1-Acetyl-2,3-Dimethylimidazolidine: A Novel Organic Reductant for Transfer Hydrogenation

Donghong Li, Yongbin Zhang, Guofu Zhou, Wei Guo*

School of Chemistry and Chemical Engineering, Shanxi University, Taiyuan 030006, P. R. of China
E-mail: guow@sxu.edu.cn

Received 25 September 2007

Abstract: 1-Acetyl-2,3-dimethylimidazolidine was synthesized and was shown to be able to directly reduce a series of aromatic, aliphatic and α,β-unsaturated aldehydes as well as imines in high yields.

Key words: 1-acetyl-2,3-dimethylimidazolidine, aldehydes, hydrogen transfer, imines, organic reductant

The investigations on heterocycles having hydrogen-donating ability as practical reductants have attracted attention in organic chemistry in recent years.[1–8] 1,4-Dihydropyridines are known to be the active part of the reduced form of the nicotinamide adenine dinucleotide (NADH; Figure 1), which plays a vital role in many biological reductions.[1] 1-Benzyl-1,4-dihydronicotinamide (BNAH), Hantzsch 1,4-dihydropyridine (HEH), 10-methyl-9,10-dihydroacridine ($AcrH_2$), and many other 1,4-dihydropyridine derivatives have been widely used as models to mimic the function of NADH, and effectively applied in the reduction of many unsaturated substrates.[2–5] In addition to 1,4-dihydropyridine derivatives, attentions have also been paid to five-membered heterocycles such as 2-phenylbenzimidazoline (PBI; Figure 1) and its derivative 1,3-dimethyl-2-phenylbenzimidazoline (DMBI; Figure 1).

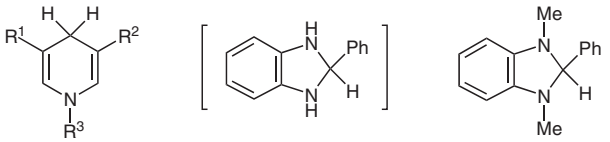


Figure 1

Twenty years ago, Chikashita and co-workers reported that DMBI and PBI could selectively reduce C–C double bonds conjugated with strong electron-withdrawing groups (CN, NO_2, $COCH_3$) to the corresponding saturated compounds.[6] Thereafter, this group reported that DMBI could react with a series of α-halocarbonyl compounds to produce the corresponding aldehydes or ketones without affecting the carbonyl group.[7] Moreover, DMBI was also used as a reductant in photoinduced electron transfer (PET) reaction systems for the reduction of α,β-epoxy ketone, aromatic ketones, etc.[8] Although, subsequent activities have been carried out to focus on the mechanistic details of these systems,[9] little attention has been paid to these heterocycles acting as reductant in organic synthesis.

In the present work, we wish to report a novel organic reductant, 1-acetyl-2,3-dimethylimidazolidine (**1c**), and its successful applications in the reduction of a series of aromatic, aliphatic and α,β-unsaturated aldehydes as well as imines in good yields.

Recently, we reported that under catalysis by *n*-butylamine, reaction of imidazolidine **1a** or **1b** (Figure 2) and aromatic aldehydes in refluxing MeCN provided 2-aryl-substituted imidazolidines as the sole product through a simple transfer reaction.[10] However, to our surprise, in the absence of *n*-butylamine, the reaction of **1a** and 4-nitrobenzaldehyde gave 4-nitrobenzyl alcohol in 26% yield. A similar result was observed for **1b** as the substrate, but with a lower yield (18%). Although the yield of the alcohol was not satisfactory in both cases, it nevertheless stimulated our interest to explore more efficient imidazolidine-type reductants for transfer hydrogenation.

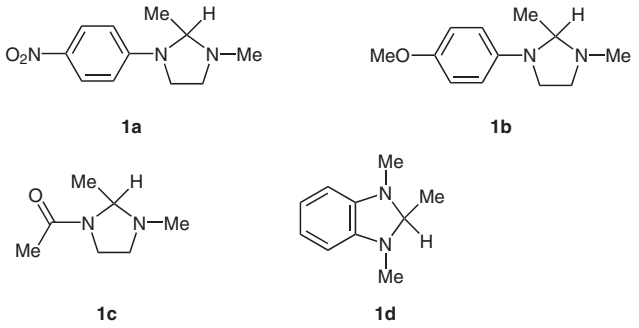


Figure 2 The organic reductants evaluated in this study

The obvious substituent effect observed with **1a** and **1b** aroused our curiosity to examine the reducing activity of imidazolidine **1c**.[11] In fact, introduction of the electron-withdrawing acetyl group to the molecule will make **1c** structurally more similar to NADH models, such as BNAH and HEH; thus, it was envisioned that imidazolidine **1c** could show good potential in reducing reactions.

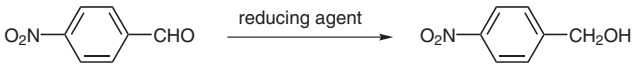
To our delight, when **1c** was reacted with 4-nitrobenzaldehyde (1 equiv) in refluxing MeCN, the desired product 4-nitrobenzyl alcohol was obtained in 65% yield after 12

SYNLETT 2008, No. 2, pp 0225–0228
Advanced online publication: 21.12.2007
DOI: 10.1055/s-2007-1000863; Art ID: W17907ST
© Georg Thieme Verlag Stuttgart · New York

hours. Importantly, when a small amount of methanol was added, the reaction was complete within two hours, and 4-nitrobenzyl alcohol was separated in the yield of 92%. In fact, in some NADH model-mediated reductions, polar solvents such as acetonitrile were quite suitable and a small amount of protic solvent such as methanol was also required.[12] It is generally thought that the proton from a protic solvent can neutralize the anionic intermediate formed upon hydride transfer so as to drive the reaction to completion. The reaction barely occurred at room temperature; however, upon addition of 10 mol% $Mg(ClO_4)_2$, the reaction was complete in four hours even at room temperature.

These results prompted us to re-examine the reactivity of **1a** and **1b** in the presence of $Mg(ClO_4)_2$ with methanol as an additive at room temperature. For comparison, PBI, DMBI and 1,2,3-trimethylbenzimidazoline (**1d**) were also examined (Table 1). As can be seen, imidazolidine **1c** was a much better hydrogen donor than **1a** and **1b**. The reaction became very sluggish when PBI, DMBI and 1,2,3-trimethylbenzimidazoline (**1d**) were used, affording only trace amount of the reduction product.

Table 1 Organic Reducing Agents Evaluated at Room Temperature[a]

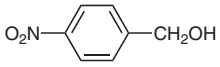
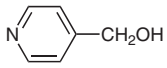
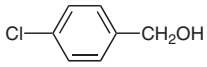
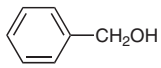
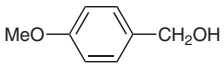
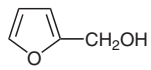
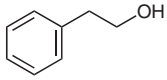
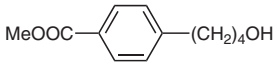
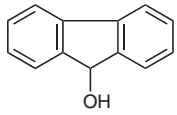
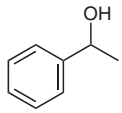


Entry	Reducing agent	Time (h)	Yield (%)[b]
1	**1a**	12	75
2	**1b**	12	56
3	**1c**	**5**	**94**
4	**1d**	12	trace
5	PBI (in situ)	12	trace
6	DMBI	12	trace

[a] Reaction conditions: reducing agent (1.0 mmol), 4-nitrobenzaldehyde (1.0 mmol), $Mg(ClO_4)_2$ (0.1 mmol), MeCN–MeOH (1:1, 4 mL), r.t.
[b] Refers to isolated yields after chromatography.

Application scope of the reducing system with **1c** as the hydrogen donor was then examined. After some trials, two sets of conditions were identified under which **1c** could effectively reduce a range of aldehydes and one ketone (9-fluorenone; Table 2). Electron-deficient aromatic aldehydes such as 4-nitrobenzaldehyde and 4-pyridinecarboxaldehyde (Table 2, entries 1 and 2) could be efficiently reduced by **1c** in refluxing acetonitrile–methanol (condition A) in good yields. However, under the same conditions, nonactivated substrates, such as 4-chlorobenzaldehyde, benzaldehyde, etc., failed to give any product. However, upon addition of 10 mol% $Mg(ClO_4)_2$, these nonactivated aromatic aldehydes could be smoothly reduced to the corresponding alcohols in good yields at room temperature (condition B; Table 2, entries 3–6). Condition B also worked well when aliphatic aldehydes were used as substrates (Table 2, entries 7 and 8). In the case of 9-fluorenone, the corresponding product could be obtained in 95% yield, although refluxing conditions were required (Table 2, entry 9). However, for nonactivated acetophenone, the reaction did not work under either set of conditions (Table 2, entry 10).

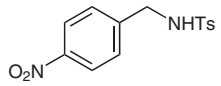
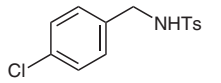
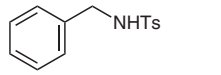
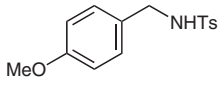
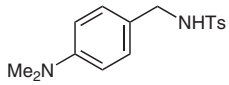
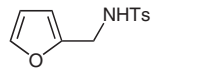
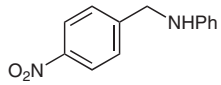
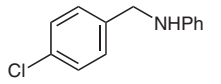
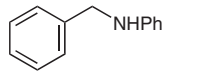
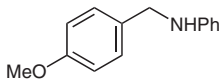
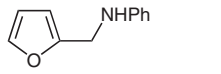
Table 2 Transfer Hydrogenation of Imidazolidine **1c** with Various Aldehydes[13]

Entry	Product	Conditions[a]	Time (h)	Yield (%)[b]
1		A	2	92
2		A	3	87
3		B	5	84
4		B	4	93
5		B	4	87
6		B	4	94
7		B	3	91
8		B	3	92
9		B[c]	13	95
10		A or B	24	n.d.[d]

[a] Reaction conditions: A = imidazolidine **1c** (1.0 mmol), substrate (1.0 mmol), MeCN–MeOH (1:1, 4 mL), reflux; B = imidazolidine **1c** (1.0 mmol), substrate (1.0 mmol), $Mg(ClO_4)_2$ (0.1 mmol), MeCN–MeOH (1:1, 4 mL), r.t.
[b] Refers to isolated yields after chromatography.
[c] The reaction was carried out at reflux temperature.
[d] Not determined.

The scope of this new reduction was further extended to a variety of imines. As shown in Table 3, for *N*-tosyl imines, the reductions worked very well in refluxing acetonitrile–methanol (condition A), and the yields exceeded 90% in all cases (entries 1–6). For *N*-phenyl imines, similar to nonactivated aromatic aldehydes, condition B proved to be appropriate and the yields of these reactions varied from 46% to 87% depending on substrates (entries 7–11). The low yield for *N*-phenyl-4-nitrobenzaldimine

Table 3 Transfer Hydrogenation of Imidazolidine **1c** with Various Imines

Entry	Product	Conditions[a]	Time (h)	Yield (%)[b]
1		A	3	99
2		A	5	98
3		A	5	92
4		A	3	96
5		A	3	91
6		A	3	92
7		B	5	46
8		B	3	78
9		B	2	81
10		B	2	85
11		B	2	87

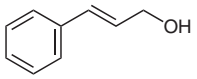
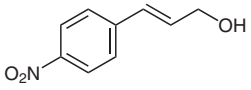
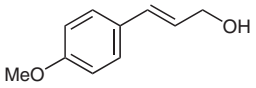
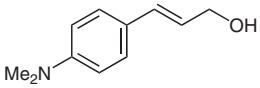
[a] Reaction conditions: A = imidazolidine **1c** (1.0 mmol), substrate (1.0 mmol), MeCN–MeOH (1:1, 4 mL), reflux; B = imidazolidine **1c** (1.0 mmol), substrate (1.0 mmol), $Mg(ClO_4)_2$ (0.1 mmol), MeCN–MeOH (1:1, 4 mL), r.t.
[b] Refers to isolated yields after chromatography.

(entry 7) was mainly due to its quick decomposition under the reaction conditions.

Recently, it was reported that Hantzsch ester could efficiently and chemoselectively reduce enals to the corresponding saturated aldehydes under the catalysis of ammonium salts of some secondary amines.[3] In contrast, under our reaction conditions, all enals examined could be reduced to the corresponding unsaturated alcohols in high yields at room temperature without any effect on the carbon–carbon double bonds (Table 4). The desired unsaturated alcohols were obtained as the sole products in all the cases tested.

The fate of **1c** in the reducing reactions is not very clear currently. However, it is a fact that the reduction involved the transfer of a hydrogen atom from the C-2 position of

Table 4 Transfer Hydrogenation of Imidazolidine **1c** with Several α,β-Unsaturated Aldehydes

Entry	Product	Conditions[a]	Time (h)	Yield (%)[b]
1		B	3	94
2		B	3	91
3		B	3	97
4		B	5	95

[a] Conditions: B = imidazolidine **1c** (1.0 mmol), substrate (1.0 mmol), $Mg(ClO_4)_2$ (0.1 mmol), MeCN–MeOH (1:1, 4 mL), r.t.
[b] Refers to isolated yields after chromatography.

1c as a hydride, as in PBI and DMBI.[6] This could be confirmed through the following experiments. When the reaction of **1c** and 4-nitrobenzaldehyde was performed in deuterated acetonitrile and methanol, 4-nitrobenzyl alcohol was obtained as the only product (Figure 3a). When the reaction of deuterated **1c** (C-2 position)[11] and 4-nitrobenzaldehyde was performed in acetonitrile and methanol, only the deuterated 4-nitrobenzyl alcohol (Figure 3b) was obtained. In addition, the free-radical chain mechanism appeared to be impossible in the current case because dinitrobenzene, a free-radical inhibitor, could not inhibit the reaction under the reaction condition.[14] Unfortunately, the oxidized form of **1c** is not clear at present due to the complexity of the ^1H NMR spectrum of this reaction product.

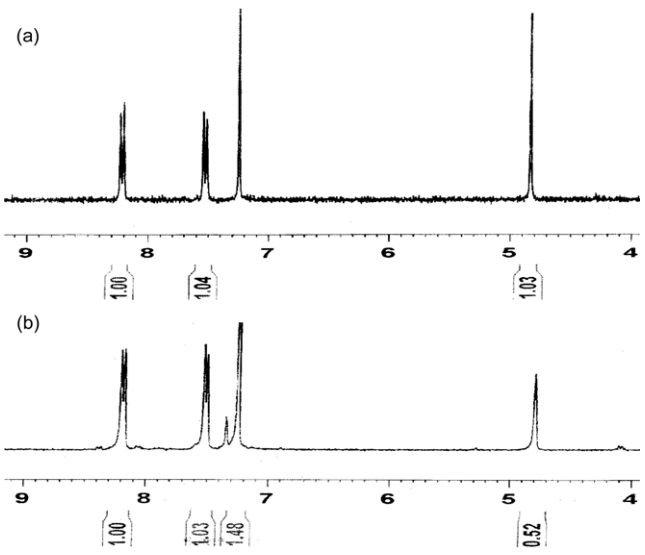
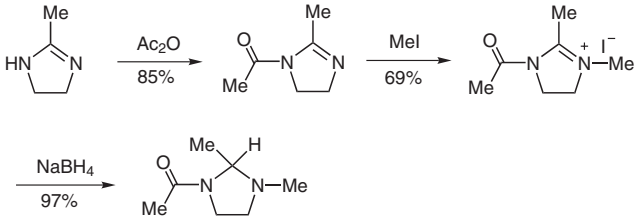


Figure 3 The ^1H NMR spectra ($CDCl_3$) of (a) 4-nitrobenzyl alcohol and (b) deuterated 4-nitrobenzyl alcohol.

In summary, we have developed a mild, efficient, and selective organic reductant, 1-acetyl-2,3-dimethylimidazolidine (**1c**), for the reduction of aromatic, aliphatic and α,β-unsaturated aldehydes as well as imines in good yields. Investigations to understand the reducing mechanism and to evaluate the process with a boarder scope of substrates are in progress in our laboratory.



Scheme 1

Acknowledgment

We thank the National Natural Science Foundation of China (No. 20502014, 20772073) for financial support.

References and Notes

(1) Stryer, L. *Biochemistry*, 3rd ed.; Freeman: New York, **1998**, Chap. 15-18.

(2) (a) Tanner, D. D.; Stein, A. R. *J. Org. Chem.* **1988**, *53*, 1642. (b) Coleman, C. A.; Rose, J. G.; Murray, C. H. *J. Am. Chem. Soc.* **1992**, *114*, 9755. (c) Rueping, M.; Sugiono, E.; Azap, C.; Theissmann, T.; Bolte, M. *Org. Lett.* **2005**, *7*, 3781.

(3) (a) Yang, J. W.; Hechavarria, M. T.; List, B. *Angew. Chem. Int. Ed.* **2004**, *43*, 6660. (b) Ouellet, S. G.; Yuttle, J. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 32. (c) Yang, J. W.; Hechavarria, M. T.; Vignola, N.; List, B. *Angew. Chem. Int. Ed.* **2005**, *44*, 108. (d) Hoffmann, S.; Seayad, A. M.; List, B. *Angew. Chem. Int. Ed.* **2005**, *44*, 7424. (e) Tuttle, J. B.; Ouellet, S. G.; MacMillan, D. W. C. *J. Am. Chem. Soc.* .

(4) (a) Kazuyuki, M.; Nishimoto, N.; Hidenobu, M.; Asuka, M.; Satoshi, O.; Yasuko, I.; Toshimasa, I.; Takeshi, I. *Chem. Commun.* **1996**, *22*, 2535. (b) Kanomata, N.; Nakata, T. *Angew. Chem. Int. Ed.* **1997**, *36*, 1207.

(5) (a) Zhu, X.-Q.; Liu, Y.-C.; Cheng, J.-P. *J. Org. Chem.* **1999**, *64*, 8980. (b) Zhu, X.-Q.; Liu, Y.; Zhao, B.-J.; Cheng, J.-P. *J. Org. Chem.* **2001**, *66*, 370. (c) Zhu, X.-Q.; Yang, Y.; Zhang, M.; Cheng, J.-P. *J. Am. Chem. Soc.* **2003**, *125*, 15298.

(6) (a) Chikashita, H.; Nishida, S.; Miyazaki, M.; Itoh, K. *Synth. Commun.* **1983**, *13*, 1033. (b) Chikashita, H.; Morita, Y.; Itoh, K. *Synth. Commun.* **1985**, *15*, 527. (c) Chikashita, H.; Itoh, K. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 1747.

(7) Chikashita, H.; Ide, H.; Itoh, K. *J. Org. Chem.* **1986**, *51*, 5400.

(8) (a) Hasegawa, E.; Yoneoka, A.; Suzuki, K.; Kato, T.; Kitazume, T.; Yanagi, K. *Tetrahedron* **1999**, *55*, 12957. (b) Hasegawa, E.; Seida, T.; hiba, N.; Takahashi, T.; Ikeda, H. *J. Org. Chem.* **2005**, *70*, 9632.

(9) (a) Tanner, D. D.; Chen, J. J. *J. Org. Chem.* **1992**, *57*, 662. (b) Lee, I. H.; Heoung, E. H.; Kreevoy, M. M. *J. Am. Chem. Soc.* **1997**, *119*, 2722. (c) Lee, I. H.; Heoung, E. H. *J. Org. Chem.* **1998**, *63*, 7275. (d) Lee, I. H.; Heoung, E. H.; Kreevoy, M. M. *J. Am. Chem. Soc.* **2001**, *123*, 7492. (e) Lee, I. H.; Ji, Y. R.; Heoung, E. H. *J. Phys. Chem. A* **2006**, *110*, 3875.

(10) Li, D.; Zhang, Y.; Xia, C.; Guo, W. *Heterocycles* **2005**, *65*, 1829.

(11) **Synthesis of 1-Acetyl-2,3-dimethylimidazolidine (1c) (Scheme 1)**:
2-Methylimidazoline (4.3 g, 51 mmol) was dissolved in CH_2Cl_2 (15 mL) at 0 °C, followed by the addition of Et_3N (5.2 g, 51 mmol). This solution was then added dropwise to a solution of Ac_2O (5.2 g, 51 mmol) in CH_2Cl_2 (5 mL). After the addition, the reaction mixture was stirred at r.t. for an additional 3 h. The resulting solution was treated with 10% $NaHCO_3$ (40 mL). After stirring for 0.5 h, the mixture was extracted with CH_2Cl_2, and the organic layers were washed with brine, and dried over anhyd Na_2SO_4. Evaporation of CH_2Cl_2 in vacuo gave 1-acetyl-2-methylimidazoline (5.46 g) as an oil (yield: 85%). This product was sufficiently pure for the next step.
1-Acetyl-2-methylimidazoline (5.8 g, 46 mmol) and MeI (8.6 mL, 138 mmol) were refluxed in Et_2O (30 mL) for 10 h. After cooling to r.t., acetone (15 mL) was added to the mixture. The mixture was stirred for several hours, and the solid obtained was collected by vacuum filtration to give 1-acetyl-2,3-dimethylimidazolinium iodide (8.5 g) as a white solid (yield: 69%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.39 (s, 3 H), 2.79 (s, 3 H), 3.41 (s, 3 H), 4.29 (m, 2 H), 4.46 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.1, 171.2, 55.5, 49.3, 38.5, 28.1, 19.2. IR (KBr): 2941, 1728, 1654, 1446, 1388, 1298, 1174, 1037 cm^{-1}.
1-Acetyl-2,3-dimethylimidazolinium iodide (0.80 g, 3 mmol) was dissolved in MeCN (10 mL) at 0 °C, followed by the addition of $NaBH_4$ (0.125 g, 3.3 mmol). After the addition, the reaction mixture was stirred at r.t. for an additional 5 h. The reaction was quenched with H_2O (50 mL). The mixture was extracted with CH_2Cl_2, and the organic layers were washed with brine, and dried over anhyd Na_2SO_4. Evaporation of CH_2Cl_2 in vacuo gave 1-acetyl-2,3-dimethylimidazolidine (**1c**; 0.42 g) as a clear oil (yield: 97%). ^{1}H NMR (300 MHz, D_2O): δ = 1.33–1.50 (3 × d, *J* = 6.3 Hz, 3 H), 2.05–2.11 (3 × s, 3 H), 2.63–2.69 (3 × s, 3 H), 3.27–3.88 (3 × m, 4 H), 4.76–4.90 (m, 1 H). IR (film): 2956, 2381, 1718, 1652, 1419, 1265, 1182 cm^{-1}. MS: *m/z* = 142 [M$^+$], 127 [M –15], 99 [M – 43]. Anal. Calcd for $C_7H_{14}N_2O$: C, 59.12; H, 9.92; N, 19.70. Found: C, 59.24; H, 9.89; N, 19.75.
The deuterated **1c** (C-2 position) was synthesized by the same procedures except that $NaBD_4$ was used. ^{1}H NMR (300 MHz, D_2O): δ = 1.22–1.36 (3 × s, 3 H), 1.93–1.99 (3 × s, 3 H), 2.51–2.56 (3 × s, 3 H), 3.15–3.73 (3 × m, 4 H).

(12) Zhang, B.; Zhu, X.-Q.; Lu, J.-Y.; He, J.; Wang, P. G.; Cheng, J.-P. *J. Org. Chem.* **2001**, *68*, 3295.

(13) **General Procedure for the Transfer Hydrogenation Reaction with Imidazolidine 1c as Reductant**
Procedure Using Condition A: To a solution of substrate (1 mmol) in MeOH (2 mL) was added a solution of imidazolidine **1c** (0.142 g, 1 mmol) in anhyd MeCN (2 mL). The reaction mixture was stirred under reflux and monitored by TLC. Upon completion, the solvent was removed in vacuo and the residue was chromatographed on silica gel to give the desired products.
Procedure Using Condition B: To a solution of substrate (1 mmol) and $Mg(ClO_4)_2$ (22.3 mg, 0.1 mmol) in MeOH (2 mL) was added a solution of imidazolidine **1c** (0.142 g, 1 mmol) in anhyd MeCN (2 mL). The reaction mixture was stirred at r.t. and monitored by TLC. Upon completion, the solvent was removed in vacuo and the residue was chromatographed on silica gel to give the desired products.

(14) Tanner, D. D.; Chen, J. J. *J. Org. Chem.* **1989**, *54*, 3842.

Copyright of Synlett is the property of Georg Thieme Verlag Stuttgart and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.