ChemPubSoc Europe

DOI: 10.1002/chem.201600479

CHEMISTRY A European Journal Full Paper

Synthetic Methods |*Hot Paper*|

Unusually Facile Thermal Homodienyl-[1,5]-Hydrogen Shift Reactions in Photochemically Generated Vinyl Aziridines

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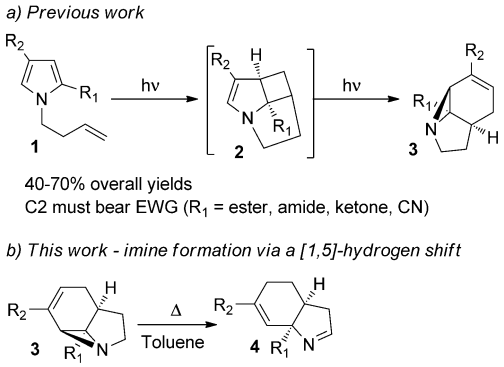
Abstract: A range of photochemically generated tri- and tetracyclic vinyl aziridines have been found to undergo a general and surprisingly low temperature ring opening through a [1,5]-hydrogen shift reaction. The rate of the process was found to be highly dependent on the structure and substitution around the azirdine ring and the alkene terminus, with some substrates being observed to undergo ring opening at temperatures as low as 25 °C. The rigid nature of these polycyclic systems precludes a conformational explanation of these rate differences, and an Eyring study confirmed a negligible entropic barrier to the reaction. However, the Eyring plots for two different aziridines systems showed a significant difference in their enthalpies of activation. It is therefore believed that the levels of aziridine ring strain, as well as electronic effects, are the dominant factors in this sequence.

Introduction

Aziridines have long proved to be useful synthetic intermediates due to their ability to undergo nucleophilic ring openings and thermal [2+3] cycloaddition reactions.[1] Vinyl aziridines possess a further manifold of reactivity[2] as the π-bond enables the possibility of S_N2' ring processes,[3] additional cycloaddition chemistry under Pd-catalysis[4] and Tsuji–Trost[5]-type processes. We recently reported the novel, photochemical synthesis of a range of tricyclic vinyl azridines **3** (via cyclobutanes **2**) starting from *N*-butenyl pyrrole precursors **1** as shown in Scheme 1, and demonstrated that scale-up of these reactions could be achieved in a simple manner through the use of a fluorinated ethylenepropylene (FEP) flow reactor.[6] Such products possess a wealth of stereochemistry and functionality for further derivatisation, perhaps most interestingly their potential as dipolarophiles and the possibility of performing nucleophilic attack at various sites.

This potential to generate a high degree of structural complexity in only two steps, combined with ease of scale-up, prompted us to investigate a number of reaction possibilities. Recent work in our laboratories[7] has demonstrated that these complex vinyl aziridines indeed undergo a variety of efficient Pd-catalysed ring-opening processes under unusually mild processes for non-activated (i.e., at N) aziridines. During this study,



Scheme 1. Thermal rearrangement of tricyclic aziridines.

it was quickly revealed that an alternative non-catalysed process was operating at temperatures greater than 50 °C. This was identified as a thermal homodienyl-[1,5]-hydrogen shift (retro-ene reaction), leading to imines **4** as shown in Scheme 1. Whereas this type of rearrangement has been extensively studied in vinylcyclopropanes,[8] such reactions have less frequently been reported to occur in vinylaziridines. Somfai[9] has studied the generality of this type of process with conformationally flexible vinylaziridines, and there have been other infrequent reports of this rearrangement, often as a competitive side reaction.[10]

In our case, it was significant to note that these reactions would proceed smoothly at relatively low temperatures; indeed, further studies showed it to operate as low as ambient temperature with some substrates. We therefore elected to study the scope and mechanism of this unusually facile reaction and the results are reported here.

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Supporting information for this article including supplementary figures and tables, full experimental procedures, analytical data, kinetics data, as well as copies of ^1H and ^{13}C NMR data is available under http://dx.doi.org/10.1002/chem.201600479.

Results and Discussion

To carry out a broad study of this reaction, we needed to synthesise a diverse range of substituted pyrroles and investigate their subsequent photochemistry. Substrates were selected based on the availability of the starting pyrroles as well as the success of the photochemical step. The substituted pyrroles were synthesised using standard heterocyclic techniques and were then irradiated at 254 nm. We also took the opportunity to explore, for the first time, the photochemistry of more complex tetrahydroindolone-derived starting materials,[11] which gave access to the more elaborate tetracyclic aziridines **5** and **7** upon irradiation at 254 nm (see Supporting information for full details).

With this diverse range of aziridines in hand, we then studied their thermal rearrangement (Table 1). As can be seen, the [1,5]-hydrogen shift reaction occurs in high yield for all substrates, tolerating a range of functional groups (ester, amide, nitrile and ketone). The yield remains high even upon substitution of the double bond (entries 7–13), with only two examples (entries 9 and 10) displaying minor products from side reactions.[12] In every case, a single diastereomer was produced. Rearrangement of compound **27** (entry 12) was also successful, indicating that deuterium could be transferred as well as hydrogen, albeit at a reduced rate compared to undeuterated **19** (entry 8, vide infra). Compounds **21**, **23**, **25**, **27**, **29** and **31** gave complete stereospecificity at the newly formed tertiary centre, and the relative stereochemistry of these products was proven through the ^{1}H NMR NOE studies. This stereospecificity is indicative of a concerted and facially selective thermal [1,5]-hydrogen shift, and this view was supported by subsequent labelling studies.

Whereas this screen showed the reaction to be highly general, we were interested to observe cases (entries 13 and 14) where more forcing conditions than toluene at reflux were required. This reinforced previous observations in which attempts had been made to perform chemistry on such aziridines; the conversion of aziridine **15** to imine **16** was first noted during an attempted nucleophilic ring opening at 50 °C, whereas aziridine **29** had been found to be unreactive under identical conditions. Remarkably, substrates **5**, **7** and **9** were seen to undergo conversion to the imine product at room temperature. This difference in reaction rate was intriguing, both from a theoretical point of view and because a better understanding of the factors accelerating this reaction might help minimise its competition as a side reaction in other transformations.[7] Additionally, previous studies, most notably those of Somfai,[9a,b] had generally shown this type of [1,5]-hydrogen shift to be facile only when an activating group (e.g., ester, phenyl) was present at the migration origin. Subsequent studies by Somfai of the [1,5]-hydrogen shift reactions of various substituted, conformationally flexible vinyl aziridines showed relatively small differences in reaction rate unless the alkene geometry was varied.[9c] These variations in rate were largely ascribed to steric effects on conformation, which we felt were unlikely to have a large impact in rigid systems such as ours. Given this, we elected to perform a more detailed study, both to confirm that a standard, concerted mechanism was still operating and also to gain a better understanding of the reason for this large variation in reaction rate.

To this end, the reactions in Table 1 reactions were performed in [D_8]toluene at 100 °C and the progress monitored using a 500 MHz NMR with 1,3,5-trimethoxybenzene as an internal standard. An initial screen of concentrations for substrates **15** and **19** (entries 6 and 8) showed the reactions to be first order. All subsequent data was found to fit first-order kinetics, and plots of ln[substrate] versus *t* gave the rate constants shown in Table 1.[13] For substrate **9**, the reaction was so rapid at 100 °C, it was repeated at 80 °C to generate a second, more accurate rate constant. Substrates **5** and **7** were found to be too reactive to be monitored at 100 °C, and were followed at the temperatures specified.

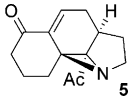
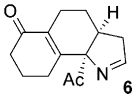
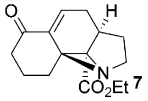
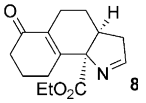
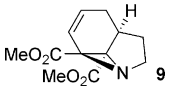
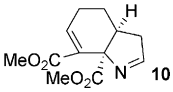
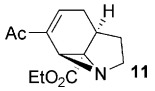
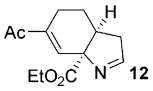
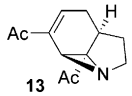
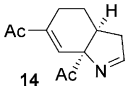
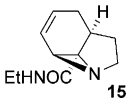
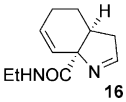
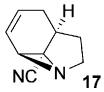
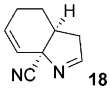
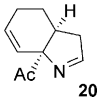
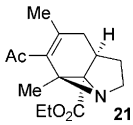
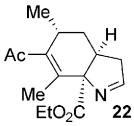
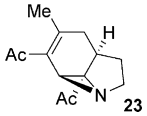
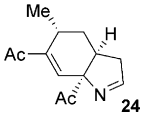
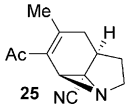
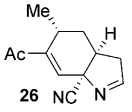
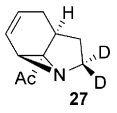
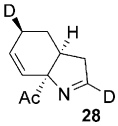
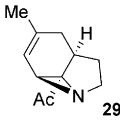
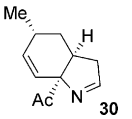
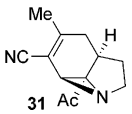
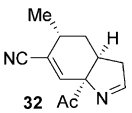
The results show some clear trends, which deserve further comment. The most reactive substrates proved to be the tetracyclic species **5** and **7**, with the next most reactive being **9**, which possessed electron-withdrawing groups (EWG) on both aziridine ring carbons. Although these high reaction rates were in some ways unsurprising as all three of these substrates were seen to rearrange upon standing at room temperature, this degree of reactivity appears not to have been previously documented in any other class of vinyl aziridine.[14] Substrates with an EWG conjugated to the double bond of the starting material (entries 4 and 5) were seen to be second fastest, with the extra EWG increasing the rate by a factor of 5 (i.e., entry 5 versus entry 8). Aziridines with a single EWG (entries 6–8) followed this pattern and reacted more slowly again. Slower still were those substrates possessing a methyl group at the migration terminus position (entries 9–13), all of which proceeded extremely slowly. It can also be seen that transfer of deuterium rather than hydrogen (entries 8 and 12) slows the reaction substantially (vide infra).

The effect of solvent polarity on the rate of reaction was of interest to us, and substrate **15** was selected to perform a brief solvent screen (Table 2). It can be seen that increasing solvent polarity leads to a small but significant increase in reaction rate, likely consistent with a small degree of charge formation in the transition state.

We then proceeded to investigate the incorporation of deuterium into the reacting aziridines. Deuterated substrates **33 a**, **33 b** and **34** were synthesised through alkylation of the pyrrole with the appropriate tether using either phase transfer or Mitsunobu reaction conditions. The tethers themselves were synthesised by reduction of the appropriate ester/aldehyde using $LiAlD_4$ (see Supporting Information for full details).

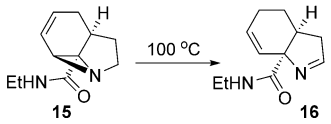
Thermolysis of bisdeuterated amide **34** showed that the transfer of deuterium rather than hydrogen slowed the reaction significantly, with a k_H/k_D of 4.0 (Table 3). However, although a primary kinetic isotope effect (KIE) is clearly present here, the presence of two deuterium atoms makes the observed effect a combination of both this and a secondary kinetic isotope effect. Additional studies on a diasteroemeric mixture of monodeuterated **33** allowed us to remove this complication by following the reaction of each diastereomer separately. The chemical shifts for the *exo*/*endo*-hydrogen atoms of

Table 1. Yields and rate constants for the [1,5]-hydrogen shift reactions.

Entry	Substrate	Product	Yield [%][a]	T [°C]	Concentration [M]	Rate, k [s^{-1}][b]	Relative rate
1	 5	 6	80	80[c]	0.144	$1.8\pm0.1\times10^{-2}$	2520
2	 7	 8	89	80[c]	0.235	$1.33\pm0.02\times10^{-2}$	1860
3	 9	 10	67	100 80[d]	0.121 0.121	$2.25\pm0.03\times10^{-3}$ $7.59\pm0.05\times10^{-4}$	315 106
4	 11	 12	85	100	0.136	$4.32\pm0.06\times10^{-4}$	60.4
5	 13	 14	83	100	0.196	$4.28\pm0.02\times10^{-4}$	59.9
6	 15	 16	100	100 100 100	0.084 0.14 0.28	$1.76\pm0.01\times10^{-4}$ $1.79\pm0.02\times10^{-4}$ $1.80\pm0.02\times10^{-4}$	25.0
7	 17	 18	90	100	0.093	$1.31\pm0.01\times10^{-4}$	18.3
8	 19	 20	98	100 100	0.25 0.13	$8.05\pm0.02\times10^{-5}$ $8.00\pm0.05\times10^{-5}$	11.3
9	 21	 22	71[e]	100	0.10	$7.26\pm0.09\times10^{-5}$	10.2
10[f]	 23	 24	71[e]	100	0.10	$<7\times10^{-5}$	<10
11	 25	 26	70	100	0.099	$6.4\pm0.1\times10^{-5}$	9.0
12	 27	 28	–[g]	100	0.094	$1.93\pm0.02\times10^{-5}$	2.7
13	 29	 30	74	100	0.24	$1.63\pm0.01\times10^{-5}$	2.3
14	 31	 32	90	100	0.20	$7.15\pm0.08\times10^{-6}$	1

[a] Isolated yield after chromatography. [b] See Supporting Information for concentration profiles and log plots. Errors calculated using a least squares analysis. [c] Reaction proved too fast to follow at 100 °C. [d] Reaction also performed at 80 °C to obtain a more accurate rate constant. [e] Yield reduced by competing elimination reaction.[12] [f] The rate constant for this substrate represents the sum of both the desired rate constant and that of the competing elimination reaction.[13] [g] Product not isolated.

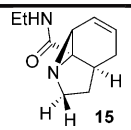
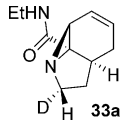
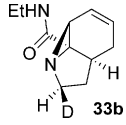
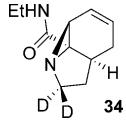
Table 2. Solvent screen for the [1,5]-hydrogen shift reaction of amide **15**.



Entry	Solvent	k [s^{-1}][a]	Relative rate
1	[D_8]toluene	$1.79 \pm 0.01 \times 10^{-4}$	1
2	[D_5]nitrobenzene	$2.79 \pm 0.06 \times 10^{-4}$	1.58
3	[D_6]DMSO	$3.66 \pm 0.05 \times 10^{-4}$	2.07

[a] See Supporting Information for concentration profiles and log plots. Errors were calculated using a least squares analysis.

Table 3. Kinetic isotope effect studies.

Entry	Substrate	k [s^{-1}][a]	k_H/k_D
1	 **15**	$1.79 \pm 0.2 \times 10^{-4}$	0.86 (**15**/**33 a**)
2	 **33a**	$2.07 \pm 0.04 \times 10^{-4}$	4.6 (**33 a**/**34**)
3	 **33b**	$0.41 \pm 0.2 \times 10^{-4}$	4.4 (**15**/**33 b**)
4	 **34**	$0.447 \pm 0.03 \times 10^{-4}$	0.92 (**33 b**/**34**)

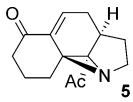
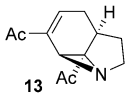
[a] See Supporting Information for concentration profiles and log plots. Errors were calculated using a least squares analysis.

the CH_2 of interest were assigned using ^{1}H NMR TOSCY and NOESY studies (see Supporting Information), allowing the identification of the two isomers, D_{exo} (**33 a**) and D_{endo} (**33 b**). Thus, following the reaction of this diastereomeric mixture by ^{1}H NMR spectroscopy allowed the rates of the two reactions to be determined. The two pairs of results give an average primary KIE of 4.5 ($k_H/k_D = 4.4$ for **15** versus **33 b**, and 4.6 for **33 a** versus **34**), and an average secondary KIE of 0.89 ($k_H/k_D = 0.86$ for **15** versus **33 a** and 0.92 for **33 b** versus **34**).

Similarly, studies involving ketone **27** were seen to give essentially the same results (Table 1, entries 8 and 12), with a combined primary and secondary kinetic isotope effect of 4.2. In addition to showing the reaction to be stereospecific through a hydrogen-atom transfer, these results are also consistent with the reaction proceeding though a concerted, although somewhat asynchronous mechanism.

Although these studies confirmed that these tricyclic substrates reacted through the same mechanism determined by Somfai for less constrained examples,[15] they shed no light on why there was such a wide range of reaction rates, or indeed why some of these species were sufficiently reactive to undergo the rearrangement at room temperature. We hypothesised that a combination of ring strain and a highly rigid conformation was responsible. Eyring plots have previously been employed to probe similar systems,[15] and we applied this approach to substrates **5** and **13**. These were chosen as they reflect the most reactive substrate (**5**) and a substantially less reactive substrate (**13**) that still underwent the rearrangement at a range of temperatures below the boiling point of [D_8]toluene. This generated the rate constants in Table 4. It can be seen that in the case of **5**, the reaction rate is appreciable even at room temperature, faster in fact than for some substrates at 100 °C (i.e., Table 1, entries 12 and 13). From the plots of ln(k/T) versus $1/T$, the enthalpies and entropies of activation were calculated (see Supporting Information) and are presented in (Figure 1).

Table 4. Variation of rate constant with temperature for substrates **5** and **13**.

Entry	Substrate	T [°C]	k [s^{-1}][a]
1	 **5**	80	$1.8 \pm 0.1 \times 10^{-2}$
		60	$2.45 \pm 0.03 \times 10^{-3}$
		40	$2.37 \pm 0.03 \times 10^{-4}$
		25	$3.40 \pm 0.01 \times 10^{-5}$
2	 **13**	100	$4.28 \pm 0.02 \times 10^{-4}$
		90	$1.651 \pm 0.003 \times 10^{-4}$
		80	$5.496 \pm 0.004 \times 10^{-5}$
		70	$1.563 \pm 0.001 \times 10^{-5}$

[a] See Supporting Information for concentration profiles and log plots. Errors were calculated using a least squares analysis.

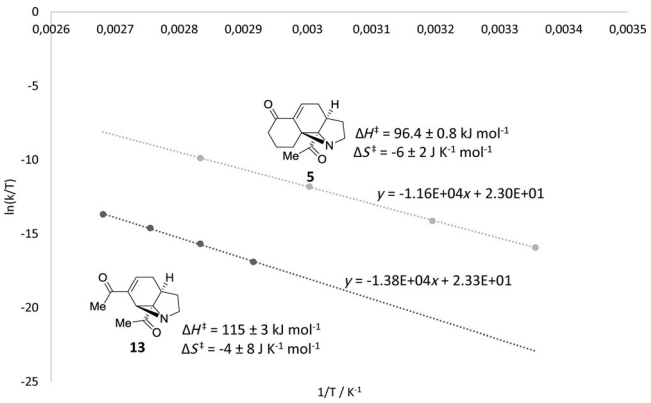


Figure 1. Eyring plots and thermodynamic parameters for the reactions of substrates **5** and **13**.

It can be seen that in both cases the entropy of activation is extremely low, suggesting that minimal reorganisation is needed to reach the reactive conformation. This is consistent with our hypothesis that the constrained and inflexible nature of these aziridines is a key factor in their high reactivity. Indeed, similar Eyring analysis of the Somfai data gives a $\Delta S^{\ddagger}$ of -61 J K^{-1} mol^{-1}, revealing a considerably larger entropic barrier.[16] This, however, does not explain the large difference in

rate constants observed across the series. This owes to the considerable variation in the enthalpy of activation, which is nearly 20 kJ mol^{-1} higher for **5** than that of **13**.

It seems probable that at least part of the explanation for this difference is the level of strain present in the aziridine ring. For comparison, the $\Delta H^{\ddagger}$ of the acyclic system investigated by Somfai[15] is 88.9 kJ mol^{-1}, making this barrier somewhat less than that of even our most reactive substrate. Clearly, the value can reflect both the degree of ring strain and other factors, making it possible that this lower barrier is owed to the presence of an activating group (i.e., CO_2tBu) at the migration origin.

These results also permit the calculation of rate constants for tetracyclic substrate **5** at other temperatures. At 100 °C, a temperature at which the high reaction rate precluded measurement by ^{1}H NMR spectroscopy, this calculated rate is 0.11 s^{-1}, more than 15000 times faster than that of the least reactive substrate (Table 1, entry 14) at the same temperature. This large variation in rate explains some of the behaviour observed when attempting catalytic reactions with these species, and clearly underlines the importance of choosing appropriate substrates for use in the palladium-catalysed processes we recently reported.

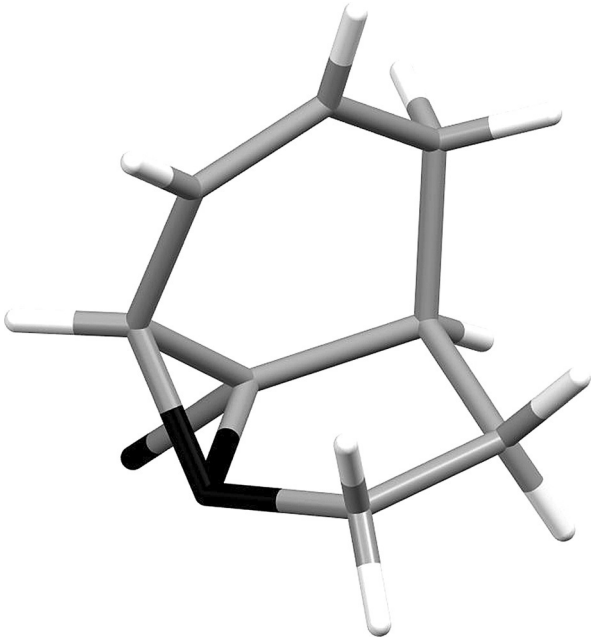


Figure 2. X-ray crystal structure of compound **17**.[17]

Conclusion

In conclusion, we have shown that the [1,5]-hydrogen shift reactions of photochemically generated tricyclic aziridines is a general process that frequently occurs at unusually low temperature. Such reactions provide easy and stereospecific access to a wide range of highly functionalised bicyclic and tricyclic imines. There is considerable variation in reaction rate, and several reactions are unusually rapid, especially in view of the lack of an activating group normally required to accelerate such processes. Given the constrained nature of these systems, and negligible entropy of activation, it is unlikely this variation is due to steric effects on the conformation of the reacting molecules as has been proposed for other systems. More plausibly, our suggestion of this acceleration instead of what would be expected is in large part due to the compounds already existing in a suitable conformation to undergo reaction. For example, Figure 2 shows the crystal structure of compound **17**,[17] demonstrating that the migrating *endo*-hydrogen is orientated above the π-system of the reacting alkene, and there is little distance (3 Å) between it and the migration terminus.

We speculate that in the anomalously fast (i.e., RT) cases, this low entropic barrier combines with an increased level of ring strain. In compounds **5** and **7**, this derives from the addition of an extra ring, and in compound **9**, it comes from the addition of a bulky substituent on the aziridine ring. In the other substrates, less strain is present and the reactions occur at lower rates; however, other effects can still be observed in these systems. For instance, the presence of an EWG conjugated to the non-reacting end of the π-system tends to lead to faster reactions, presumably by reducing the enthalpy of activation, and substitution of the migration terminus leads to reduced reaction rates, although it remains unclear whether this is an entropic or enthalpic effect.

Although this additional mode of reactivity has the potential to cause complications when attempting other transformations on these aziridines, we have shown that it is a general and synthetically useful process in its own right. In addition, the kinetic data shows that certain structural features accelerate this thermal process, enabling better design of photochemical products for further catalytic transformation.

Acknowledgements

We would like to thank EPSRC for funding (EP/K006053/1), Mairi Haddow for X-ray crystallography, and Dr. Craig Butts and Mr. Paul Lawrence for their invaluable assistance with the NMR studies.

Keywords: aziridine · photochemistry · reaction kinetics · rearrangement · sigmatropic

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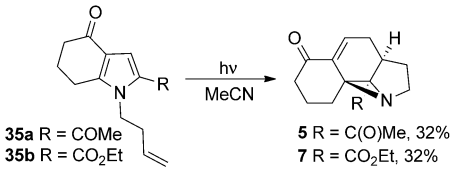
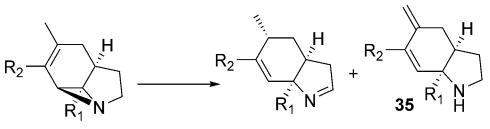
[11] Irradiation of tetrahydroindolones **35a** and **35b** yielded tetracyclic aziridines **5** and **7**, respectively, in moderate yield. These yields are lower than would be anticipated due to the [1,5]-hydrogen shift reactions of these species proceeding efficiently at room temperature, leading to difficulties in their purification and the products being isolated as mixtures with the corresponding imine. Yields of the remaining photochemical reactions are tabulated in the SI.



[12] In the cases of **21** and **23**, elimination products of type **35** were also formed.



[13] In the case of **23**, the competing elimination reaction was appreciable (final ratio 3:2); in this case, the rate constant is therefore a sum of the first-order rate constants for these two processes (see Supporting Information).

[14] The only rate constants available for such systems are those of Somfai (see ref. [15]). Our most reactive system (**5**) rearranges 58 times faster ($k = 1.8 \times 10^{-2}\ s^{-1}$ versus $3.104 \times 10^{-4}\ s^{-1}$) under similar conditions (80 °C, in toluene and *para*-xylene, respectively).

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[16] Comparison of our data with that of ref. [15] was complicated by their use of an Arrhenius rather than an Eyring plot to calculate entropy. Consequently this value represents a recalculated $\Delta S^{\ddagger}$ using the raw data given in ref. [15] (p-xylene) using an Eyring approach. For comparison, the original, Arrhenius-derived value by Somfai was $\Delta S^{\ddagger} = -53\ J K^{-1} mol^{-1}$.

[17] CCDC 1488690 (**17**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

Received: February 1, 2016
Published online on July 6, 2016