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Oxidative Rearrangement of Cyclic Tertiary Allylic Alcohols with IBX in DMSO

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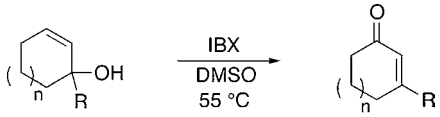
ABSTRACT

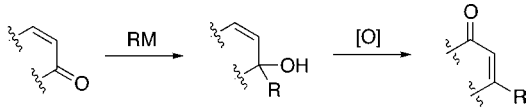


R = alkyl, aryl: n = 0, 1

A practical and environmentally friendly method for oxidative rearrangement of five- and six-membered cyclic tertiary allylic alcohols to *β*-disubstituted α,*β*-unsaturated ketones by the IBX/DMSO reagent system is described. Several conventional protecting groups (e.g., Ac, MOM, and TBDPS) are compatible under the reaction conditions prescribed.

Methods enabling the transposition of a functional group from one carbon to another offer a wide range of latitude in synthesis of architecturally complex molecules.[1] The alkylative carbonyl transposition of α,*β*-unsaturated ketones,[2] which entails the 1,2-addition of organometallic reagents to α,*β*-unsaturated ketones and the oxidative rearrangement of the resulting tertiary allylic alcohols to yield *β*-disubstituted α,*β*-unsaturated ketones, is representative of such methods, and several synthesis achievements relying on this sequence have been reported in the literature (Scheme 1).[3] To our knowledge, however, there is only one method using more than a stoichiometric amount of hazardous oxochromium(VI)-based oxidants[4,5] such as PCC and PDC that effects the key oxidation step. We herein report an eco-friendly method for the oxidative rearrangement of cyclic tertiary allylic alcohols to *β*-substituted cyclic ketones.

Scheme 1. Alkylative Carbonyl Transposition Sequence



Regarding the ecological profiles on available oxidizing agents and the mechanism of the oxochromium(VI)-mediated oxidative rearrangement where the Cr═O substructure plays crucial roles[2,6] (Scheme 2), we presumed that less toxic, hypervalent iodine-based reagents[7] capable of serving an

(1) Schlecht, M. F. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Ley, S. V., Eds.; Pergamon: Oxford, 1991; Vol. 7, pp 815−837.

(2) (a) Babler, J. H.; Coghlan, M. J. *Synth. Commun.* **1976**, *6*, 469. (b) Dauben, W. G.; Michno, D. M. *J. Org. Chem.* **1977**, *42*, 682. (c) Sundararabhan, P.: Herz, W. *J. Org. Chem.* **1977**, *42*, 813.

(3) (a) Mohr, P. J.; Halcomb, R. L. *J. Am. Chem. Soc.* **2003**, *125*, 1712. (b) Hanada, K.; Miyazawa, N.; Ogasawara, K. *Org. Lett.* **2002**, *4*, 4515. (c) Nagata, H.; Miyazawa, N.; Ogasawara, K. *Chem. Commun.* **2001**, 1094. (d) Trost, B. M.; Pinkerton, A. B. *Org. Lett.* **2000**, *2*, 1601. (e) Majetich, G.; Song, J.-S.; Leigh, A. J.; Condon, S. M. *J. Org. Chem.* **1993**, *58*, 1030. (f) Luzzio, F. A.; Moor, W. J. *J. Org. Chem.* **1993**, *58*, 2966 and references therein. (g) Takano, S.; Inomata, K.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1989**, 271

(4) For a recent review on an oxochromium(VI)-based oxidant, see: Luzzio, F. A. *Org. React.* **1998**, *53*, 1.

(5) For an eminent review on chromium-catalyzed oxidations, see: Muzart, J. *Chem. Rev.* **1992**, *92*, 113. See also: Riahi, A.; Hénin, F.; Muzart, J. *Tetrahedron Lett.* **1999**, *40*, 2303.

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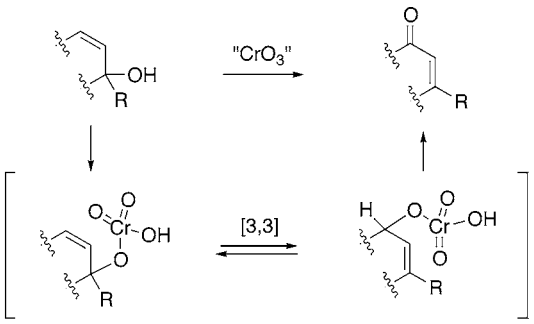
Scheme 2. Cr(VI)-Mediated Oxidative Rearrangement of Tertiary Allylic Alcohols



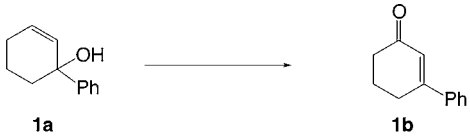
I═O structural motif would complementarily surrogate the function of Cr(VI)-based reagents.

Using 1-phenyl-2-cyclohexen-1-ol (**1a**), we probed the ability of a panel of hypervalent iodine compounds to promote the desired oxidative rearrangement (Table 1).

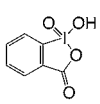
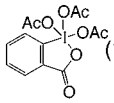
It was revealed that 1.5 equiv of an iodine(V)-based reagent, 1-hydroxy 1,2-benziodoxal-3(*1H*)-one-1-oxide (IBX), in DMSO[7] gradually promoted the oxidative rearrangement of **1a** at room temperature to yield 78% 3-phenyl-2-cyclohexenone (**1b**) as the sole product with 17% recovered **1a** after 24 h (entry 1). The gentle warming of the reaction using 1.5 equiv of IBX at 55 °C caused a marked acceleration to afford 85% **1b** within 1 h, along with 13% 1-phenyl-1,3-cyclohexadiene as the only detectable byproduct (entry 2). The use of 3 equiv of IBX reasonably enhanced the efficacy of the reaction to yield 93% **1b** (entry 3). It was noted that IBX in DMSO immediately oxidized 3-phenyl-2-cyclohexen-1-ol to **1b** at room temperature, indicating that heat is effectual for allylic transposition.

$PhIO_2$[9] in DMSO also effected the oxidative rearrangement with almost the same efficacy as IBX at the high temperature of 90 °C, suggesting the important role of the carboxy group in IBX in enhancing the reaction[10] (entry 4). The Dess−Martin periodinane[11] suffered from a significant side reaction to yield 46% 3-acetoxy-1-phenyl 2-cyclohexene (entry 5). HIO_3 and I_2O_5,[12] which seem to be more atom-efficient, gave **1b** in a moderate yield of 40%, due to the decomposition

Table 1. Reaction Properties of Hypervalent Iodine Reagents



1a **1b**

entry	oxidant	(equiv)	solvent	temp (°C)	time (hr)	yield (%)
1		(1.5)	DMSO	rt	24	78[a]
2		(1.5)	DMSO	55	1	85[b]
3		(3.0)	DMSO	55	0.5	93
4	$PhIO_2$	(1.5)	DMSO	90	1	87
5		(1.5)	CH_2Cl_2	rt	0.2	25[c]
6	HIO_3	(1.5)	DMSO	rt	1	40
7	I_2O_5	(1.5)	DMSO	rt	1	40
8	PhIO	(1.1)	DMSO	55	5	0[d]
9	PhIO (1.2), KBr (1.0)		H_2O	rt	1	0
10	PhIO (1.5),CAS (0.8)		CH_2Cl_2	rt	2	38
11	$PhI(OAc)_2$	(1.5)	CH_2Cl_2	rt	5	0

[a] **1a** (17%) was recovered. [b] 1-Phenyl-1,3-cyclohexadiene (13%) was also obtained. [c] 1-Acetoxy-1-phenyl-2-cyclohexen-1-ol (46%) was obtained.[d] 3-Phenyl-2-cyclohenen-1-ol (35%) was obtained with 65% recovery of **1a**.

caused by the considerably acidic properties of the reagents used (entries 6 and 7). The iodine(III)-based oxidant PhIO did not exhibit an oxidizing ability in DMSO. The recently developed oxidation reagents PhIO/KBr/H_2O[13] also failed to afford **1b** (entries 8 and 9). At this point, it is interesting to point out that the heating of a 1:1.1 mixture of **1a** and PhIO in DMSO at 55 °C caused allylic transposition to yield 35% 3-phenyl-2-cyclohexen-1-ol and 65% starting **1a**. This result indicates that PhIO does not exhibit an oxidizing ability under these conditions.[14] After some experiments, it was also noted that the addition of a substoichiometric amount of CSA induces the oxidation of **1a** by PhIO to yield 38% **1b**, although the reaction involved considerable decomposition (entry 10).

Having established the novel use of IBX in the DMSO system in oxidative allylic transposition, we next investigated the scope and limitations of the present method using various

(6) Oxidative rearrangement can also go through an allylic cation generated by solvolysis of the chromate ester, as similarly described in Scheme 4 (vide infra). See also ref 4.

(7) (a) Varvoglis, A. *Hypervalent Iodine in Organic Synthesis*; Academic Press: London, 1997. (b) Wtrth, T.; Hirt, U. H. *Synthesis* **1999**, 1271. (c) Zhdankin, V.; Stang, P. J. *Chem. Rev.* **2002**, *102*, 2523. (d) Wirth, T. *Hypervalent Iodine Chemistry*; Springer-Verlag: Berlin Hiderberg, 2003. (e) Wirth, T. In *Organic Synthesis Highlights V*; Schmalz, H.-G., Wirth, T., Eds.; Wiely-VCH: Weiheim, 2003; pp 144−150.

(8) (a) Frigerio, M.; Santagostino, M. *Tetrahedron Lett.* **1994**, *43*, 8019. (b) Frigerio, M.; Santagostino, M.; Sputore, S.; Palmisano, G. *J. Org. Chem.* **1995**, *60*, 7272. (c) Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537.

(9) Kazmeirczak, P.; Skulski, L.; Kraszkiewicz, L. *Molecules* **2001**, *6*, 881.

(10) We reasoned that the carboxy group imparts considerable solubility in DMSO and suitable acidity to IBX.

(11) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.

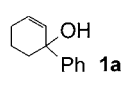
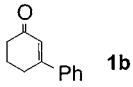
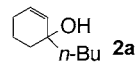
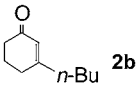
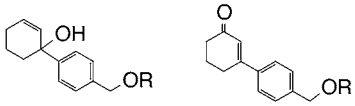
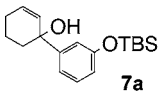
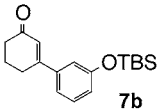
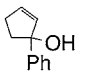
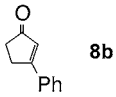
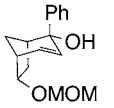
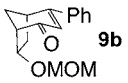
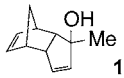
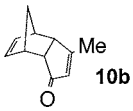
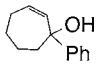
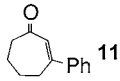
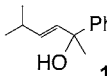
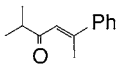
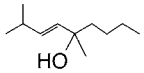
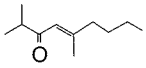
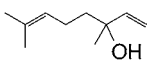
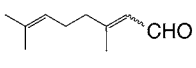
(12) Nicolaou, K. C.; Montagnon, T.; Baran, P. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 1386.

(13) (a) Tohma, H.; Takizawa, S.; Maegawa, T.; Kita, Y. *Angew. Chem., Int. Ed.* **2000**, *39*, 1306. (b) Tohma, H.; Maegawa, T.; Takizawa, S.; Kita, Y. *Adv. Synth. Catal.* **2002**, *344*, 328.

(14) PhIO has been found to oxidize various alcohols to carbonyl compounds in refluxing dioxane; see: Takaya, T.; Enyo, H.; Imoto, E. *Bull. Chem. Soc., Jpn.* **1968**, *41*, 1032.

tertiary allylic alcohols (Table 2). Compared with the phenyl-substituted substrate **1a**, the alkyl-substituted substrate **2a** was prone to dehydration under standard conditions[15] (entries 1 and 2). We eventually found that the addition of 2 equiv of pyridine is effective in suppressing undesired side reactions in this particular case to yield 81% **2b** (entry 3).[16] Conventional protecting groups such as Ac, MOM, and TBDPS were tolerated under the standard reaction conditions (entries 4−6). However, the TBS group attached to the primary alcohol was partially deprotected[17] and oxidized to yield 29% 3-(4-formylphenyl)-2-cyclohenenone as the byproduct, together with 49% **5b**. Notably, TBS on phenol was intact (entry 8). The five-membered substrate **8a** also yielded a transposed product with approximately the same efficacy as the six-membered substrate (entry 9). Both the conformationally constrained bicyclic and tricyclic compounds **9a** and **10a**, respectively, required slightly harsh conditions, but they gave the expected products of **9b** and **10b** in 79% yields (entries 10 and 11). The seven-membered substrate **11a** suffered from dehydration to yield 53% 1-phenyl-1,3-heptadiene, and the desired enone **11b** was obtained in a moderate yield of 38% (entry 11). However, the potency of IBX on oxidative rearrangement crucially decreased in the case of acyclic substrates (entries 13−15). From these results, we confirmed the general applicability of the IBX-mediated oxidative rearrangement to five- and six-membered cyclic tertiary allylic alcohols.

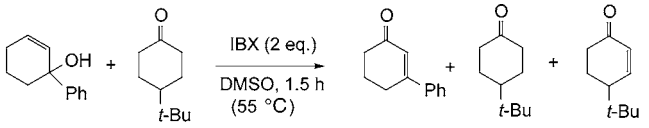
Table 2. Scope of IBX-Enhanced Oxidative Rearrangement[a]

entry	substrate	product	time (hr)	yield (%)[b]
1	 **1a**	 **1b**	1	85 (90[2])
2	 **2a**	 **2b**	2.5	56[c]
3			3.5	80[d]
4	 **3a, 3b:** R = Ac		1	81
5	**4a, 4b:** R = MOM		1	88
6	**5a, 5b:** R = TBDPS		1	82
7	**6a, 6b:** R = TBDMS		1	49[e]
8	 **7a**	 **7b**	4	84
9	 **8a**	 **8b**	0.5	80
10	 **9a**	 **9b**	10	79
11	 **10a**	 **10b**	2	79[f] (63[3f])
12	 **11a**	 **11b**	1	38[g]
13	 **12a**	 **12b**	8	57[h]
14	 **13a**	 **13b**	8	38
15	 **14a**	 **14b**	10	0 (78[2])

[a] Standard reaction conditions employed 2 equiv of IBX in DMSO at 55 °C. [b] Numbers in parentheses are reported yields using PCC. [c] 1-Butyl-1-cyclohexene (33%) was obtained. [d] Pyridine (2 equiv) was added. [e] 3-(4-Formylphenyl)-2-cyclihexenone (29%) was also obtained. [f] IBX (5 equiv) was used. [g] 1-Phenyl-1,3-cycloheptadiene (53%) was obtained. [h] *E*:*Z* = 98:2. Diastereomeric ratio was determined by ^{1}H NMR analysis.

To gain insight into the chemoselectivity of the multitalented oxidizing agent IBX,[18] an intermolecular competition experiment was undertaken in which **1a** was preferentially converted into **1b** in the presence of 1 equiv of 4-*tert*-butylcyclohexanone (**15**) in DMSO at 55 °C (Scheme 3).

Scheme 3. Intermolecular Competitive Reaction



1a (1 eq.) + **14** (1 eq.) → **1b** (87 %) + **14** (87 %) + **15** (13 %)

This result, presumably, reflects a lower activation energy for the allylic transposition when compared to that of single electron-transfer process mediated by IBX.

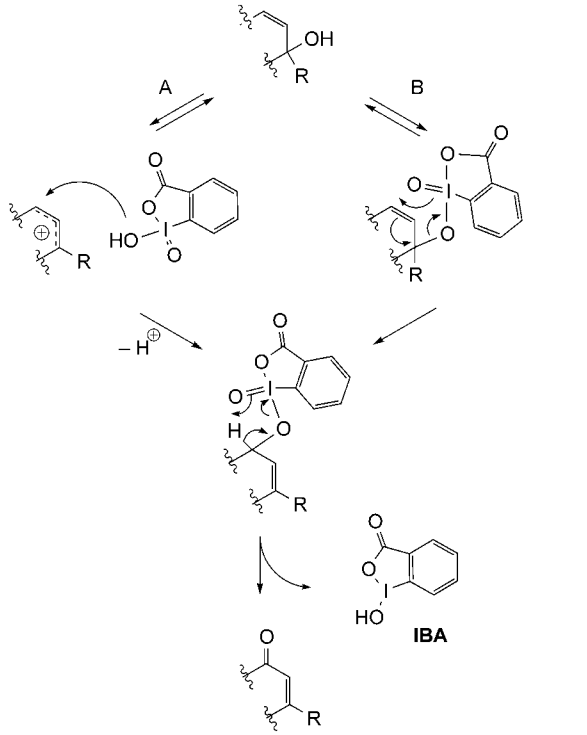
We speculate that there are two pathways that operate in the IBX-mediated oxidative rearrangement.[19] Considering the

(15) **Representative Procedure for IBX-Mediated Oxidative Rearrangement of *tert*-Allylic Alcohols.** IBX (1.2 mmol) was added to a solution of **1a** (0.57 mmol) in DMSO (3 mL), and the mixture was heated at 55 °C for 1 h. After cooling, the pale-yellow colored mixture was diluted with Et_2O and washed with H_2O and brine. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The remaining residue was purified by column chromatography on silica gel to give 85% of **1b**.

(16) Addition of pyridine had unpredictable results. For example, it suppressed the dehydration of **1a** and decreased the yield of **1b** to 70% due to the contamination of dark-brown byproducts derived from pyridine.

(17) Wu, Y.; Huang, J.-H.; Shen, X.; Hu, Q.; Tang, C.-J.; Li, L. *Org. Lett.* **2002**, *4*, 2141.

Scheme 4. Plausible Reaction Mechanisms



mild acidity of IBX,[18b] it is possible to induce the solvolysis of the tertiary alcohol to an allylic cation that subsequently collapses with an IBX at less substituted termini to generate an isomeric iodic ester that undergoes oxidation, as in pathway A (Scheme 4). Alternatively, tertiary iodic ester formation[20] and the following rearrangement may precede the oxidation, as in pathway B.

In summary, we disclosed the additional use of IBX in the DMSO system, which allows us to perform the oxidative transposition of five- and six-membered cyclic tertiary allylic alcohols in an ecologically and user-friendly manner.

Supporting Information Available: Experimental details, copies of ^{1}H and ^{13}C NMR spectra, and complete characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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