOTOAMINATION DIRECTED TOWARD THE SYNTHESIS OF HETEROCYCLIC COMPOUNDS

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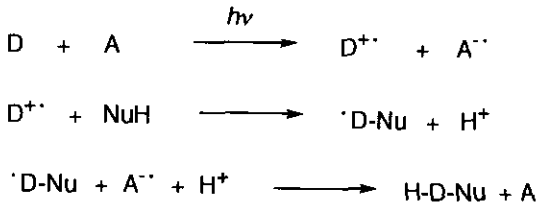
Abstract — This paper reviews the recent author's studies on the photoamination *via* electron transfer which were applied to the introduction of the amino group to C-C double bonds of several kinds of the substrates involving arenes, stilbenes, and benzo[*a,d*]cycloalkenes. The aminated products were used as the precursors for the synthesis of the heterocyclic compounds involving benzylisoquinolines, aporphines, isopavines, dibenzo[*a,d*]cycloheptenimines, and oxazepines.

INTRODUCTION

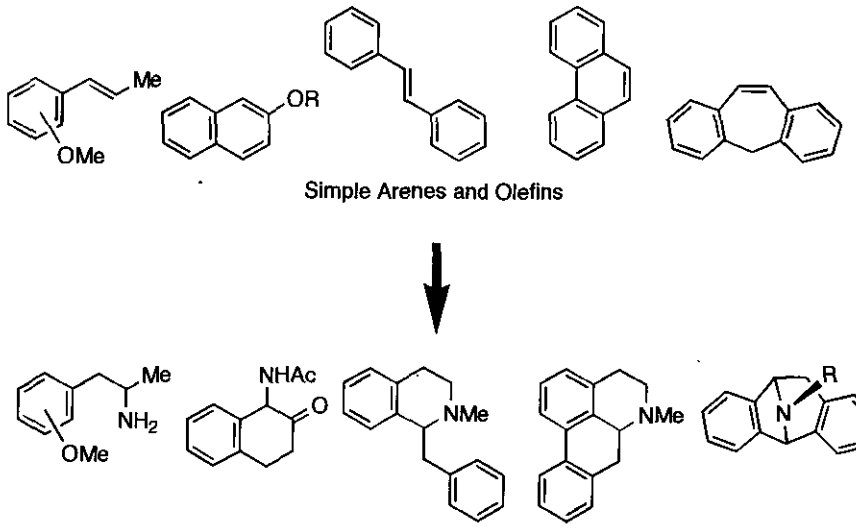
Photochemical electron transfer (PET) reaction between an electron donor (D) and an electron acceptor (A) can provide the cation radical of D ($D^{+\bullet}$) and the anion radical of A ($A^{-\bullet}$). It is synthetically important to change the polarity of electron rich substrates to the electron poor cationic species. The $D^{+\bullet}$ thus formed allows the nucleophilic attack of nucleophiles (NuH or Nu^-) to give adduct radicals (•D-Nu) after deprotonation. The one-electron reduction of •D-Nu with $A^{-\bullet}$ followed by a protonation gives the final products. The mechanism for the photoinduced nucleophilic addition (PNA) is outlined in Scheme 1.

As a synthetic application of PET, the PNA has developed a useful tool to introduce certain functional groups to a C=C double bonds and the strained C-C single bonds.[1] Since first report on PNA of MeOH to



Scheme 1. Mechanism for PNA Reaction

1,1-diphenylethene by Arnold in 1973,[2] most of preceding works on PNA of a variety of aryl-substituted olefins[3] and strained compounds[4] involving products analysis, the selectivity, and the efficiency, as well as the additive effect,[3g,4e,g] the solvent effect,[3k] and the mechanism[3i] have been investigated by use of alcohol as nucleophile. Ammonia and amines that are so stronger nuclophile than alcohols can add to the cation radicals of a variety of substrates, especially, the delocalized cation radicals such as arenes and stilbenes which are inert to the photoinduced nucleophilic addition of alcohols. Thus, we extensively developed a convenient method *via* PET to introduce an amino group into the electron-rich substrates such as arenes,[5] stilbenes,[6] 1,1-diarylalkenes,[7] 1-arylpropenes[8], and benzocycloalkenes[9] (*photoamination*). Moreover, our interest is directed toward synthetic application of the photoamination (Scheme 2). The present review describes our results of the application of photoamination to synthesis of heterocyclic compounds from simple hydrocarbons.

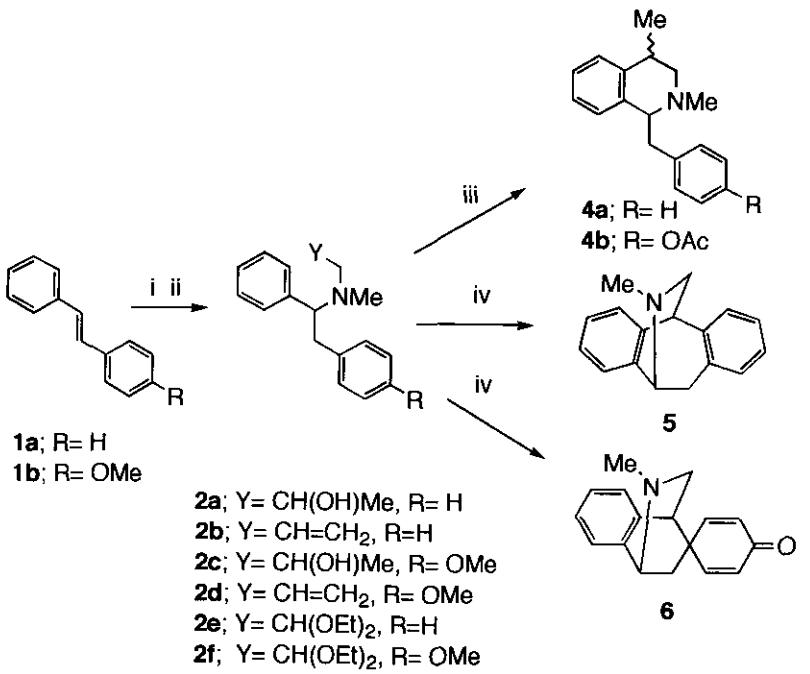


Scheme 2. Synthetic Application of Photoamination

1. Isoquinolines

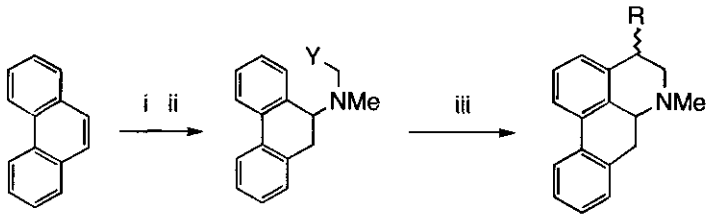
Recently the photochemical constructions of isoquinolines have been extensively investigated. Typical examples are the photochemical coupling reaction between the iminium salts and benzylsilane by Mariano and co-workers[10] and the photochemical cyclization of enamide by Naito and Ninomiya.[11] We applied the photoamination of stilbene (**1a**), *p*-methoxystilbene (**1b**), and phenanthrene (**1c**) to the construction of isoquinoline moiety.[12] The photoamination of **1** was performed by the irradiation of an MeCN/benzene/H_2O (7 : 2 : 1) solution containing **1**, *p*- or *m*-dicyanobenzene (*p*- or *m*-DCB), and an amine by a high pressure mercury lamp. The photoamination of **1a-b** with amino alcohols, allylamine, and aminoacetaldehyde diethyl acetal followed by the methylation with HCO_2H/H_2CO gave *N*-(1,2-diarylethyl)amino alcohols (**2a** and **2c**), *N*-(1,2-diarylethyl)allylamine (**2b** and **2d**), and *N*-(1,2-diarylethyl)aminoacetaldehyde diethyl acetals (**2e** and **2f**), respectively (Scheme 3). Also, *N*-substituted *N*-methyl-9-amino-9,10-dihydrophenanthrenes (**3a-c**) were obtained by the photoamination of **1c** with alkylamines followed by the methylation (Scheme 4).

The **2a** and **2b** were treated with trifluoromethanesulfonic acid (TFSA) to give the 2,4-dimethyl-1-benzyl-1,2,3,4-tetrahydroisoquinolines (**4a**) in 60 and 94 % yields, respectively. Treatment of **2c** and **2d** with TFSA gave 2,4-dimethyl-1-(*p*-acetoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (**4b**) after the acetylation



Scheme 3. Reagents: i *hν*/H_2NCH_2-Y/DCB, ii HCO_2H/HCHO, iii CF_3SO_3H, iv BF_3

with acetic anhydride in 89 and 80 % yields, respectively. These isoquinolines were obtained as a mixture of diastereomers in the ratios of 1 : 0.3 - 0.7. The cyclization of benzylamino acetals (**2e**) was performed with gaseous BF_3 in dichloromethane to give the isopavines (**5**; 89 %). But mineral acids (e.g. HCl, H_2SO_4) and $BF_3{\cdot}OEt_2$ were not effective for the cyclization of these benzylamino acetals. Moreover, the treatment of **2f** with BF_3 gave **6** (28 %). Cyclization of **3a** and **3c** with TFSA gave the aporphine derivative (**7a**) in 41 and 62 % yields, respectively. The treatment of **3b** with TFSA gave **7b** (36 %).



1c

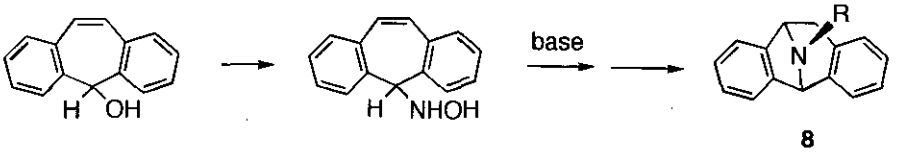
3a; Y= CH(OH)Me
3b; Y= CH(OH)Et
3c; Y= $CH{=}CH_2$

7a; R= Me
7b; R= Et

Scheme 4. Reagents: i *hv*/ H_2NCH_2-Y / *p*-DCB, ii HCO_2H/HCHO, iii CF_3SO_3H

The cyclization of *N*-(1,2-diarylethyl)amino alcohols can readily proceed *via* the carbocation generated by TFSA. The treatment with BF_3 is effective for the cyclization of the *N*-substituted amino acetals as Vinot has already reported for the cyclization of several amino acetals.[13] Benzylamino acetals and benzylamino alcohols are known to be the precursors for the preparation of such the isoquinolines as isopavine and benzylisoquinoline alkaloids.[14] Thus, the photoamination of diarylethenes followed by the cyclization provided a new route for the preparation of isoquinolines.

2. Dibenzo[*a,d*]cyclohepten-5,10-imines



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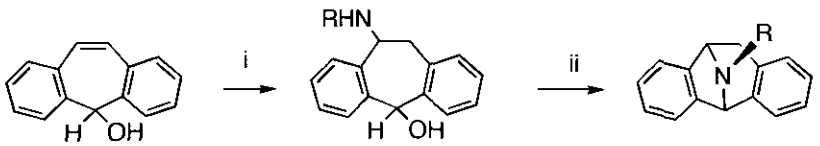
Scheme 5. Merck's method

10,11-Dihydro-5*H*-dibenzo[*a,d*]cyclohepten-5,10-imines (**8**) have been of interest as anticonvulsant and neuroprotective agents.[15] Lamanec and co-workers of Merck Co., Inc. have reported on a synthesis of **8** (R= OH, OR) by a Ritter reaction of 5-hydroxyamino-5*H*-dibenzo[*a,d*]cycloheptenes (Scheme 5).[16] We

applied the photoaminations of *5H*-dibenzo[*a,d*]cyclohepten-5-ol (**9a**) to the synthesis of **8**.[9] Irradiation of a deaerated MeCN-H_2O solution containing **9a**, *p*-DCB, and alkylamine (RNH_2) for 8 h by a high-pressure mercury lamp gave 10-alkylamino-10,11-dihydro-*5H*-dibenzo[*a,d*]cyclohepten-5-ols (**10a-i**) as a mixture of *cis* and *trans* isomers in relatively good yields (Scheme 6 and Table 1). The transannular cyclizations of **10a-i** were performed by the heating with AcOH at 100°C for 5 h to give *N*-alkyl-10,11-dihydro-*5H*-dibenzo[*a,d*]cyclohepten-5,10-imines (**8a-i**). AcOH was most effective in acids tested, e.g. *p*-toluenesulfonic acid and CF_3SO_3H. The transannular reaction with AcOH proceeded readily without the side reactions except for the cases of **8a**, **8g** and **8h** where the acetylation occurred at the amino and the hydroxy groups. Similarly, 5-substituted *N*-alkyl-derivatives (**8j-m**) were synthesized in 54-89 % yields



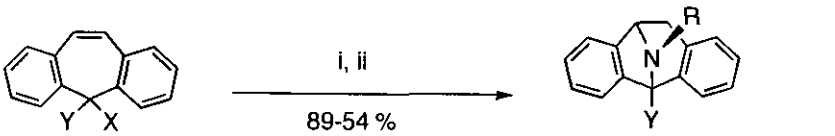
9a **10** **8a-i**

Scheme 6. Reagents; i hv/RNH_2/*p*-DCB, ii AcOH

Table 1. Synthesis of **8a-i** *via* the Photoamination of **9a** Followed by the Cyclization Reaction

	Photoamination [a]		Cyclization[b]	
R	**10** Yield/%[c]	Conv. of **9a**/%	**8** Yield/%[d]	
H	48	71	**8a**	82[e]
Me	60	92	**8b**	82
Et	85	89	**8c**	73
i-Pr	77	92	**8d**	90
Et(Me)CH	76	90	**8e**	82
CH_2=$CHCH_2$	41	87	**8f**	78
$HOCH_2CH_2$	58	79	**8g**	70[f]
$HOCH_2CH$(Me)	73	94	**8h**	72[f]
$EtOCOCH_2$	60	85	**8i**	47

a) The photoamination was performed by irradiating an MeCN-H_2O (9:1; 100 ml) solution containing **9a** (6 mmol), *p*-DCB (12 mmol), and RNH_2 (30 mmol) for 8 h when the photoamination proceeded upto > 71% conversion. b) The transannular reaction was performed by heating of **10** with AcOH at 100°C for 5 h. c) Based on **9a** used. d) Based on **10** used. e) Isolated as the acetamide. f) Isolated as the acetate.



9b; X,Y= $O(CH_2)_2O$
9c; X=Y= OMe

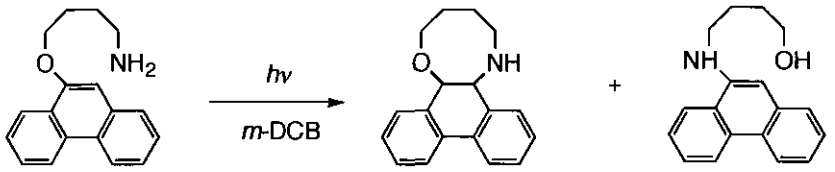
8j; R= Me Y= $O(CH_2)_2OH$
8k; R= Me Y= OMe
8l; R= Et Y= OMe
8m; R= *i*-Pr Y= OMe

Scheme 7. Reagents; i hv/RNH_2/*p*-DCB, ii AcOH

by the photoamination of the 5,5-disubstituted 5*H*-dibenzo[*a,d*]cycloheptenes (**9b-c**) with RNH_2 for 8 h followed by a sequential treatment of the photolysates with AcOH (Scheme 7). Thus, the present transannular reaction can provide directly *N*-alkyl anaolgs of **8** from the precursors, although Merck's method previously reported was restricted to the transannular reaction of *N*-methoxy, *N*-hydroxy- and *N*-amino precursors.[16] Since **9** and the related compounds were easily prepared from commercially available 5*H*-dibenzo[*a,d*]cyclohepten-5-one and since the photoamination and the transannular reactions were performed under mild conditions, the present method will be developed as a new synthetic tool for the preparation of 10,11-dihydro-5*H*-dibenzo[*a,d*]cyclohepten-5,10-imine derivatives.

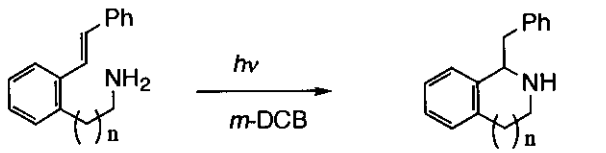
3. Intramolecular Photoamination

Intramolecular photoamination was applied to the synthesis of heterocylic compounds. The photoamination of 9-(4-amino-1-butoxy)phenanthrene (**11**) gave phenanthro[*9,10-b*]-4-oxazepine derivatives (**12**) in a *cis* to *trans* isomer ratio of 65 : 35, along with 4-[*N*-(9-phenanthrylamino)]butanol (**13**) (Scheme 8).[17] Recently Lewis *et al.* applied the photoamination to the intramolecular amination of *o*-(3-aminoethyl)stilbenes (**14a**) which gave 1-benzyl-1,2,3,4-tetrahydroisoquinoline (**15a**; 76 %).[18] Similarly the photoamination of *o*-(3-aminopropyl)stilbenes (**14b**) afforded benzazepine derivative (**15b**; 70 %)



11 **12** **13**

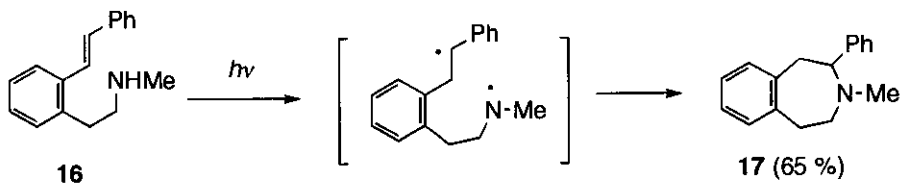
Scheme 8



14a; n= 1
14b; n= 2

15a; n= 1 (76 %)
15b; n= 2 (70 %)

Scheme 9



16

17 (65 %)

Scheme 10

(Scheme 9). Also they reported that the irradiation of *N*-methyl derivative of **14a** (**16**) in the absence of DCB gave **17** (65 %) *via* an electron and a proton transfer in the excited singlet state of **16** (Scheme 10).

4. The scope and limitation

In general, the photosensitization with 9,10-dicyanoanthracene, 1-cyanonaphthalene, and 1,4-dicyanonaphthalene was used in order to achieve the efficient PNA of alcohols, cyanide ion,[19] and carboxylic acid[20] to the substrates which have only weak or no absorption at longer wavelength. However, our investigations have demonstrated that the photosensitizations with these sensitizers are not effective for the photoamination with RNH_2, since the excited states of the sensitizers are efficiently quenched by RNH_2. Moreover the redox photosensitization[3b,f] using a redox pair of phenanthrene/*p*-dicyanobenzene which is usual means for the efficient PET reaction could not be applied to the photoamination, since the trapping of the cation radical of phenanthrene by the amines would prevent the hole transfer from the cation radical of phenanthrene to the substrates. Therefore, the substrates for the photoamination were restricted to the substrates which have relatively strong absorption at longer wavelength than 300 nm, revealing it is requisite for the substrates to have the aromatic ring. Moreover, it is preferred for the efficient PET reaction that the oxidation potentials of the substrates are relatively low. Recently we have developed the additive effect of polyphenylbenzene and other benzene derivatives (π-donor effect) as new type of method to enhance the yields of the photoamination.[21]

As an electron acceptor, we usually used *m*- and *p*-DCB which have weak absorption even at 300 nm, a shorter wavelength limit of light transmission of a Pyrex reaction vessel. The PET with *p*-DCB occurs preferably than that with *m*-DCB but the resulting anion radical of *m*-DCB plays as a stronger reducing agent than that of *p*-DCB, because the reduction potential of *m*-DCB is more negative than that of *p*-DCB. Moreover, the anion radical of *p*-DCB has potentially strong coupling ability with the stable cation radicals of the substrates (D), giving the *p*-cyanophenylated products of D. For the nucleophiles, ammonia and primary alkylamines having functional groups such as hydroxy, vinyl, ester, cyano, and acetal groups can be safely used without other side reactions, since the amino group has the stronger nucleophilicity and the photoamination can be performed under mild conditions. However, the secondary amines of which oxidation potentials are relatively low could not be used because of the occurrence of the electron exchange of $D^{+\bullet}$ with the amines.

The aminated dihydroarenes and the aminated 1,2-diarylethane moieties formed by the photoamination of arenes and stilbenes were not so stable for thermolysis.[22] For example, the glc analysis showed no peaks of the aminated products in some cases because of the decomposition by thermolysis at the injection temperature. Therefore, it is necessary to select the suitable reagents for the cyclization which can be used under mild conditions.

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