Published in final edited form as:

Green Chem. 2010 ; 12(9): 1556–1559. doi:10.1039/C0GC00198H.

Remarkable facilitation of hetero-cycloisomerizations with water and other polar protic solvents: metal-free synthesis of indolizines†

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Abstract

Hetero-cycloisomerization reactions of propargylic alcohol derivatives leading to indolizines have been demonstrated to proceed in the presence of water alone. This stands as a significant advance over the previous methods using Pt, Cu or Ag salts paired with ligands in organic solvents such as benzene, acetonitrile or methylene chloride.

In the last decade, an increasing focus on developing green chemical processes has emerged. Synthetic organic chemists have begun to rise to the green challenge by developing atom economical reactions,¹ minimizing use of toxic reagents and adopting environmentally benign solvents² in an effort to achieve ideal chemical transformations. Cycloisomerizations are reactions that have gained popularity under the green chemistry umbrella because they are inherently atom economical and are often promoted by catalysts, which in principle can be recovered and reused.³

The development of π -Lewis acid-mediated cycloisomerizations is an active area of research.⁴ A variety of salts derived from metals including Cu, Hg, Ag, Au, Pt, In and Ga have proven to be very useful catalysts for these processes. Along these lines, our laboratory has developed several of these reactions mediated by Pt, Ga and In salts.⁵ For example, we^{5a} and others⁶ have reported the hetero-cycloisomerization of pyridine propargylic alcohol derivatives (*e.g.*, **1**, Scheme 1) in the presence of π -Lewis acids to yield indolizines (**3**) *via* the presumed intermediacy of **2**. The previously reported conditions required to effect this cycloisomerization include metal catalysts, organic solvents and often, specific ligands to modulate the reactivity of the metal employed (eqn (1)–(3)). As a consequence of these conditions, obtaining pure indolizine products often requires purification, such as column chromatography, even when the starting material is completely converted to the desired product.

We became interested in devising new protocols to improve these transformations by eliminating the expensive π -Lewis acid catalysts as well as the organic solvents that have been traditionally utilized for these reactions. Commensurate with these considerations, trace amounts of the heavy metals would be avoided in the reaction products, rendering these processes more attractive to the pharmaceutical industry, where the heterocyclic products are likely to find the most use.⁷ In this Communication, we report our initial results that indicate pure water, *without any additives*, efficiently facilitates the cycloisomerization

†Electronic supplementary information (ESI) available: Experimental and spectra.

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depicted in Scheme 1 and that this simple protocol may find application in other hetero-cycloisomerization reactions as well.

Despite the long recognized positive influence of water on the efficiency of select organic reactions such as the Diels–Alder reaction,⁸ only relatively recently has it begun to be investigated heavily as an alternative solvent for a variety of transformations.⁹ Several aspects of the hetero-cycloisomerization reaction shown in Scheme 1 made it attractive to study on/in water.¹⁰ First, because these reactions proceed *via* charged reactive intermediates, we hypothesized that the corresponding transition states would be stabilized by water, which has a relatively high static permittivity ($\epsilon_T = 78.4$).¹¹ Additionally, our qualitative examination of these reactions suggested that they should have negative activation volumes,¹² and should therefore be accelerated in water as discussed by Lubineau and others.¹³ Despite the potential for facilitation of the hetero-cycloisomerization reactions using water, several challenges were evident. For example, hydration of the alkyne fragment in **1**, as well as hydrolysis of the protecting group (P) could be competitive with the desired transformation. Of more significant concern was the possible interception of the charged intermediate (*e.g.*, **2**) by water.

(1)

(2)

(3)

In an initial experiment, pyridine propargylic ester **4** (Table 1), which has been previously used by our group in hetero-cycloisomerizations, was investigated (see eqn (1)). We were delighted to find that the desired transformation proceeded using pure water¹⁴ at 100°C over 2 h to form the corresponding indolizine **5** in 95% yield (entry 3). This yield compares favorably with the yield obtained in organic solvent using either PtCl_2 with phosphine ligands or InCl_3 (as reported by us previously, see Table 1, entries 1 and 2), AgBF_4 ^{6a} or CuI ^{6b} as the catalyst (eqn (2) and eqn (3), respectively).

As shown in Table 2, the scope of the hetero-cycloisomerization reaction of pyridine propargylic alcohol derivatives using water is comparable to that observed using metal salts as previously reported by us,^{5a} as well as by Gevorgyan^{6a} and Liu.^{6b} Of note, a silyl (TBS) protective group, which was problematic in the metal-catalyzed reaction, is tolerated under the metal-free conditions (entry 4).

Although the benefits of conducting these transformations using water are clear (*i.e.*, low cost, ease of operation and improved safety), the basis for the success of these reactions is not well understood at this time. We have carried out several preliminary experiments to gain some insight into the facilitation of the heterocyclization reactions presented in Table 2 by water. We note that even though a number of the substrates in neat form or as a solution in benzene undergo transformation to the corresponding indolizines in the absence of catalyst over prolonged heating (*ca.* 18 h), the yields are generally low and accompanied by significant decomposition (entry 6).¹⁵ These observations suggest that the effect of water extends beyond simply creating a high effective concentration based on the hydrophobic effect¹⁶ and that hydrogen-bonding is likely important. We also found that other polar protic solvents were effective for this hetero-cycloisomerization, including 1,1,1-trifluoroethanol, ethanol, and methanol (Table 3, entries 3–5). However, polar aprotic solvents such as DMF and DMSO led to no observable product formation (entries 7 and 8, respectively), overall supporting the hypothesis that hydrogen bonding facilitates the cyclization.

Further insight was gained into the mechanism of the hetero-cycloisomerization by the qualitative observation that the reactions proceed more slowly in D₂O as compared to H₂O (complete conversion of **4** to **5** in D₂O after 3 h *versus* 2 h in H₂O, see Table 3, entries 1 and 2). Additionally, deuterium is incorporated at the C2 position (eqn (4)). Subjecting protio indolizine product (**5**) to the reaction conditions in D₂O, did not lead to any observable exchange (eqn (5)), suggesting that the deuterium incorporation observed (eqn (4)) occurs prior to product formation. This result is consistent with the observations of Sharpless *et al.*¹⁰ for the cycloaddition of quadricyclane with dimethyl azodicarboxylate, which likely reflects a solvent isotope effect.^{17,18}

(4)

(5)

The synthesis of indolizines reported herein constitutes, to our knowledge, the first examples of cycloisomerizations that are facilitated solely by water. Given the number of metal catalysts, solvents and additives that have been investigated in the burgeoning number of π -Lewis acid-catalyzed isomerization reactions, it is remarkable that more attention has not been paid to water not only as a potential solvent, but as a catalyst for these reactions. An analysis of the previously developed metal-based methods for the cycloisomerization of propargylic alcohol derivatives to indolizines *versus* our metal-free conditions is illustrated

in Table 4. The major advantages of the reaction employing water are that (1) no metal catalysts or additives are required, (2) toxic organic solvents are not used, (3) no purification is necessary, avoiding the waste generated by silica gel column chromatography and (4) yields of indolizine products are similar or higher under the metal-free conditions as compared to those employing metal catalysts. We believe that our observations portend significant gains toward achieving ideal transformations. Although our initial studies have focused on the formation of indolizines *via* a cycloisomerization reaction, it is our anticipation that the use of water in place of expensive metal catalysts and organic solvents can be applied more broadly. A survey of a number of cycloisomerization reactions using water is currently underway in our laboratories and our results in this regard, as well as a detailed analysis of the water-facilitated transformations reported herein, will be disclosed in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Notes and references

1. (a) Trost BM. *Acc Chem Res.* 2002; 35:695–705. [PubMed: 12234199] (b) Trost BM. *Angew Chem, Int Ed Engl.* 1995; 34:259–281.
2. (a) Nelson, WM. *Green Solvents for Chemistry: Perspectives and Practice.* Oxford University Press; 2003. (b) DeSimone JM. *Science.* 2002; 297:799–803. [PubMed: 12161645]
3. (a) Poliakoff M, Fitzpatrick JM, Farren TR, Anastas PT. *Science.* 2002; 297:807–810. [PubMed: 12161647] (b) Anastas PT, Zimmerman JB. *Environ Sci Technol.* 2003; 37:94A–101A.(c) Anastas, PT.; Warner, JT. *Green Chemistry, Theory and Practice.* Oxford University Press; Oxford: 1998.
4. For recent reviews, see: (a) Michelet V, Toullec PY, Genet JP. *Angew Chem, Int Ed.* 2008; 47:4268–4315.(b) Fürstner A, Davies PW. *Angew Chem, Int Ed.* 2007; 46:3410–3449.
5. (a) Smith CR, Bunnelle EM, Rhodes AJ, Sarpong R. *Org Lett.* 2007; 9:1169–1171. [PubMed: 17309277] (b) Bunnelle EM, Smith CR, Lee SK, Singaram WS, Rhodes AJ, Sarpong R. *Tetrahedron.* 2008; 64:7008–7014.(c) Prasad BAB, Yoshimoto FK, Sarpong R. *J Am Chem Soc.* 2005; 127:12468–12469. [PubMed: 16144376] (d) Simmons EM, Sarpong R. *Org Lett.* 2006; 8:2883–2886. [PubMed: 16774281] (e) Hardin AR, Sarpong R. *Org Lett.* 2007; 9:4547–4550. [PubMed: 17845052]
6. (a) Seregin IV, Schammel AW, Gevorgyan V. *Org Lett.* 2007; 9:3433–3436. [PubMed: 17637023] (b) Yan B, Zhou Y, Zhang H, Chen J, Liu Y. *J Org Chem.* 2007; 72:7783–7786. [PubMed: 17718578]
7. (a) Michael JP. *Alkaloids.* 2001; 55:91–258. [PubMed: 11704985] (b) Michael JP. *Nat Prod Rep.* 1999; 16:675–696.(c) Hagishita S, Yamada M, Shirahase K, Okada T, Murakami Y, Ito Y, Matsuura T, Wada M, Kato T, Ueno M, Chikazawa Y, Yamada K, Ono T, Teshirogi I, Ohtani M. *J Med Chem.* 1996; 39:3636–3658. [PubMed: 8809154] (d) Reddy MV, Rao MR, Rhodes D, Hansen MS, Rubins K, Bushman FD, Venkateswarlu Y, Faulkner D. *J Med Chem.* 1999; 42:1901–1907. [PubMed: 10354398] (e) Anderson WK, Heider AR, Raju N, Yucht J. *J Med Chem.* 1988; 31:2097–2102. [PubMed: 3184121]
8. (a) Rideout DC, Breslow R. *J Am Chem Soc.* 1980; 102:7816–7817.(b) Breslow R. *Acc Chem Res.* 1991; 24:159–164.
9. (a) Breslow, R. *Green Chemistry.* Anastas, PT.; Williamson, TC., editors. Vol. ch 13. Oxford University Press; 1998. (b) Vilotijevic I, Jamison F. *Science.* 2007; 317:1189–1192. [PubMed: 17761875] (c) Carpita A, Ribecai A. *Tetrahedron Lett.* 2009; 50:6877–6881.
10. (a) Narayan S, Muldoon J, Finn MG, Folkin VV, Kolb HC, Sharpless KB. *Angew Chem, Int Ed.* 2005; 44:3275.(b) Li CJ. *Chem Rev.* 2005; 105:3095–3165. [PubMed: 16092827]
11. For a recent discussion of static permittivity and other bulk properties of water, see: Pirrung MC. *Chem–Eur J.* 2006; 12:1312–1317.
12. Brower KR. *J Am Chem Soc.* 1961; 83:4370–4300.

13. (a) Lubineau A. *J Org Chem.* 1986; 51:2142–2144.(b) Lubineau A, Augé J. *Top Curr Chem.* 1999; 206:2–39.
14. De-ionized water with a pH of 6.3 was employed. Lowering the pH of the solvent led to significant decomposition.
15. See supporting information for further details on reactions run neat and in benzene[†].
16. Otto S, Engberts JBFN. *Org Biomol Chem.* 2003; 1:2809–2820. [PubMed: 12968330]
17. (a) Pirrung (ref. 11) suggests that the decreased rate in D₂O as compared to H₂O observed by Sharpless *et al.* may be explained by more difficult mixing in the former solvent because of the 23% higher viscosity of D₂ O. However, it should be noted that the example by Sharpless *et al.* is a bimolecular reaction, whereas the reactions reported herein are likely unimolecular, which should minimize the dependence on mixing.
18. Reactions run with D₂O in place of H₂O result in deuterium incorporation at the 2 position of the indolizine product.

[†]Electronic supplementary information (ESI) available: Experimental and spectra.

Scheme 1.
Cycloisomerization of a propargylic ester to form an indolizine.

Table 1

Hetero-cycloisomerization of **4**

entry	catalyst	solvent	<i>T</i> /°C	time/h	yield (%)
1	PtCl ₂ (5 mol %)	PhH	70	3	95
2	InCl ₃ (5 mol %)	PhH	40	4	85
3	—	H ₂ O	100	2	95

Table 2

Scope of the hetero-cycloisomerization reaction to form indolizines. Reaction conditions: H₂O, 100°C

entry	substrate	product	time/h	yield (%)	yield Pt-cat. (%) 5a	ref.
1			2	95	95	
2			15	85	83	

entry	substrate	product	time/h	yield (%)	yield Pt-cat. (%)	ref.
3			2	97	79	
4			8	97	57	
5			15	99	—	

Table 3

Solvent influence on the hetero-cycloisomerization reaction

entry	solvent	time/h	yield (%)
1	H ₂ O	2	>95
2 ^a	D ₂ O	3	>95
3	CF ₃ CH ₂ OH	2	>95
4	EtOH	3	>95
5	MeOH	3	>95
6	benzene	5	<5
7	DMF	5	<5
8	DMSO	5	<5

^aDeuterium was incorporated at C2 of indolizine product **5**.

Table 4

Comparison of the methods for the cycloisomerization of propargyl alcohol derivatives to indolizines

method	catalyst	additives	solvent	<i>T</i> /°C	purification
ref. 6a	AgBF ₄ (3 mol %)	—	CH ₂ Cl ₂	rt	column chromatography		
ref. 6b	CuI (5 mol %)	Et ₃ N	CH ₃ CN	rt	column chromatography		
ref. 5a	PtCl ₂ (5 mol %)	JohnPhos	benzene	70	column chromatography		
this work	—	—	H ₂ O	100	none		