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COMMUNICATION

Facile synthesis of spiroisoquinolines based on photocycloaddition of isoquinoline-1,3,4-trione with oxazoles†

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Photocycloaddition of isoquinoline-1,3,4-trione and 5-methoxyoxazoles affords spiroisoquinolineoxetanes with high regio- and diastereoselectivity. The spiroisoquinolineoxetanes can be conveniently converted into novel spiroisoquinolineoxazoline derivatives through acid catalyzed sequential reactions.

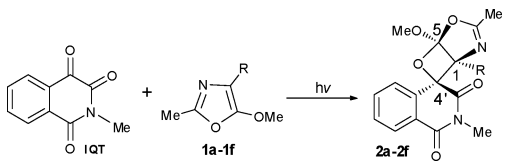
Photocycloaddition combined with subsequent ring rearrangement has been used as an efficient way to build various heterocyclic frameworks in organic synthesis.[1,2] Transformation of oxetanes derived from Paterno–Büchi reactions catalyzed by acids or other catalysts is of recent research interest.[3] Griesbeck *et al.* have developed a convenient method to prepare α-amino-β-hydroxy carboxylic acid derivatives through acid catalyzed hydrolysis of photocycloadducts derived from 5-alkoxyoxazoles with aldehydes.[4] Isoquinolinetriones are important biologically active compounds[5] and they have been used as building blocks in the synthesis of benzo[*c*]phenanthridine alkaloids.[6] The C4 carbonyl group in isoquinoline-1,3,4-trione (**IQT**) has been proven to be a reactive site for photocycloaddition with alkynes,[7] which inspired us to build spiroisoquinoline frameworks through photoreactions of **IQT**.

Photocycloaddition of carbonyl groups on indole or isoquinoline rings with various species have been of consistent research interest for us since it may serve as a convenient method to construct complex heterocyclic frameworks.[7,8] Photocycloaddition of **IQT** with alkenes to give spiroisoquinolineoxetanes has rarely been reported. Here we report the highly selective photocycloaddition of **IQT** with 5-methoxyoxazoles and the unusual acid catalyzed transformation of the photocycloadducts. Combining these highly selective and efficient reactions together, we developed a facile method to construct structurally important motifs such as spiroisoquinolines[9] and spirooxazolines.[10]

Photocycloaddition of **IQT** with 5-methoxyoxazoles proceeded with excellent chemo-, regio- and diastereoselectivity. As shown in Table 1, irradiation of the reaction mixture containing **IQT** and 2-methyl-5-methoxyoxazoles **1a–1f** resulted in spiroisoquinolineoxetanes **2a–2f** as the predominant products. Using excess amounts of 2-methyl-5-methoxyoxazoles in the photoreaction could accelerate the conversion of **IQT**. Upon complete conversion of **IQT**, the photocycloadducts could be obtained through a simple work-up procedure as described in the experimental section. Unlike the thermally unstable bicyclic oxetanes derived from photocycloaddition of aldehydes with 5-methoxyoxazoles,[4] oxetanes **2a–2f** were thermally stable unless in an acidic environment.

The chemoselectivity of the photocycloaddition of **IQT** with **1a–1f** to form oxetanes was much higher than that found in photoreactions of other *o*-quinones such as *N*-acetylisatin and phenanthrenequinone with oxazoles.[8a,8b] The regioselectivity in the formation of oxetanes was similar to that found in the photocycloaddition of 5-methoxyoxazoles with aldehydes or ketones.[4] The regioselectivity of the photocycloaddition is due to the most stable allylic type 1,4-diradical intermediate in the Paterno–Büchi reaction.[11] The diastereoselectivity of the photocycloaddition greatly favored the formation of oxetanes with *exo*-configuration, which can be well rationalized by the relative stability of the triplet

Table 1 Photocycloaddition of IQT with oxazoles **1a–1f**[a]



Entry	R	Oxazole	Irrad. time/hr	Products and yields[b](%)
1	**H**	**1a**	10	**2a** (85)
2	**Me**	**1b**	10	**2b** (88)
3	***i*-Pr**	**1c**	12	**2c** (90)
4	***i*-Bu**	**1d**	16	**2d** (90)
5	**2-(Methylthio)ethyl**	**1e**	24	**2e** (85)
6	**Bn**	**1f**	10	**2f** (90)

[a] Irradiation with >400 nm light in CH_3CN solution. [b] Isolated yields.

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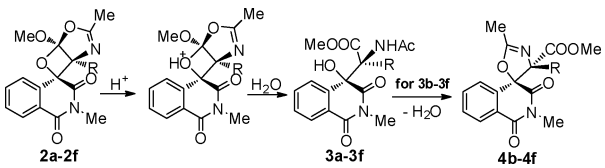
† Electronic supplementary information (ESI) available: General experimental procedures, characterization data, copies of NMR spectra for all new compounds and IR spectra for **2d 3d** and **4d**, ORTEP drawing of **3d** and **4bi**. CCDC reference numbers 800193, 800194, 800196. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1ob05143a

diradical conformation suitable for intersystem crossing before bond formation.[12]

Acid-catalyzed hydrolysis of the spiroisoquinolineoxetanes was then investigated. Novel spiroisoquinolineoxazoline products **4** were detected in the final products, which indicated that unusual cascade reactions could be induced in acid-catalyzed hydrolysis of spiroisoquinolineoxetanes. Therefore we studied the reactions of **2a–2f** upon treatment with different amounts of concentrated hydrochloride acid in detail. As shown in Scheme 1, hydrolysis of the spiroisoquinolineoxetanes catalyzed by HCl gave the α-amino-β-hydroxy carboxylic ester **3**, most of which could further cyclize to give spiroisoquinolineoxazoline **4**. The structures of **3** and **4** have been confirmed by X-ray crystallographic analysis of the representative products **3b** (see ESI†) and **4b** (Fig. 1).



Scheme 1 Reactions of spiroisoquinolineoxetanes **2** catalyzed by HCl.

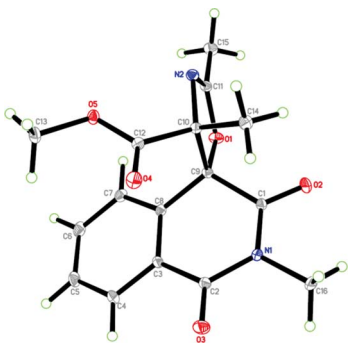


Fig. 1 X-Ray crystal structure of **4b**.

The products and yields of HCl catalyzed reactions of **2a–2f** are shown in Table 2. It is noteworthy that the spiroisoquinolineoxetanes with different substituent groups on C1 of the oxetane ring gave different ratios of **3** to **4** in the final products upon treatment with 3 eq. of HCl (entry 1–6). Hydrolysis of **2a**, which has no substitutuent group on C1, gave the α-amino-β-hydroxy carboxylic ester **3a** exclusively. **3a** could not be further converted into the corresponding spiroisoquinolineoxazoline even upon treatment with a large excess amount of HCl. On the other hand, for **2c**, which has a bulky *i*-Pr group substituted at C1, the corresponding α-amino-β-hydroxy carboxylic ester **3c** was extremely unstable and showed a strong tendency for cyclization to form **4c** even on silica gel during flash column chromatography. Therefore only **4c** was isolated as the final product in the reaction of **2c** treated with 3 eq. of HCl (entry 3). When a large excess amount of concentrated HCl was used to treat **2b–2f**, only spiroisoquinolineoxazolines **4b–4f** were isolated as the final products with yields up to 93% (entry 7–11).

Ring opening of **2** leading to **3** was similar to the well-established acid-catalyzed hydrolysis of bicyclic oxetanes,[4] whereas the subsequent ring closure to give **4** was unusual and has not been reported before. As shown in the X-ray crystallographic analysis of **3b** and **4b**, the relative configurations of the two stereogenic centers were consistent. It indicated that none of the bonds linked with C4′ or C1 in **2** had been cleaved in the reaction catalyzed by HCl. The presence of the C3′ carbonyl group on the isoquinoline ring might have pushed the cyclization step since it could present extra steric hindrance in **3**. Presence of a large substituent group R also could present extra steric hindrance in **3** and therein promote the cyclization process.

Table 2 HCl catalyzed transformation of spiroisoquinolineoxetanes

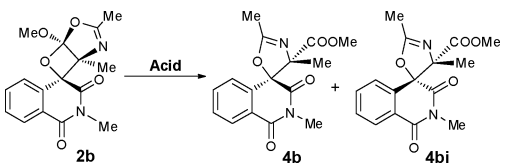
Entry	Oxetane	Eq. of HCl	Time/h	Products and yields[a] (%)
1	**2a**	3	1	**3a**(90)
2	**2b**	3	3	**3b**(70), **4b**(10)
3	**2c**	3	3	**4c**(85)
4	**2d**	3	4	**3d**(40), **4d**(35)
5	**2e**	3	4	**3e**(41), **4e**(40)
6	**2f**	3	3	**3f**(39), **4f**(40)
7	**2b**	150	5	**4b**(80)
8	**2c**	150	4	**4c** (93)
9	**2d**	150	3	**4d**(90)
10	**2e**	150	0.5	**4e**(88)
11	**2f**	150	1	**4f**(92)

[a] Isolated yields.

The transformation of spiroisoquinolineoxetanes catalyzed by different types and amounts of acids was then extensively studied. Other than strong inorganic acids, organic acids and Lewis acids could also be used as the catalyst for the ring rearrangement of spiroisoquinolineoxetanes to form spiroisoquinolineoxazolines. As shown in Table 3, a catalytic amount of strong Brønsted acids such as trifluoroacetic acids (TFA) and methanesulfonic acid (MsOH) could catalyze direct conversion from **2b** to **4b** efficiently. A catalytic amount of Lewis acids such as $BF_3{\cdot}Et_2O$ and $TiCl_4$ could also turn **2b** into **4b** rapidly. However, a weak organic acid such as acetic acid or bulky Lewis acid such as $Ti(OiPr)_4$ proved to be ineffective catalysts at room temperature (entry 5 and 10).

Two diastereoisomers **4b** and **4bi** were obtained upon treatment of **2b** with organic acids or Lewis acids. The relative ratio of **4b**

Table 3 Transformation of **2b** catalyzed by different acids[a]

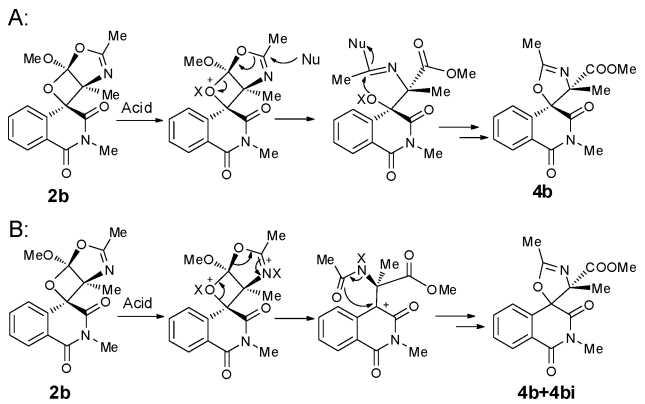


Entry	Acid	Eq. of acid	Time (mins)	Overall yields[b] of **4b** and **4bi**	**4b** : **4bi**[c]
1	$BF_3{\cdot}Et_2O$	0.15	30	96	1 : 3.5
2	$BF_3{\cdot}Et_2O$	10	15	97	2 : 5
3	$TiCl_4$	0.15	45	94	10 : 1
4	$TiCl_4$	10	8	96	1 : 5
5	$Ti(OiPr)_4$	3	600	NR[d]	—
6	MsOH	0.15	50	92	1 : 1.3
7	MsOH	10	25	95	1 : 10
8	TFA	0.5	90	92	4 : 1
9	TFA	10	20	90	2 : 3
10	CH_3COOH	3	600	NR[d]	—

[a] In anhydrous CH_3CN. [b] Isolated yields of the crude products containing **4b** and **4bi**. [c] Relative ratio of **4b** : **4bi** was determined by ^1H NMR of the crude products. [d] No reaction at room temperature.

to **4bi** was different when **2b** was treated with different types and amounts of acids. As shown in Table 3, a large excess amount of organic acids or Lewis acids facilitated the formation of **4bi** in which one of the stereogenic centers has inverted its configuration. A control experiment using different acids to treat **4b** showed that **4b** could not be converted into **4bi** directly. It indicated that the two diastereoisomers were generated independently from **2b** *via* different reaction pathways.

Two reaction pathways were proposed as shown in Scheme 2. In pathway A, none of the stereogenic centers was involved in bond cleavage and thus their relative configuration remained. While in pathway B, the C–O bond between the isoquinoline C4′ and the oxetane O underwent bond cleavage, leading to the C4′ carbocation as an intermediate. Nucleophilic attack of the carbonyl group to the carbocation could proceed from different directions to give **4b** and **4bi**, respectively. Reaction of **2b** catalyzed by different types and amounts of acids proceeded simultaneously and competitively *via* pathways A and B, which resulted in different ratios of **4b** and **4bi** in the final products.



Scheme 2 Proposed pathway for the formation of **4b** and **4bi**.

In summary, we have discovered a novel acid-catalyzed transformation from spirooxetanes to spirooxazolines. The acid-catalyzed transformation of the spiroisoquinolineoxetanes **2** has been found to be highly related to the substituent groups on the oxetane rings as well as the type and amount of acid used. Bulky substituent groups on the oxetane ring showed favorable steric effects on the transformation from **2** to spiroisoquinolineoxazolines **4**. A large excess amount of HCl also favored transformation from **2** to **4**. Strong Brønsted acids and Lewis acids could catalyze direct transformation from **2** to **4** efficiently but *via* different pathways. Based on the photocycloaddition of **IQT** with 5-methoxyoxazoles and this novel acid-catalyzed transformation of the photocycloadducts, facile synthesis of spiroisoquinolines could be realized. Further study on different substrates as well as different transformation pathways is now underway.

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