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Stereospecific photochemistry of Δ^2-1,2,3-triazolines in solution and in the solid state: scope and mechanistic studies†

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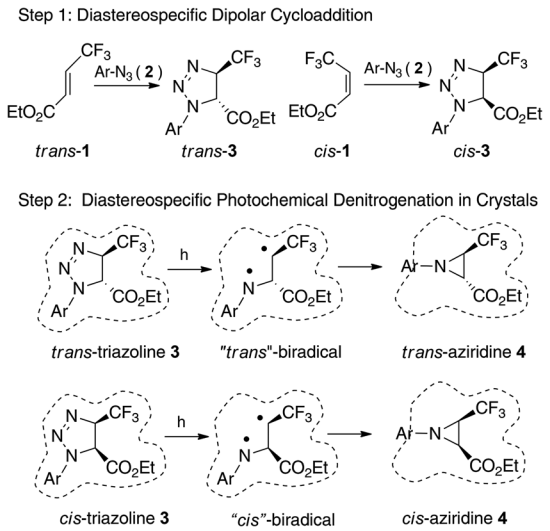
The stereospecific photochemistry of ten *N*-aryl-substituted *cis*- or *trans*-Δ^2-1,2,3-triazolines to form the corresponding *cis*- or *trans*-aziridines was investigated both in solution and in the solid-state. We found that photochemical reactions in the solid state are more stereospecific than in solution for the 8 crystalline Δ^2-1,2,3-triazolines. Additionally, triplet sensitization for some triazolines results in triplet biradicals, which provide the more thermodynamically favored *trans*-aziridine regardless of the starting triazoline stereochemistry. Product analyses as a function of temperature and solvent polarity suggest that the electronic excitation of the Δ^2-1,2,3-triazolines results in the formation of a 1,3-biradical intermediate.

Introduction

Aziridines are nitrogen-containing three-membered heterocycles widely explored for their interesting reactivity and biological potential.[1–6] Some of the most common strategies for the stereospecific synthesis of aziridines[7] involve the addition of nitrenes to alkenes, or the addition of carbenes into imine double bonds. Unfortunately, improved selectivity requires the use of expensive metal catalysts and toxic volatile solvents, such that alternative strategies are desirable. Knowing that solid-state photochemistry is a viable green-chemistry alternative for the preparation of valuable synthetic targets,[8–13] we recognized an opportunity to explore a two-step strategy for the stereospecific synthesis of substituted aziridines. As illustrated in Scheme 1, we proposed the use of (*cis*)- or (*trans*)-alkenes **1** to carry out 1,3-dipolar cycloadditions with azides **2** to form (*cis*)- or (*trans*)-substituted 1,2,3-triazolines **3**.[8] The second step would involve the photoinduced diastereospecific generation of the desired aziridines **4** by the formation of an intermediate 1,3-alkylaminyl biradical in the crystals of the pure 1,2,3-triazoline **3**.

The viability of the strategy as shown in Scheme 1 was recently reported in a brief letter.[8] It was shown that the hydrogen-bond-catalyzed dipolar cycloadditions of trifluoromethyl acrylates *trans*-**1** and *cis*-**1** with 2-fluorenyl azide **2D** (Scheme 2) are not only stereospecific, but remarkably regioselective, yielding the compound where the *N*-aryl group is located vicinal to the ester group. The crystallization of the two triazoline isomers proceeded well, and the solid state photochemistry occurred with high diastereomeric yields. In this article, we increased the number of aryl azides studied to include phenyl azide (**2A**), 2-naphthyl azide (**2B**), 4-biphenyl azide (**2C**), and 4-(triphenylmethyl)phenyl azide (**2E**). All the dipolar cycloaddition reactions were highly regioselective and stereospecific, each giving a single triazoline diastereomer (Scheme 2). Eight out of the ten triazolines prepared turned out to be crystalline solids and photochemical experiments



Scheme 1

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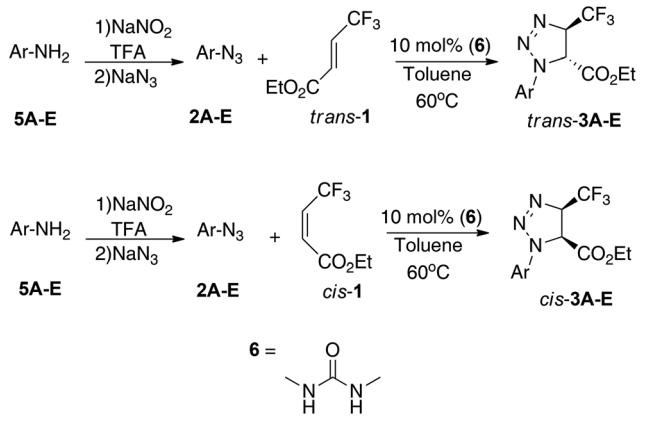
† Electronic supplementary information (ESI) available: Synthetic and photochemical procedures, as well as IR, ^{1}H and ^{13}C NMR. See DOI: 10.1039/c7pp00187h



Scheme 2

showed that the previously observed results are robust, with solid state diastereomeric ratios that are consistently greater (99 : 1 to 87 : 13) than those observed in acetonitrile solution (85 : 15 to 66 : 34).

Experimental

Chemicals

All of the aryl amines and solvents employed were commercially available and used without further purification.

Synthesis of aryl azides (2A–2E)

The following general protocol was used to synthesize the aryl azides. Aniline (6 mmol) was dissolved in 5 mL of trifluoroacetic acid. The solution was cooled to 15 °C and kept at this temperature throughout the reaction. An aqueous solution (2 M) of sodium nitrite was slowly added (32 mmol) and the reaction mixture was stirred for 30 min. Subsequently, an aqueous solution of sodium azide (32 mmol, 2 M) was added dropwise. The resulting mixture was allowed to warm to room temperature for one more hour. The reaction mixture was neutralized to pH 7 and extracted three times with 20 mL of dichloromethane. The crude mixture was purified by column chromatography using 1 : 7 (ethyl acetate : hexanes).

Synthesis of Δ^2-1,2,3-triazolines

All triazolines were synthesized using the following general procedure: ethyl 4,4,4-trifluorocrotonate (0.3 mmol), **2A** (0.3 mmol), and *N*,*N*′-dimethylurea (0.03 mmol) were dissolved in 1.5 mL of dry toluene and the reaction mixture was stirred for 32 hours at 60 °C under an argon atmosphere. After the initial 32 hours, an additional 0.3 mmol of ethyl 4,4,4-trifluorocrotonate was added to the reaction mixture. After 33 more hours of heating, the reaction was cooled when the disappearance of azide by TLC was observed. The crude mixture was rotary evaporated under vacuum and the reaction mixture was purified by column chromatography using an ethyl acetate : hexane mixture (1 : 7) as the eluent.

Solution photochemistry

Triazoline (*ca.* 5 mg) was dissolved in 1 mL of either deuterated acetonitrile or acetone in an NMR tube and the solution was freeze–pump–thawed for 3 cycles to ensure no gas was present in the reaction. The NMR tube was photolyzed using a medium-pressure Hg Hanovia lamp with a Pyrex emersion well filter with a cutoff of $\lambda \leq 290$ nm. The reactions were monitored by ^{1}H NMR and showed completion in less than one hour.

Solid-state photochemistry

Triazoline (*ca.* 3 mg) was crushed between two microscope slides and exposed to light from a medium-pressure Hg Hanovia lamp with a Pyrex emersion well filter with a cutoff of $\lambda \leq 290$ nm. The reaction was monitored by ^{1}H NMR and was completed in less than one hour.

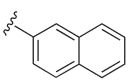
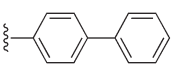
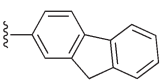
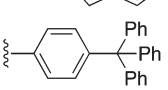
Results and discussion

Synthesis and characterization

To establish the stereospecificities of product formation in terms of the ratios of *trans*- and *cis*-aziridine products, various 1,2,3-triazolines were synthesized using a 1,3-dipolar cycloaddition of five different aryl azides (**2A–2E**) and the two geometric isomers of dipolarophile **1** (Table 1). The aryl groups used in this study contain phenyl (**2A**), 2-naphthyl (**2B**), 4-biphenyl (**2C**), 2-fluorenyl (**2D**), and 4-trityl phenyl (**2E**) as illustrated in Table 1.

Commercially available aryl amines were easily converted to their corresponding aryl azides (**2A–E**) under standard conditions in good yields ranging from 74–99% (Table 1).[12] The newly formed azide products were characterized by ^{1}H, and ^{13}C NMR spectroscopy, which matched the reported spectra from the literature, and the azido functional groups were shown to display the characteristic IR stretch at *ca.* 2200 cm^{-1} (see the ESI†). With the aryl azides in hand for the 1,3-dipolar cycloaddition, we used commercially available ethyl

Table 1 Isolated yields of aryl azides (**2A–E**) and aryl triazolines (*trans*-**3A–E** and *cis*-**3A–E**)

Structure	Azide yields	Triazoline yields	
	74% (**2A**)	22% (*trans*-**3A**)	12% (*cis*-**3A**)
	98% (**2B**)	80% (*trans*-**3B**)	14% (*cis*-**3B**)
	83% (**2C**)	51% (*trans*-**3C**)	21% (*cis*-**3C**)
	99% (**2D**)	65% (*trans*-**3D**)	18% (*cis*-**3D**)
	86% (**2E**)	74% (*trans*-**3E**)	22% (*cis*-**3E**)

(*E*)-4,4,4-trifluorobut-2-enoate (*trans*-**1**) as the dipolarophile for the cycloaddition. Alkene *trans*-**1** was selected due to its inherently electron poor nature resulting from the effects of the ethoxy ester and trifluoromethyl groups. Ethyl (*Z*)-4,4,4-trifluorobut-2-enoate (*cis*-**1**) was obtained by isomerizing *trans*-**1** under UV irradiation to afford the photostationary state of 3 : 1 (*trans*-**1** : *cis*-**1**). The samples of *cis*-**1** were subsequently purified by column chromatography. Triazolines were synthesized by performing 1,3-dipolarr cycloadditions by heating azides **1A–E** with either *trans*-**1** or *cis*-**1** in toluene with 10 mol% of dimethyl urea, which served as a hydrogen bond-donor catalyst, to obtain triazolines *trans*-**3A–E** and *cis*-**3A–E** in low to modest yields. The regiochemistry and stereochemistry of the triazolines were assigned based on ^{1}H and ^{13}C, which matched with the previous reports on Δ^{2}-1,2,3-triazolines *cis*-**3D** and *trans*-**3D**, which included their single crystal X-ray structures.[8] Furthermore, the differential scanning calorimetric analysis of triazoline *trans*-**3D** shows a relatively sharp endothermic transition which correlated with the melting temperature determined visually, and was immediately followed by a broad exothermic transition that corresponds to the thermal denitrogenation. This is illustrated in Fig. 1 with the DSC data from *trans*-**3D**, which melts at 131 °C and has a minimum for the decomposition peak at 171 °C.

Photochemical studies

Triazolines *trans*-**3A–E** and *cis*-**3A–E** were irradiated in solution using either acetonitrile-d_3 or acetone-d_6, or in the neat solid-state, using a medium-pressure Hg lamp (450 watts) equipped with a Pyrex filter to provide $\lambda \geq$ *ca.* 290 nm. To our delight, only the corresponding aziridine photoproducts were observed both in solution and in the solid state (Table 2). Solution experiments were carried out with *ca.* 5 mg ml^{-1} triazoline solutions that had been subjected to three freeze–pump–thaw cycles to ensure that photoreactions occurred free from oxygen. Solid state experiments were carried out with *ca.* 3 mg of finely powdered crystals sandwiched between two microscope slides. The reaction progress was monitored by ^{1}H NMR spectroscopy, which was also used to determine the ratio of

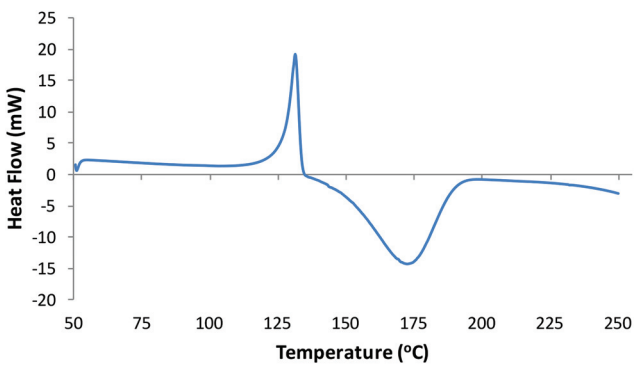
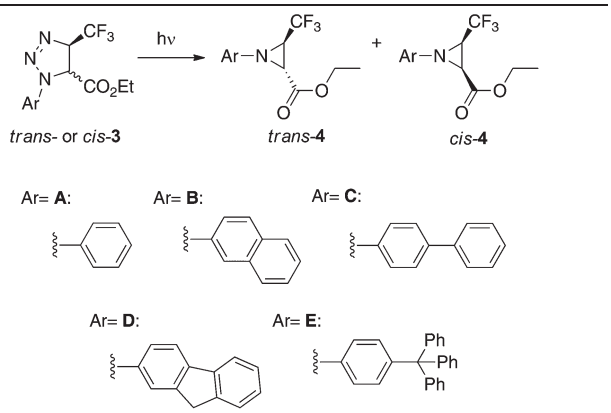


Fig. 1 Differential Scanning Calorimetry (DSC) of triazoline *trans*-**3D**. A sharp peak at 131 °C indicates melting and a broad peak at 171 °C shows denitrogenation of triazoline to form aziridine.

Table 2 Ratios of *cis*- and *trans*-aziridines from triazolines in solution and solid state[a]



Entry	Compound	CD_3CN *trans* : *cis*	$(CD_3)_2CO$ *trans* : *cis*	Crystals *trans* : *cis*
1	*trans*-**3A**	85 : 15	79 : 21	n.a.[b]
2	*trans*-**3B**	83 : 17	75 : 25	n.a.[b]
3	*trans*-**3C**	82 : 18	99 : 1	90 : 10
4	*trans*-**3D**	76 : 24	99 : 1	83 : 17
5	*trans*-**3E**	73 : 27	97 : 3	83 : 17
6	*cis*-**3A**	29 : 71	52 : 48	1 : 99
7	*cis*-**3B**	21 : 79	43 : 57	6 : 94
8	*cis*-**3C**	34 : 66	96 : 4	17 : 83
9	*cis*-**3D**	32 : 68	99 : 1	10 : 90
10	*cis*-**3E**	28 : 72	43 : 57	12 : 88

[a] Product ratios determined in triplicate with estimated errors of ±3%. [b] Triazolines were liquids at 300 K.

trans- to *cis*-aziridines identified by the different ^{1}H coupling constants, $J_{trans} \approx 2.3$ Hz and $J_{cis} \approx 6.5$ Hz.[14]

The photochemical results summarized in Table 2 include the product ratios obtained in triplicate with all five *trans*-triazolines in the top five entries, and those determined with the *cis*-triazolines in the bottom five. It is estimated that errors in the table are in the range of ±3%. The results obtained under direct excitation in acetonitrile solutions, upon triplet sensitization in acetone, and by direct irradiation in the crystalline solid state, are included in the left, middle, and right columns, respectively. The results of experiments carried out in acetonitrile revealed a high level of stereospecificity, with each triazoline isomer resulting in the preferential formation of the corresponding same isomeric aziridine product. As in the previous examples, this result implies that the biradical intermediates resulting from the denitrogenation of the five-membered heterocycle are formed in the singlet state and have no time to equilibrate before the bond formation to form the three-membered ring. Thus, the irradiation of *trans*-triazolines resulted in *trans* : *cis* ratios ranging from 85 : 15 to 73 : 27 (Table 2, third column, entries 1–5) and the direct photoexcitation of *cis*-triazolines resulted in analogous but opposite selectivities, from 21 : 79 to 34 : 66 (Table 2, third column, entries 6–10).

Experiments carried out in acetone, which is used both as a solvent and triplet sensitizer, are expected to reveal the reactiv-

ity of the longer-lived triplet state biradicals. In this case, unable to form the singlet state photoproduct before intersystem crossing to the singlet state, triplet biradicals are expected to have a greater opportunity for conformational equilibration. Thus, at a first approximation, one may expect the stability of the triplet state biradical to parallel the stability of the product, such that the *trans*-aziridine isomers should be preferred in the triplet-sensitized reaction. To verify this we performed calculations on the ground state energies of the equilibrium conformers of *trans*-**4A–D** and *cis*-**4A–D** at the B3LYP/6-31G* level of theory. We confirmed that the *trans* aziridines are indeed more stable than the *cis* aziridines. Energy differences of 2.6 and 2.3 kcal mol^{-1} were observed, respectively, for the *N*-phenyl (**4A**) and *N*-(4-phenyl) (**4C**) compounds, with the corresponding values of 6.3 and 6.4 kcal mol^{-1} for the analogous 2-naphthyl (**4B**) and 2-fluorenyl (**4D**) structures. We omitted aziridines **4E** due to their large size and long computing time, assuming that similar results should be observed. While our expectations on the relative energies of the *cis* and *trans N*-aryl aziridines were confirmed, we discovered that the experimental results of reactions carried out in acetone are not straightforward, as shown in the fourth column in Table 2. On one hand, one can see that five entries, including *trans*-**3C**, *trans*-**3D**, *trans*-**3E**, *cis*-**3C** and *cis*-**3D**, yield the *trans*-aziridine isomer in yields greater than 96% and conform to our original expectations. However, the stereoselectivities observed with compounds *trans*-**3A** and *trans*-**3B** are diminished to *ca.* 75 and 79% *trans*, respectively, and those observed from *cis*-**3A**, *cis*-**3B** and *cis*-**3E** are closer to 50 : 50. Additional measurements revealed that the product ratios are not dependent on the extent of conversion or irradiation time, and experiments carried out with other triplet sensitizers, including benzophenone, xanthone and biacetyl, all using the same freeze–pump–thaw method, showed that the products in the table do reflect the reactivity of the triplet excited state. The fact that different product ratios are observed from triplet sensitized experiments that start from the *cis*- and *trans*-isomers of the same triazoline indicates that biradical equilibration does not take place. For example, *trans*-**3A** and *cis*-**3A** give aziridine **4A** in *trans* : *cis* ratios that are 79 : 21 and 52 : 48, respectively. This observation indicates that intersystem crossing and ring closure compete with the rate of conformational equilibration, a fact that has been shown for a number of short chain 1,3-biradicals and 1,4-biradicals.[15–18]

Photochemical experiments in the crystalline solid state included the samples of *trans*-triazolines **3C–E** and *cis*-triazolines **3A–E**. The samples of *trans*-(*N*-phenyl)- and *trans*-*N*-(2-naphthyl)-triazolines *trans*-**3A** and *trans*-**3B** were liquids under ambient conditions. We were able to confirm that, as expected, stereospecificities obtained in the solid state are greater than those obtained under direct irradiation in solution. For example, the reaction of *N*-(4-biphenyl)-*trans*-triazoline **3C** improved the formation of *trans*-aziridine **4C** from 82% in solution to 90% in the solid state (entry 3, columns 3 and 5). Similar observations were made with *trans*-triazolines **3D** and **3E**, and with all *cis*-triazolines, which systematically give the *cis*-aziridine as the preferred photoproduct with yields that range from 83% (*cis*-**3C**) to 99% (*cis*-**3A**). While a higher stereospecificity was expected in the solid state compared to solution, it appears that hindered bond rotation in the 1,3-biradical intermediate is not large enough to guarantee a very high specificity in all cases. The lack of correlation with respect to the size of the *N*-aromatic substituent suggests that isomerization occurs by bond rotation about the biradical $ArNC(CO_2Et)–CHCF_3$ bond. This hypothesis is suggested by a previously reported example where the stereospecificity of a 4-methyl-4-trifluoromethyl triazoline analog was shown to be quantitative.[8]

Mechanistic analysis

To explore the type and range of experimental parameters that affect the photoreaction, and perhaps the subtle differences between the product ratios of *trans* : *cis* aziridine in solution and in the solid-state, we first analysed the role of solvent polarity. While we postulated a biradical intermediate resulting from a homolytic cleavage reaction (Fig. 2), we reasoned that a zwitterionic intermediate would have different stabilizing interactions in different solvents, which may result in different *trans* : *cis* aziridine ratios.[19] The results of photochemical experiments using triazoline *trans*-**3C** in methanol, acetonitrile and carbon tetrachloride, which range in $E_T(30)$ values from 32–55 kcal mol^{-1},[20] showed no changes in stereospecificity (Table 3).

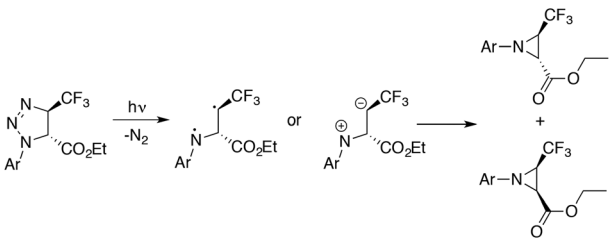
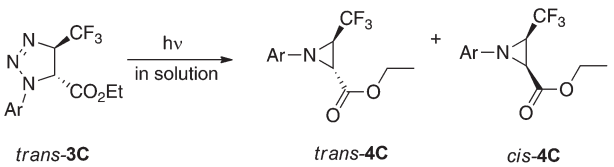


Fig. 2 Plausible biradical intermediate *versus* zwitterionic intermediate to form aziridines.

Table 3 Solution-state photochemistry of triazoline *trans*-**3C** in solvents with different polarities[a]



trans-**3C** *trans*-**4C** *cis*-**4C**

Solvent	$E_T(30)$ (kcal mol^{-1})	*trans*-**4C** (%)	*cis*-**4C** (%)
Methanol[a,b]	55	80	20
Acetonitrile[a]	46	82	18
Carbon tetrachloride[a]	32	81	19

[a] Product ratios determined in triplicate with estimated errors of ±3%. [b] Products showed both methyl ester and ethyl ester.

A plausible mechanism to account for different *trans* : *cis* aziridine ratios under direct excitation in solution and in solids would be that the *trans*-triazolines form stereospecifically to the *trans*-aziridine product, but continuous irradiation may provide a pathway for isomerization. However, experiments carried out with pure aziridine *trans*-**4C** in solution and in the solid state for several hours under the previously utilized reaction conditions led to no observable change, ruling out the possibility of *trans*-aziridine isomerization. In order to determine whether one can steer the ratios of *cis*- to *trans*-aziridines in the solid state, we analysed the effects of temperature from 25 °C to −196 °C. We observed a decrease in the stereospecificity of the reaction through this temperature range with the *trans* : *cis* ratio changing from 84 : 16 at 25 °C to 66 : 33 at −40 °C and below, showing that the optimum temperature to provide the highest *trans*/*cis* aziridine ratios is around room temperature.

Conclusions

In conclusion, we have synthesized ten different diastereomerically pure triazolines and investigated their stereospecificities to form aziridines in solution and in the solid state. We have shown that the photochemistry of Δ^2-1,2,3-triazolines are moderately stereospecific in solution and more so in the solid state. The solid-state photochemistry of triazolines provides an efficient and solvent-free method to synthesize their corresponding aziridines. Specifically, we found that the photochemistry of Δ^2-1,2,3-triazolines in singlet excited states would afford the kinetically controlled *trans*- to *cis*-aziridine ratios, whereas efficient triplet sensitization would form the thermodynamically controlled product ratios. Using various solvent studies, variable temperature studies, and product analysis, we propose that the photochemistry of Δ^2-1,2,3-triazolines to form aziridines follows a homolytic cleavage to expel nitrogen and form the 1,3-biradical species.

Conflicts of interest

The authors declare no competing financial interest.

Acknowledgements

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