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A Cascade of Acid-Promoted C−O Bond Cleavage and Redox Reactions: From Oxa-Bridged Benzazepines to Benzazepinones

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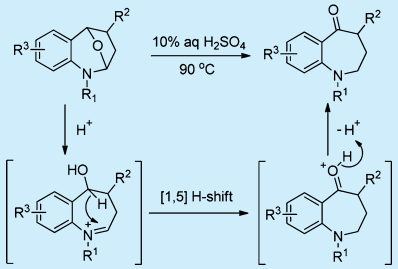
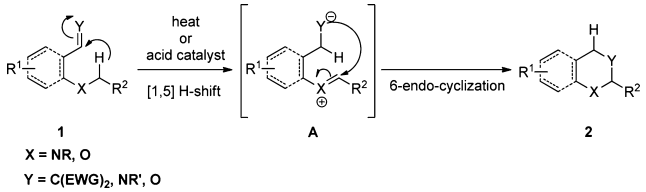
Supporting Information

ABSTRACT: A sequence of C−O bond cleavage and redox reactions in oxa-bridged azepines was realized under acid promoted conditions. This protocol provides an atom-economical and straightforward approach to access benzo[*b*]azepin-5(2*H*)-ones in high yields. The formal synthesis of tolvaptan was achieved by exploiting this new transformation.



Recently, [1,5]-hydride transfer/cyclization processes, namely, the "internal redox process", have attracted much attention for their unique features. They are synthetically powerful strategies for the construction of various heterocycles.[1] As demonstrated in Scheme 1, this type of process involves the cleavage of a C−H bond α to a heteroatom via a 1,5-hydride shift to give zwitterionic intermediate **A**, followed by subsequent 6-endo cyclization to the cation species to yield structurally diverse nitrogen- or oxygen-contained heterocycle **2**.[1p,2]

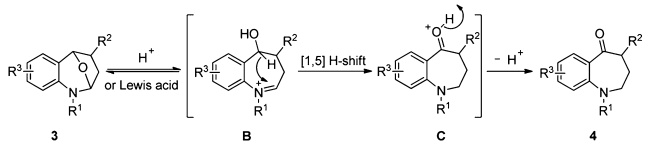
Scheme 1. Typical Internal Redox Process



In most cases, an activated hydride acceptor, basically an electronically deficient unsaturated bond, is required to be located in an appropriate position to a hydride donor. Moreover, the participation of benzylic C−H bonds[3] without an adjacent heteroatom and even of aliphatic nonbenzylic C−H bonds[4] in this type of reaction has been reported. These typical "internal redox processes" are commonly activated either thermally or by an acid catalysist.[2c,d,3f,5] Furthermore, progress has been made toward catalytic enantioselective variants as well as finding applications in key disconnections of total syntheses.[5b,6] However, to the best of our knowledge, there is no precedent of a cascade involving a C−O bond cleavage/hydride-transfer process.

As part of the research program related to the development of synthetic methodologies for novel heterocycles,[7] we recently reported acid-promoted reductive ring openings of aza-bridged azepines.[8] We recognized the presence of the driving force of a similar "internal redox process" in structure **3** and envisioned an expeditious route to a benzo[*b*]azepin-5(2*H*)-one skeleton, which is encountered in numerous biologically active compounds,[9] via a C−O bond cleavage/1,5-hydride transfer sequence (Scheme 2). A cascade of three transformations (acid promoted C−O bond cleavage, 1,5-hydride transfer, and loss of a proton) in oxa-bridged benzazepines **3** would afford benzo[*b*]azepin-5(2*H*)-one derivatives **4**.

Scheme 2. Potential Cascade Reactions of C−O Bond Cleavage/1,5-Hydride Transfer From Benzazepine 3 to Benzazepinone 4



We speculated that the C−O bond of oxa-bridged azepines **3**, prepared by a carbonyl-ene type reaction, could cleave to form iminium ion **B** in the presence of a Brønsted or Lewis acid. The subsequent internal redox process in structure **B** should occur via a 1,5-hydride transfer to give intermediate **C**. Intermediate **C** would readily lose a proton to lead to benzazepinones **4**. This overall reaction is an intramolecular redox process and thus may not require a stoichiometric oxidant. We thus decided to investigate the acid-promoted transformation of **3** to **4**. The details of this successful investigation and the application to the formal synthesis of tolvaptan are disclosed.

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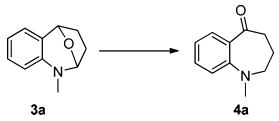
We chose substrate **3a** which was synthesized by a recently reported procedure[7h] to examine an array of Brønsted and Lewis acids to optimize the reaction conditions (Table 1).

Table 1. Optimization of Reaction Conditions[a]



entry	acid/solvent	temp (°C)	time (h)	yield (%)
1	1 equiv of $TiCl_4$/DCM	0–25	6	NR[b]
2	15 equiv of 3 N HCl/MeOH	reflux	3	64
3	15 equiv of TFA/(H_2O/THF)	reflux	5.5	73
4	HCOOH	reflux	1	70
5	15% aq H_2SO_4	reflux	0.5	87
6	15% aq H_2SO_4	90	1.5	90
7	15% aq H_2SO_4	70	4	88
8	15% aq H_2SO_4	50	2	NR[b]
9	5% aq H_2SO_4	90	3	87
10	10% aq H_2SO_4	90	2	91
11	20% aq H_2SO_4	90	1	89

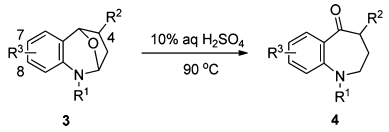
[a]Unless indicated otherwise, the reaction was carried out on 0.5 mmol scale in solvent (2 mL). [b]Starting material **3a** was recovered.

Treatment of **3a** with $TiCl_4$ in dried methylene dichloride (DCM) yielded no expected product, and starting material **3a** was recovered (entry 1, Table 1). Various acids, such as 3 N HCl, TFA, HCOOH, and H_2SO_4, were screened, and the desired **4a** was obtained in moderate to excellent yield (entries 2–5, Table 1). We found that 15% aq H_2SO_4 under reflux conditions gave the best result (entry 5). Further screening of other reaction parameters (such as reaction temperature and acid concentration) revealed that a minimum temperature of 70 °C is necessary for the reaction to take place, and product **4a** was produced in a higher yield within a shorter time at 90 °C (entries 6–11, Table 1). Eventually, optimum reaction conditions of 10% aq H_2SO_4 at 90 °C led to **4a** in 91% yield (entry 10, Table 1).

With the optimized reaction conditions, the scope of this reaction cascade was explored, and the results are listed in Table 2. First, we tested the generality of this C–O bond cleavage/1,5-hydride transfer process from oxa-bridged azepines **3** with various substituents at the nitrogen atom. Substrates **3a–f** substituted at the nitrogen atom with an alkyl or aromatic group proceeded smoothly to produce the corresponding benzo[*b*]azepin-5(2*H*)-ones **4a–f** in good to excellent yields (entries 1–6, Table 2). It is worth noting that when R^1 is an aromatic group, the reaction rate decreased as the electronic density of the phenyl ring decreased (entries 4–6, Table 2).

Oxa-bridged azepines **3g–i** with phenyl, *p*-methoxyphenyl, and *p*-F-phenyl at C-4 reacted smoothly to yield the corresponding products **4g–i** in moderate yields at reduced rates (entries 1, 7–9, Table 2). The substituent at the fused benzene ring had strong effects on the reactivity. For instance, substrate **3j** with a methoxy group at the C-8 position dramatically sped up the reaction (completed in 10 min) (entry 10, Table 2). The faster reaction rate is likely due to the increasing hydride shift ability by the electron-donor group; thus, the reorganization is speeded up. The low yield may be due to side reactions since substrate **3j** is too electron-rich. In contrast, substrate **3k** with the methoxy group at the C-7

Table 2. Scope of the Ring Opening/1,5-Hydride Transfer Sequence[a]



entry	R^1	R^2	R^3	4	time	yield (%)
1	Me	H	H	**4a**	2 h	91
2	allyl	H	H	**4b**	1.5 h	82
3	Bn	H	H	**4c**	2.5 h	85
4	Ph	H	H	**4d**	14 h	77
5	4-MeO-Ph	H	H	**4e**	7.5 h	81
6[b]	4-NO_2-Ph	H	H	**4f**	63 h	83
7	Me	Ph	H	**4g**	7 h	60
8	Me	4-MeO-Ph	H	**4h**	12 h	56
9	Me	4-F-Ph	H	**4i**	8 h	57
10	Me	H	8-MeO	**4j**	10 min	30
11	Me	H	7-MeO	**4k**	6 h	75
12	Me	H	7-Me	**4l**	1 h	90
13	Me	H	8-Cl	**4m**	2 h	76
14	Me	H	7-Cl	**4n**	3 h	80
15	Me	H	7-NO_2	**4o**	6 h	NR[c]

[a]Unless indicated otherwise, the reaction was carried out on 0.5 mmol scale in solvent (2 mL). [b]10% aq H_2SO_4 reflux. [c]No reaction. Recovered only starting material.

position was much less reactive and required a longer reaction time to provide the corresponding product **4k** in a good yield (entry 11, Table 2). This observation can be rationalized by the decrease of the hydridophilicity of the iminium ion by the electron-donating resonance effect of the methoxy group (in the *para* vs *meta* position with respect to iminium ion), as well as by reducing the hydride donor ability of the hydroxy group by the σ-effect of the methoxyl oxygen atom (Scheme 2). Moreover, substrate **3l** with the methyl group at the C-7 has no significant effect on the reactivity (entry 12, Table 2). The deactivating chloro substituent was well tolerated at the C-7 or C-8 position, although it reduced the reactivity of substrate **3m** and **3n** to require a longer reaction time (entries 13, 14, Table 2). However, NO_2 at the C-7 position decreases the availability of the N lone pair of **3** for assisting the ring opening of the oxa-bridge, and prevents the **3** to **4** conversion (entry 15, Table 2).

The formal synthesis of tolvaptan[10] was selected to showcase the synthetic potential of the present transformation (Scheme 3). Substitution of 5-chloro-2-fluorobenzaldehyde **5** with diallylamine gave product **6** in 85% yield. The carbonyl-ene reaction of benzaldehyde **6** afforded epoxybenzo[*b*]azepine **7**. Compound **7** proceeded smoothly with the cascade reaction to give desired product **8** in excellent chemical yield (88%). Removal of the allyl group in benzo[*b*]azepin-5(2*H*)-one **8** with a palladium catalyst furnished amine **9**, the key precursor to tolvaptan **10** reported by Kondo.[10a] The NMR spectra of **9** coincided with those of the literature. Therefore, a formal synthesis of tolvaptan (**10**) was achieved.

In summary, a new cascade reaction of C–O bond cleavage and a 1,5-hydride transfer process was developed. Through this internal redox reaction process, various benzazepines could be readily transformed to the desired benzo[*b*]azepin-5(2*H*)-ones in good to excellent chemical yields. The application of this method to the formal synthesis of tolvaptan was also

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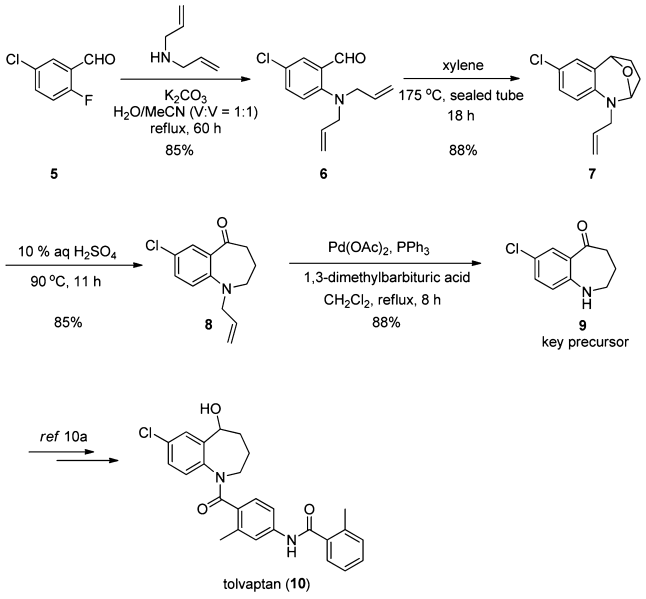
Scheme 3. Formal Synthesis of Tolvaptan



demonstrated. This cascade provides a new entry for the expeditious construction of the benzazepine skeletons.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and full spectroscopic data for all new compounds are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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