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Intramolecular photoaddition reactions of (aminoalkyl)styrylamides

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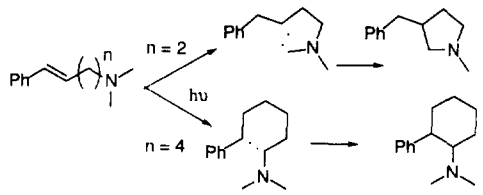
Abstract

The photochemical reactions of a family of styrene–spacer–amine molecules in which the spacer consists of a rigid amide group in the middle of a flexible alkane chain have been investigated. Our study of the photophysics of these molecules has shown that the amide linker can facilitate intramolecular styrene–amine exciplex formation (J. Phys. Chem., in press). We report here the photochemical behavior of these amide-linked (aminoalkyl)styrylamides. Several tertiary amines are found to undergo regioselective α-C–H addition to the styrene double bond resulting in the formation of medium-ring lactams. A secondary amine undergoes N–H addition yielding an azalactam. The dependence of these reactions upon spacer structure, amine and amide substitution, and solvent polarity is discussed. © 1998 Elsevier Science S.A.

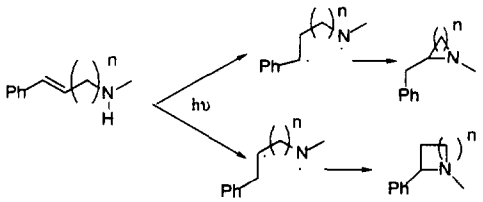
Keywords: (Aminoalkyl)styrylamide; Lactams; Photochemical synthesis

1. Introduction

The application of intramolecular addition reactions to the synthesis of medium- and large-ring compounds is a topic of current interest [1,2]. We previously reported that the intramolecular addition reactions of (aminoalkyl)styrenes provides a direct method for the synthesis of common ring systems [3,4]. Tertiary (aminoalkyl)styrenes undergo α-C–H addition to yield either nitrogen heterocycles or aminocycloalkanes, depending on the origin of the α-C–H (Scheme 1), whereas secondary (aminoalkyl)styrenes undergo N–H addition to yield nitrogen heterocycles (Scheme 2). These reactions were proposed to occur via photoinduced electron transfer to yield an exciplex intermediate, followed by proton transfer and radical combination. The absence of concise methods for the synthesis of (aminoalkyl)styrenes with long polymethylene spacers tempered our enthusiasm for extending these reactions to the preparation of medium- and large-ring adducts.



Scheme 1.



Scheme 2.

Spacers containing both flexible polymethylene and rigid ester or amide elements have been employed in several recent investigations of intramolecular photoaddition reactions [5–12]. The ester or amide linkage serves to facilitate the preparation of donor–spacer–acceptor systems and may also serve as a conformational control element, decreasing the entropy of activation for formation of a macrocyclic intermediate or product [13]. The ester or amide can be positioned either at one end or in the middle of the polymethylene chain. In the accompanying paper the photochemical reactions of amide-linked (aminoalkyl)stilbenes in which the amide is directly attached to the stilbene are described [14]. We report here our investigation of the photochemical behavior of a family of (aminoalkyl)styrylamides in which the amide group is separated from the styrene chromophore by one or two methylenes (Chart 1). In most cases, regioselective intramolecular addition is observed resulting in the formation of medium-ring lactams or azalactams. The photophysical behavior of these molecules is described elsewhere [15].

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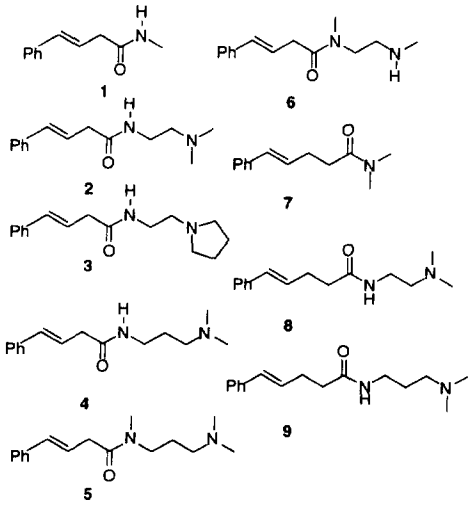


Chart 1. (Aminoalkyl) styrylamides

2. Experimental details

2.1. General methods

^{1}H and ^{13}C NMR spectra were recorded on Varian VXR-300 and Varian Gemini 300 MHz spectrometers in $CDCl_3$ solvent with TMS as an internal standard. Infrared spectra of 0.005–0.02 M solutions of amines in dichloromethane or chloroform were recorded in 1 mm path length NaCl cells using a Biorad FTS60 spectrometer. Mass spectra were obtained using a Hewlett Packard 5985 GC/VG70-250E MS system using an ionizing voltage of 70 eV.

Irradiations were performed in a Rayonet reactor equipped with 300 nm lamps. Photoisomerization and photoaddition quantum yields were determined for 3 ml aliquots of ~0.005 M benzene or acetonitrile solutions in Pyrex test tubes sealed with white rubber septa. Solutions were purged with dry nitrogen prior to irradiation. Irradiated solutions were analyzed for isomer formation at < 10% conversion using the photoisomerization of *trans*-1-phenylpropene as the actinometer ($\Phi_t = 0.14$) [16]. Preparative irradiations were conducted under similar conditions and were stopped when < 10% of the starting material remained by GC analysis. Evaporation of the solvent under reduced pressure and column chromatography (silica gel) using 9:1 chloroform: MeOH yielded the pure products.

Benzene (Aldrich) was refluxed over sodium metal and distilled prior to use. Acetonitrile (Aldrich) was used without further purification. Compounds **1–9** were prepared as previously described [15].

2.2. Characterization of photoproducts

2.2.1. 6-Dimethylamino-5-phenyl-1-azacycloheptan-2-one (2a)

Irradiation of **2** resulted in formation of **2a** as a yellow oil in 48% yield. ^{1}H NMR δ 7.28 (m, 5H), 4.76 (dd, J = 8.4, 5.4 Hz, 1H), 3.81 (d of t, J = 7.2, 14.4 Hz, 1H), 2.68 (d of t, J = 6.6, 14.1 Hz, 1H), 2.51 (m, 2H), 2.35 (m, 2H), 1.87 (m, J = 5.7 Hz, 1H). ^{13}C NMR (decoupled) δ 175.6, 141.4, 129.0, 128.1, 126.6, 62.7, 56.5, 45.6, 38.4, 30.3, 28.7. HRMS *m/z* 232.1575 (calc.) and 232.1591 (obs.); major fragments (rel. intensity) 232 (6), 71 (36), 58 (100). IR ($CHCl_3$) 1720 cm^{-1}.

2.2.2. 6-Pyrolidino-5-phenyl-1-azocylcoheptan-2-one (3a)

Irradiation of compound **3** afforded **3a** as an orange oil in a 16% yield. ^{1}H NMR δ 7.31 (m, 5H), 4.78 (d, 1H), 3.82 (m, 1H), 2.98 (s, 1H), 2.75 (m, 1H), 2.56 (m, 8H), 1.75 (m, 4H), 1.24 (m, 1H). ^{13}C NMR δ 175.7, 141.3, 129.0, 128.1, 126.6, 62.7, 54.1, 53.1, 39.4, 30.3, 28.6, 23.4. HRMS *m/z* 258.362 (calc.), 258.173 (obs.); major fragments 258(M), 191, 170, 161, 117(100), 84, 57.

2.2.3. 6-Dimethylamino-5-phenyl-1-azacycloheptan-2-one (4a)

Irradiation of **4** afforded **4a** as a yellowish oil in a 40% yield. ^{1}H NMR δ 7.28 (m, 5H), 4.76 (dd, J = 8.4, 5.4 Hz, 1H), 3.81 (d of t, J = 7.2, 14.4 Hz, 1H), 2.68 (d of t, J = 6.6., 14.1 Hz, 1H), 2.51 (m, 2H), 2.35 (m, 2H), 1.87 (m, J = 5.7 Hz, 1H). ^{13}C NMR (decoupled) δ 175.6, 141.4, 129.0, 128.1, 126.6, 62.7, 56.5, 45.6, 38.4, 30.3, 28.7. HRMS *m/z* 232.1575 (calc.) and 232.1591 (obs.); major fragments (rel. intensity) 232 (6), 71 (36), 58 (100). IR ($CHCl_3$) 1720 cm^{-1}.

2.2.4. 5-Methyl-9-phenyl-1,5-diazacyclodecan-8-one (5a)

Irradiation of compound **5** afforded compound **5a** as a yellow oil in 17% yield. Partially assigned ^{1}H NMR δ 2.96 (s, 3H), 2.21 (s, 3H). HRMS *m/z* 260.1888 (calc.) and 260.1874 (obs.); major fragments (rel. intensity) 260 (100), 156 (35), 113 (72), 71 (73), 58 (65). IR ($CHCl_3$) 1720 > cm^{-1}.

2.2.5. 1-Methyl-8-phenyl-1,4-diazacyclooctan-5-one (6a)

Irradiation of compound **6** afforded compound **6a** as a yellow oil in 42% yield. ^{1}H NMR δ 7.30 (m, 5H), 3.87 (t, J = 7.8 Hz, 1H), 3.65 (ddd, J = 15.3, 6.0, 3.0, 1H), 3.38 (ddd, J = 15.3, 7.8, 3.0, 1H), 3.23 (ddd, J = 14.7, 6.0, 3.0, 1H), 3.04 (ddd, J = 14.7, 7.8, 3.0, 1H), 2.98 (s, 3H), 2.70 (m, 2H), 2.52 (d of t, J = 12.0, 6.0 Hz, 1H), 2.35 (d of t, J = 7.8, 6.0 Hz, 1H). ^{13}C NMR (decoupled) δ 175.3, 142.7, 128.2, 127.2, 126.8, 62.3, 55.4, 50.6, 35.5, 34.1, 32.4, 31.3. HRMS *m/z* 232.1575 (calc.) and 232.1562 (obs.); major fragments (rel. intensity) 232 (41), 189 (26), 146 (30), 104 (100), 91 (38), 44 (88). IR ($CHCl_3$) 1720 cm^{-1}.

2.2.6. 1-Methyl-9-phenyl-1,4-diazacyclodecan-5-one (8a)

Irradiation of compound **8** afforded compound **8a** as a white solid (m.p. 134–137°C) in 42% yield. ^{1}H NMR δ 7.25 (m, 5H), 3.65 (m, 1H), 2.99 (d of t, J = 4.0, 9.3 Hz, 1H), 2.84 (d, J = 13.5 Hz, 1H), 2.49 (m, 2H), 2.40 (s, 3H), 2.33 (m, 2H), 2.11 (m, 3H), 1.79 (m, 1H), 1.64 (m, 2H). ^{13}C NMR (decoupled) δ 175.0, 145.1, 128.5, 128.1, 126.4, 63.8,

51.7, 45.3, 45.1, 38.9, 38.6, 32.2, 22.8. HRMS 246.1732 *m/z* (calc.) and 246.1738 (obs.); major fragments (rel. intensity) 246 (35), 98 (44), 71 (48), 58 (100), 44 (49). IR ($CHCl_3$) 1720 cm^{-1}.

2.2.7. 7-Dimethylamino-6-phenyl-1-azacyclooctan-2-one (8b)

Irradiation of compound **8** afforded compound **8b** as a yellow oil in 24% yield. ^1H NMR δ 7.28 (m, 5H), 4.76 (dd, J=8.4, 5.4 Hz, 1H), 3.81 (d of t, J=7.2, 14.4 Hz, 1H), 3.41 (m, 2H), 3.37 (d, J=7.2 Hz, 2H), 2.89 (s, 3H), 2.44 (t, J=7.2 Hz, 2H), 2.35 (s, 6H), 1.77 (m, J=7.2 Hz, 2H). ^{13}C NMR (decoupled) δ 170.8, 141.7, 128.7, 127.5, 126.7, 61.7, 57.0, 45.6, 43.7, 32.4, 32.0, 17.0. HRMS *m/z* 246.1732 (calc.) and 246.1736 (obs.); major fragments (rel. intensity) 246 (5), 71 (57), 58 (100). IR ($CHCl_3$) 1720 cm^{-1}.

2.2.8. 7-Dimethylamino-6-phenyl-1-azacyclononan-2-one (9a)

Irradiation of compound **9** afforded compound **9a** as a red oil in 30% yield. ^1H NMR δ 7.28 (m, 5H), 4.68 (dd, J=4.6, 8.4 Hz, 1H), 3.95 (d of t, J=6.3, 13.5 Hz, 1H), 2.51 (m, 3H), 2.38 (s, 6H), 2.17 (m, 1H), 1.89–1.64 (m, 6H). ^{13}C NMR (decoupled) δ 171.1, 148.0, 128.7, 127.6, 126.7, 61.0, 56.7, 44.6, 43.7, 32.3, 31.9, 24.7, 17.0. HRMS *m/z* 260 (calc.) and 260.1880 (obs.); major fragments (rel. intensity) 260 (29), 72 (14), 58 (100). IR ($CHCl_3$) 1720 cm^{-1}.

3. Results and discussion

The synthesis of the 4-phenyl-3-butenamides **1–6** and the 5-phenyl-4-pentenamides **7–9** from the corresponding phenylalkenoic acids has been reported [15]. The ^1H NMR spectra of the tertiary amides **5** and **6** display two sets of signals assigned to the *E* and *Z* conformers. Integration of these signals indicates that the conformers are present in a ca. 1:1 ratio, as has been observed for other tertiary (aminoalkyl)amides [17]. The secondary amides **1–4** and **7–9** display only one set of ^1H NMR signals attributed to the *Z* conformational isomer.

The absorption and fluorescence spectra of the styrylamides **1–9** are similar to those of *trans*-1-phenylpropene [16]. The photophysical properties of **1–9** have previously been reported [15]. The model amides **1** and **7** have fluorescence quantum yields and lifetimes similar to those of *trans*-1-phenylpropene. Thus, the amide substituent does not strongly perturb the styrene-like excited singlet state. The (aminoalkyl)styrylamides **2–6**, **8** and **9** all have substantially lower fluorescence quantum yields and shorter lifetimes than those of the model styrylamides **1** and **7**. These changes are attributed to efficient intramolecular electron-transfer quenching of the styrene singlet by the appended amine [15].

Irradiation of the styryl amides **1–9** in benzene or acetonitrile solution results in trans→cis isomerization as the major photoprocess at low conversions. Quantum yields for isomerization (Φ_i) are reported in Table 1. The values are all lower than that for *trans*-1-phenylpropene (Φ_i=0.14) [16] and display no consistent dependence upon structure or solvent polarity. 1-Arylpropenes can isomerize via both singlet and triplet mechanisms [16] and styrene–amine exciplexes can undergo intersystem crossing to yield locally excited styrene triplets which decay to a mixture of *cis* and *trans* isomers [4]. Thus, the low quantum yields reported in Table 1 cannot be readily interpreted.

Irradiation of the (aminoalkyl)styrylamides **2–6**, **8**, and **9** in benzene solution also results in the formation of intramolecular adducts. A single adduct was detected by gas chromatography following irradiation of **2–6** and **9**, whereas two adducts were detected from **8**. The adducts account for most of the consumed starting material at moderate conversions. The adducts were isolated by column chromatography (see Section 2). Adduct yields reported in Table 1 are unoptimized isolated yields, uncorrected for recovered starting material. Adduct structure assignments (Chart 2) are based on mass spectral fragmentation and ^1H and ^{13}C NMR spectra and supported by COSY ^1H NMR. The adducts formed from tertiary amines are assigned to lactam structures in which the dialkylamino group is either exocyclic (**2a–5a**, **8a** and **9a**) or endocyclic (**8b**) with respect to the lactam ring. Adducts presumably are formed via hydrogen transfer to the styrene β carbon from the either the methylene group α to the amine or an *N*-methyl group, as shown in Scheme 3 for the case of **8**. The adduct **6a** is formed via hydrogen transfer to the styrene β carbon from the amine nitrogen, as shown in Scheme 4.

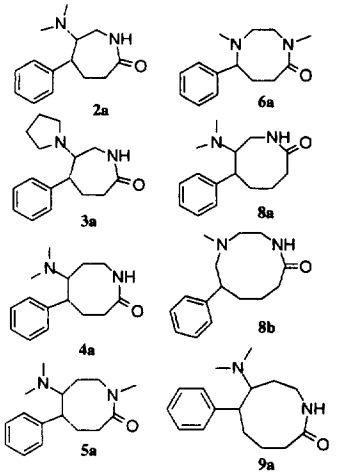


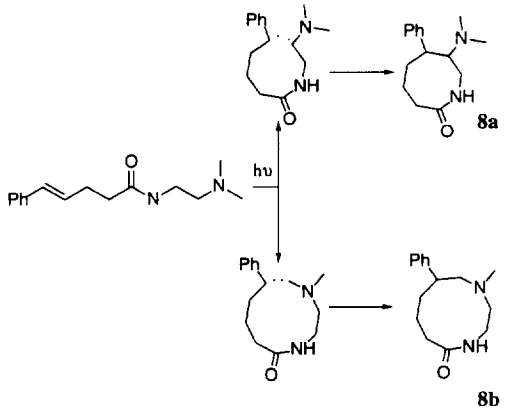
Chart 2. Intramolecular adducts

Quantum yields for adduct formation (Φ_a) are reported in Table 1. Values of Φ_a are smaller for the tertiary amines derived from 4-phenyl-3-butenoic acid **2–5** than for the derivatives of 5-phenyl-4-pentenoic acid **8** and **9**. Irradiation of the secondary amine **6** in acetonitrile solution results in adduct formation with a quantum yield of 0.018, somewhat less than the value in benzene solution. No adduct formation is observed upon irradiation of the tertiary amines in acetonitrile solution. The observation of efficient intramolecular quenching of styrene fluorescence for all of the amide-linked (ami-

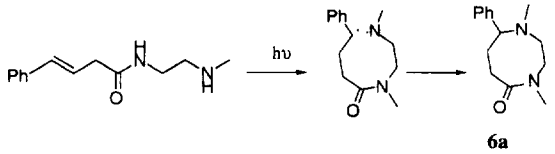
Table 1
Quantum yields for isomerization and addition and preparative yields for adduct formation

Compound	Φ_i (Benzene)	Φ_i (MeCN)	Φ_{add} (Benzene)	Adduct yield, % [a]
1	0.065	0.053	–	
2	0.028	0.008	0.008	48
3	0.012	–	0.003	16
4	0.031	0.005	0.006	40
5	0.029	0.018	0.007	17
6	0.037	0.012	0.030	42
7	0.030	0.025	–	–
8	0.022	0.005	0.020, 0.019	42, 24 [b]
9	0.030	0.007	0.018	30

[a] Yields of intramolecular adduct formation irradiated in benzene solution (unoptimized and uncorrected for recovered starting material).
[b] Compound **8** forms two photoproducts upon irradiation.



Scheme 3.



Scheme 4.

noalkyl)styrenes indicates that the low quantum yields for adduct formation must result from inefficient hydrogen transfer or biradical ring formation. Plausibly, exciplex conformations which do not provide least-motion pathways for hydrogen transfer are nonreactive. This is consistent with the absence of adduct formation in the polar solvent acetonitrile, which is known to favor extended conformations of the exciplex [4].

The formation of intramolecular adducts exclusively via α-C–H addition of tertiary amines and N–H addition of secondary amines has previously been observed for the reactions of singlet arenes and aryl olefins [2–4]. The addition reactions of tertiary amines occur only in nonpolar solvents, whereas addition reactions of secondary amines occur in polar as well as nonpolar solvents. These differences in the behavior of secondary vs. tertiary amines have been attributed to hydrogen bonding of the secondary amine cation radical and the arene anion radical, which facilitates the N–H transfer process [2]. Both the regioselectivity of addition to the styrene double bond (α vs. β carbon) and of tertiary amine C–H abstraction (*N*-methyl vs. α-methylene) has been observed to be dependent upon the chain length of the (aminoalkyl)styrene with linkers consisting of one to five methylenes [3,4]. The chain-length dependence of regioselectivity was attributed to the occurrence of hydrogen transfer via a least motion pathway in a folded exciplex intermediate. In the case of the (aminoalkyl)styrylamides, adducts are formed exclusively via C–H transfer to the styrene β-carbon from the α-methylene of tertiary amines, except in the case of **8** for which C–H transfer also occurs from the *N*-methyl (Scheme 3).

Selective hydrogen transfer to the styrene β-carbon yields the more stable benzyl radical and thus would be expected in the absence of conformational constraints imposed by the linker. More surprising is the selective hydrogen abstraction from the α-methylene vs. *N*-methyl. Prior studies of the deprotonation of tertiary amine cation radicals have shown a modest selectivity for *N*-methyl vs. α-methylene, comparable to the statistical factor favoring *N*-methyl hydrogen abstraction from the tertiary (aminoalkyl)styrenes [18,19]. Hasegawa and co-workers [5–7] have observed selective intramolecular hydrogen abstraction of *N*-methyl vs. α-methylene hydrogens in the photocyclization reactions of some tertiary (aminoalkyl)-β-oxoesters. Whereas the reactions of both the styrylamides and the oxoesters proceed via an electron-transfer, proton-transfer mechanism, the difference in regioselectivity suggests a difference in the proton-transfer step. In the case of the (aminoalkyl)styrenes, proton transfer occurs via a singlet exciplex and the regioselectivity of proton transfer is determined by the geometry of the folded exciplex [4]. In the case of the (aminoalkyl)-β-oxoesters, proton transfer presumably occurs via a triplet radical ion pair [5] which may not have a well-defined geometry. Random encounters of the aryl ketone anion radical and amine cation radical might result in selective *N*-methyl hydrogen transfer. It is, of course, possible that the hydrogen transfer process in one or both of these reactions is non-regioselective and that the observed selectivity is a consequence of competition of the biradical cyclization step with reversion to starting materials or telomer formation, as observed by Hasegawa et al. [6] for some (*N*,*N*-dimethylamino)ethyl esters of γ-oxo acids.

4. Conclusion

In summary, intramolecular photoaddition of secondary and tertiary (aminoalkyl)styrylamides provides a convenient method for the preparation of medium-ring lactams and azalactams. Whereas the unoptimized yields are only fair, the formation of a single regioisomer in most cases facilitates

product isolation. Since intramolecular exciplex formation has been observed for tertiary (aminoalkyl)styrylamides with longer spacers than those used in this investigation [15], it is possible that macrocyclic lactams may also be assessable by extension of these reactions to higher homologues. The use of secondary (aminoalkyl)styrylamides in these reactions would have the advantage of providing a single azalactam regioisomer. The recent success of Griesbeck et al. [12] in obtaining macrocyclic lactams from the photochemical decarboxylation of amide-linked ω-phthalimidoalkanoates underscores the utility of amide-linkers in intramolecular photochemical addition reactions.

Acknowledgements

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