SYNTHESIS OF ISOQUINOLINE PRECURSORS BY PHOTOAMINATION OF STILBENES WITH BIFUNCTIONAL ALKYLAMINES

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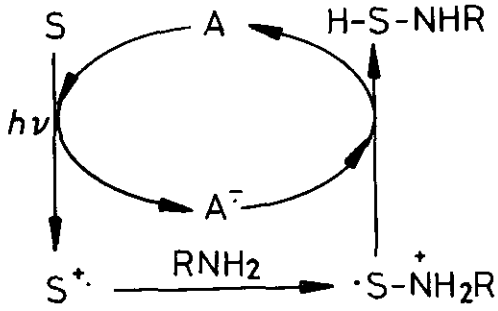
Abstract ---- *Irradiation of stilbenes* (1) with amino alcohols or amino acetaldehyde diethyl acetal in the presence of p-dicyanobenzene gave the corresponding N-substituted 1,2-diarylethylamines (2) in good yields. The resulting benzylamino alcohols and benzylamino acetals were treated with CF_3SO_3H and gaseous BF_3, respectively, to give isoquinolines (4, 5 and 6).

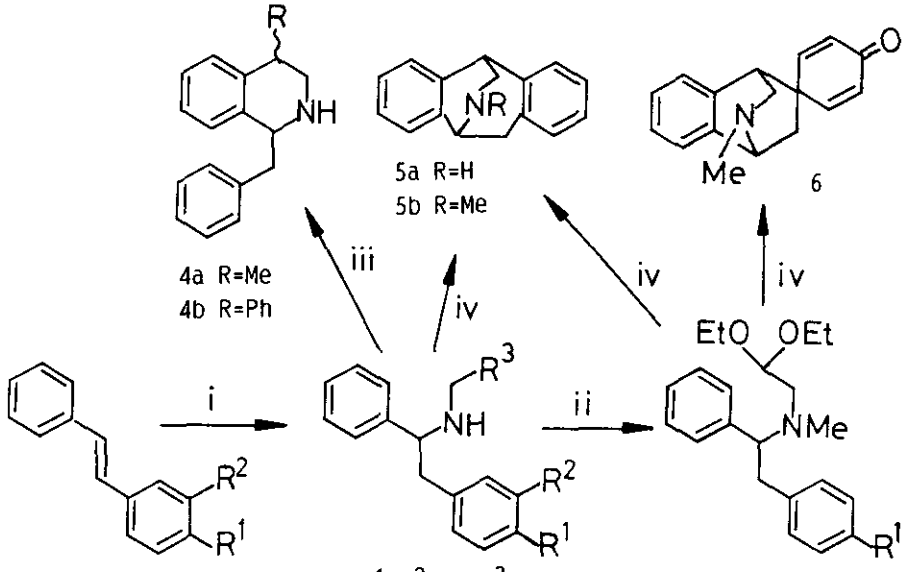
A large number of synthetic approaches to isoquinolines have been developed for many years.[1] In recent years, a new approach for heterocyclic ring construction has been grown in photochemistry.[2] We have developed a direct photoamination with amines which proceeds by a mechanism involving nucleophilic addition of amines to the cation radical of substrates ($S^{+\cdot}$) generated by photochemical electron transfer to an electron acceptor (A) (*Scheme* 1).[3] As the photoamination provides a versatile and useful tool for the direct introduction of amino group into electron-rich substrates, we attempted to apply the photoamination to the synthesis of heterocyclic compounds. Benzylamino acetals and benzylamino alcohols have been found to be important precursors of such isoquinolines as isopavine and benzylisoquinoline alkaloids.[4] Herein, we wish to report the preparation of these



Scheme 1.

precursors by the photoamination of stilbenes (**1**) with bifunctional alkylamines and the following cyclization by CF_3SO_3H or BF_3.

An acetonitrile-benzene-water (7:2:1) solution containing **1a-c**, p-dicyanobenzene (DCNB), and an amine was irradiated through a Pyrex by a high-pressure mercury lamp to give the corresponding N-substituted 1,2-diarylethylamine (**2a-f**) in good yields except for the case of **1c**, as shown in Scheme 2 and Table 1. 2-Hydroxy-1-propylamine, 2-hydroxy-2-phenylethylamine, and 2-ethanolamine were used for the synthesis of benzylamino alcohols (**2a-c**), whereas amino acetaldehyde diethyl acetal was used for the synthesis of benzylamino acetals (**2d-f**). It should be noted that these bifunctional alkylamines readily added to **1** without reactions of the other functional groups. The photoamination of **1b** and **1c** occurred at the benzylic position of phenyl group with high selectivities.



i) hν /DCNB/$H_2NCH_2R^3$ ii) HCHO/HCO_2H iii) CF_3SO_3H iv) BF_3

Scheme 2.

Table 1. Photoamination of 1 with Bifunctional Alkylamines[a)]

run no.	1	$H_2NCH_2R^3$	2 (yield/%)[b)]	recov. of 1/%	recov. of DCNB/%
1[c)]	**1a**	$H_2NCH_2CH(OH)Me$	**2a** (93)	6	98
2[c)]	**1a**	$H_2NCH_2CH(OH)Ph$	**2b** (82)	7	96
3	**1a**	$H_2NCH_2CH_2OH$	**2c** (97)	0	93
4	**1a**	$H_2NCH_2CH(OEt)_2$	**2d** (86)	1	91
5	**1b**	$H_2NCH_2CH(OEt)_2$	**2e** (73)[d)]	7	95
6	**1c**	$H_2NCH_2CH(OEt)_2$	**2f** (30)	57	94

a) An acetonitrile-benzene-H_2O (7:2:1) solution (100 ml) containing **1** (5 mmol), DCNB (5 mmol), and the amine (25 mmol) was irradiated for 8-45 h. b) Isolated yields based on 1 used. c) For an acetonitrile-benzene (8:2) solution. d) Accompanying the formation of 14 % yield of N-(1-p-methoxyphenyl-2-phenylethyl)amino acetaldehyde diethyl ether.

It is proposed that the photoamination of 1 proceeds by a mechanism shown in Scheme 1; the cation radical of 1 ($1^{+\cdot}$) generated by photochemical electron transfer to DCNB are nucleophilically attacked by the amine followed by the one-electron reduction of aminated radical by the anion radical of DCNB to give the final products. Therefore, the regiochemistry of amination can be attributed to the population densities of positive charge in $1^{+\cdot}$; thus, the amino group was mainly introduced into the benzylic position of phenyl group of **1b** and **1c** where the highest positive charge might develop.[5]

The benzylamino alcohols (**2a** and **2b**) were treated with CF_3SO_3H to give the benzylisoquinolines (**4a** and **4b**), in 72 and 98% yields, respectively.[6] *N-Methylation of* **2d** and **2e** was performed with $HCHO/HCO_2H$ to give **3a** and **3b**, in 98 and 69% yields, respectively. The cyclization of benzylamino acetals was performed with gaseous BF_3 which has been used for the cyclization of several benzylamino acetals by Vinot;[7] the treatment of **2d** and **3a** with BF_3 in CH_2Cl_2 gave isopavines (**5a** and **5b**) in 80 and 89% yields, respectively.[8] But mineral acids were not effective for the cyclization of these benzylamino acetals. Moreover, the treatment of **3b** with BF_3 *gave the isoquinoline (6) in 28% yield,*[9] whereas the reaction of **2e** with BF_3 gave the untractable materials.

Thus, it is found that the photoamination of 1 is a convenient method to prepare isoquinoline precursors such as benzylamino alcohols and benzylamino acetals.

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4. S. F. Dyke and A. C. Ellis, Tetrahedron, 1971, **27**, 3803; S. F. Dyke, A. C. Ellis, R. G. Kinsman, and A. W. C. White, Tetrahedron, 1974, **30**, 1193; R. Elliott, F. Hewgill, E. McDonald, and P. McKenna, Tetrahedron Lett., 1980, **21**, 4633.
5. Details for the relationships between regioselectivity and the substituents on the aryl groups in stilbenes will be published elsewhere.
6. **4a** and **4b** were formed as a mixture of cis and trans isomers.
7. N. Vinot and R. Quelet, Bull. Soc. Chim. Fr., **1959**, 1164; N. Vinot, Ann. Chim., 1958, **3**, 475.
8. **5a**: ^{1}H-Nmr ($CDCl_3$) δ 2.28 (br s, 1H), 3.21 (dd, J= 17.7, 3.3 Hz, 1H), 3.31 (dd, J= 11.5, 4.7 Hz, 1H), 3.49 (dd, J= 17.6, 3.7 Hz, 1H), 3.69 (d, J= 11.3 Hz, 1H), 3.89 (d, J= 3.9 Hz, 1H), 4.33 (t, J= 3.6 Hz, 1H), 7.04-7.25 (m, 8H); ^{13}C-nmr δ 41.3, 46.6, 50.4, 54.8, 124.9, 125.5, 125.9, 126.7, 126.8, 127.2, 127.9, 131.3, 135.1, 139.9, 141.2, 142.7; ms (m/z) 221 (M^+); Acetamide of **5a**: mp 205.5-205 °C (from MeOH). Anal. Calcd for $C_{18}H_{17}NO$: C, 82.10; H, 6.51; N, 5.48. Found: C, 82.37; H, 6.49; N, 5.48.
9. **6**: ^{1}H-Nmr δ 1.58 (dd, J= 13.6, 2.3 Hz, 1H), 1.83 (dd, J= 10.8, 1.8 Hz, 1H), 2.14 (s, 3H), 2.34 (dd, J= 13.6, 3.3 Hz, 1H), 2.77 (br s, 1H), 3.70-3.80 (m, 2H), 6.04 (dd, J= 10.2, 1.5 Hz, 1H), 6.12 (dd, J= 10.2, 2.8 Hz, 1H), 6.34 (dd, J= 10.2, 1.5 Hz, 1H), 7.11-7.36 (m, 4H), 7.43 (dd, J= 10.2, 2.8 Hz, 1H); ^{13}C-nmr δ 38.5, 39.7, 44.7, 44.9, 53.8, 57.5, 124.5, 125.0, 126.9, 127.2, 127.6, 128.4, 137.1, 139.4, 154.4, 155.9, 185.5; ms (m/z), 251 (M^+).

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