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Tetrabutylammonium-assisted diastereoselective [6π]-photocyclization of acrylanilides

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ABSTRACT

Tetrabutylammonium salts are remarkably effective for increasing diastereoselectivities in [6π]-photocyclization reactions of acrylanilides. This TBA^+-assisted photocyclization is applicable to a variety of acrylanilides to afford *trans*-dihydroquinolones. Using a d_5-labeled substrate, it was elucidated that a tetrabutylammonium ion shields a zwitterionic intermediate from an intermolecular H-transfer, which enables preferential occurrence of the [1,5] H-shift to give *trans* products stereoselectively.

Introduction

[6π]-Photocyclization reactions of acrylanilides are an attractive method for the construction of the dihydroquinolone framework through a C–C bond formation between sp^2 carbons without using any reagents.[1–7] This reaction consists of two successive processes, the first of which is a 6π-electrocyclic ring closure that occurs in a conrotatory manner, and the second step is an intra- or intermolecular H-transfer, which has been established by a number of publications.[2–7] In view of the stereochemical outcome, the ring closure and the H-transfer processes determine enantio- and diastereoselectivity, respectively (Scheme 1). Control of the enantioselectivity has been performed using chiral hosts,[3,4] templates[3,5] and auxiliaries,[6] and axially chiral substrates.[7] In contrast, diastereoselective approaches remain unexplored except in solid-state reactions.[4] This is due to the difficulty of controlling a reaction with three possible H-transfer pathways (a)–(c), which are keys to the diastereo-determining process. In a zwitterionic intermediate, **A**, illustrated in Scheme 1, the pathway (a) is an intramolecular [1,5] H-shift leading to *trans* products, and the pathways (b) and (c) are intermolecular H-transfer processes leading to *trans* and *cis* products, respectively. As dihydroquinolones are key intermediates for the synthesis of n-NOS inhibitors[8] and the framework structures of several natural products,[9] the development of a general method for the diastereoselective synthesis of dihydroquinolinones is of importance.

In our previous report, tetraalkylammonium salts were effective for controlling the conformation of substrates in Norrish-Yang reactions through an ammonium-π interaction.[10] We presumed that the addition of an ammonium would affect the diastereoselectivity of the [6π]-electrocyclic reaction by inhibiting the H-transfer pathway (c). The concept underlying our strategy is outlined in Scheme 2. If the tetrabutylammonium ion (TBA^+) forms a complex with the zwitterionic intermediate **A** and shields it from an intermolecular H-transfer, an intramolecular suprafacial [1,5] H-shift predominantly proceeds to give a *trans* compound diastereoselectively. In this communication, we report that tetrabutylammonium salts effectively assist the formation of *trans*-dihydroquinolones in the [6π]-photocyclization of acrylanilides.

Results and discussion

In an initial investigation, photocyclization reactions of 1-cyclopentene-1-carboxyanilide (**1a**)[11] were carried out by irradiation with a 450 W high-pressure mercury lamp in various reaction conditions (Table 1). Irradiation of **1a** in CH_2Cl_2 gave *cis*-[12] and *trans*-dihydroquinolones (**2a**) with no selectivity (entry 1). In contrast, irradiation in the presence of tetrabutylammonium salts gave *trans*-**2a** predominantly (entries 2–7); the stereochemistry of the compounds was confirmed by the X-ray structural analysis[13]

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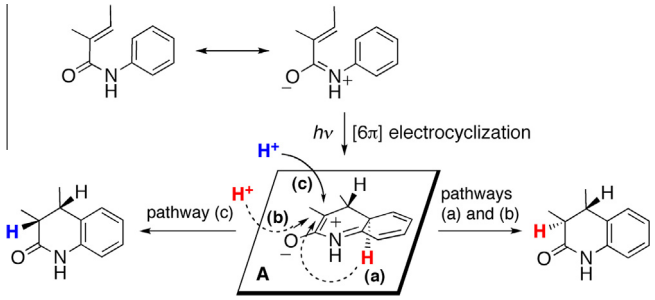
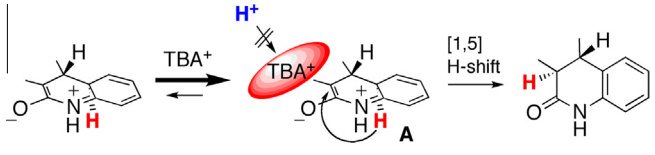


Scheme 1. A mechanism for the [6π]-photocyclization of acrylanilide to *cis*- and *trans*-dihydroquinolones through intra- and intermolecular H-transfer reactions.

(Fig. S1). Among various counter anions, chloride and bromide anions are effective for the stereoselectivity and the yield, respectively. The lower conversion seen when using Bu_4NF is due to the formation of an unfavorable conformation for cyclization due to a H-bond between the fluoride ion and the NH moiety.[14] When the reaction was conducted at −40 °C, the selectivity was improved (entry 5). The chain length of the ammonium salts had little effect on the selectivity (entries 4, 8 and 9). Tetrabutylphosphonium bromide also effectively gives a similar result, whereas, CsF had little influence on the diastereomer ratio (entries 10 and 11); this suggests that oniumions are required for the selective formation of the *trans* isomer. THF and CF_3Ph were more effective solvents than CH_2Cl_2 in giving *trans*-**2a** (entries 12–15). Lowering the temperature gave a higher selectivity (entry 16). Decreasing the amount of tetrabutylammonium bromide (TBAB) from 5.0 to 3.0 equiv had little effect on the diastereomer ratio (entry 17). Further decreasing the amount from 3.0 to 1.0 equiv resulted in a small reduction of the *trans* isomer (entry 18). The fact that 0.5 equiv of TBAB is still effective for the *trans*-selectivity suggests a catalytic behavior of TBAB (entry 19).

The scope of this method was studied using a variety of compounds, **1b**–**1h**. Table 2 shows the results for the photocyclization of these substrates in both the presence and absence of TBAB. In all cases, the *trans*-selectivities in the presence of TBAB are much higher than those in the absence of TBAB. The *trans* and *cis* stereochemistry of the products was assigned by comparing the ^{1}H NMR chemical shifts of the methine protons with those of *cis*- and *trans*-**2a** (Table S4). Irradiation of **1b** and **1c**, having an electron-withdrawing and a donating group, produced *trans*-**2b** and **2c** as major products, respectively (entries 1–4). The *trans* selectivity in the case of **1c** improved when the reaction was conducted at −20 °C (entry 5). In the case of *N*-methyl substrate **1d**, the selectivity was similar to that of unsubstituted **1a** (entry 6). This is in contrast to the reported supramolecular photochemistry, in which the NH moiety is important in the formation of host-guest complexes.[3] In the case of **1e**, which has an indene moiety, TBAB is effective at improving the *trans* selectivity (entries 8 and 9). X-ray structural analyses of both the *trans* and *cis* diastereomers of **2e** confirmed their stereochemistry[13] (Figs. S2 and S3). It is interesting that while irradiation of **1f** produced *cis*-**2f** as a major product, the addition of TBAB changed the selectivity to afford *trans*-**2f** in high yields (entries 10 and 11).



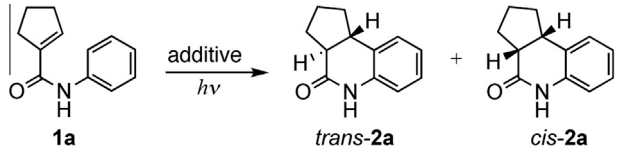
Scheme 2. A Strategy for the preferential occurrence of the [1,5] H-shift by blocking the intermolecular H-transfer using a TBA^+.

The present method can be applied to heterocyclic compounds, such as furan[15] and thiophen[16] derivatives. It has been reported that the photocyclization of these compounds is accompanied by dehydrogenated and rearranged products via secondary reactions.[15,16] Irradiation of **1g**[4b] for 24 h produced **2g** in a very low yield (entry 13), whereas the TBAB was highly effective at increasing the yield of *trans*-**2g**[4b] (entry 12). In the case of the thiophene derivative **1h**, the lower yield and selectivity were much improved by the addition of TBAB to give *trans*-**2h** in a good yield (entries 14 and 15). These results suggest that TBA^+ seems to prevent the usual secondary reactions.

All these results clearly show that TBAB enhances the diastereoselectivity to yield *trans*-isomers throughout the [6π]-photocyclization reactions of various substrates. It should be noted that no isomerization from *cis*-**2a** to *trans*-**2a** was detected; stirring *cis*-**2a** in the presence of TBAB for 5 h did not produce *trans*-**2a**. In addition, the structure optimization of *cis*- and *trans*-**2a** and **2e** by DFT calculations at the B3LYP/6-31G* level shows that the *cis* isomers are much more stable than the *trans* isomers. The energies of *trans*-**2a** and **2e** are 2.45 and 1.93 kcal/mol higher than those of *cis*-**2a** and **2e**, respectively (Figs. S8 and S9). These are consistent with the results of the isomerization experiment described above. Although several methods have been reported for the synthesis of *cis*-dihydroquinolones,[8,9] no general methods for the synthesis of the *trans* isomers have been reported. Therefore, the present results would provide the first general route for the synthesis of *trans*-dihydroquinolones.

To elucidate the effect of the ammonium ion on the H-transfer processes, we employed d_5-labeled[3,17] **1e**-d_5 as a substrate. The results are shown in Scheme 3. The D/H ratios of the *trans* **2e**-d_5/d_4 in the absence and presence of TBAB are 95/5 and 98/2, respectively (Fig. S4). This shows that the intramolecular [1,5] D-shift, pathway (a) in Scheme 1, is a major process, and the intermolecular H-transfer of pathway (b) is a minor process for the formation of the *trans* isomer. In contrast, the D/H ratio of the *cis* **2e**-d_5/d_4

Table 1
[6π]-Photocyclization of acrylanilide **1a**



Entry[a]	Additive	Equiv	Solv	Temp (°C)	Time (h)	Conv (%)[b]	*trans*/*cis*[b]
1	—	0	CH_2Cl_2	rt	6	93	53:47
2	Bu_4NF	5	CH_2Cl_2	rt	6	33	69:31
3	Bu_4NCl	5	CH_2Cl_2	rt	6	91	79:21
4	Bu_4NBr	5	CH_2Cl_2	rt	6	>99	76:24
5	Bu_4NBr	5	CH_2Cl_2	-40	16	95	89:11
6	Bu_4NI	5	CH_2Cl_2	rt	6	81	75:25
7	Bu_4NPF_6	5	CH_2Cl_2	rt	6	52	70:30
8	Et_4NBr	5	CH_2Cl_2	rt	6	45	70:30
9	$(C_8H_{17})_4NBr$	5	CH_2Cl_2	rt	6	>99	73:27
10	Bu_4PBr	5	CH_2Cl_2	rt	6	>99	68:32
11	CsF	5	CH_2Cl_2	rt	6	>99	41:59
12	—	0	THF	rt	6	94	56:44
13	Bu_4NBr	5	THF	rt	6	>99	84:16
14	—	0	CF_3Ph	rt	16	>99	30:70
15	Bu_4NBr	5	CF_3Ph	rt	16	>99	85:15
16	Bu_4NBr	5	CF_3Ph	−20	16	98	91:09
17	Bu_4NBr	3	CF_3Ph	rt	16	>99	85:15
18	Bu_4NBr	1	CF_3Ph	rt	16	>99	84:16
19	Bu_4NBr	0.5	CF_3Ph	rt	16	>99	81:19

[a] The reactions were conducted in 0.1 M solution.
[b] Determined by ^{1}H NMR.