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Iodine as a Chemoselective Reoxidant of TEMPO: Application to the Oxidation of Alcohols to Aldehydes and Ketones

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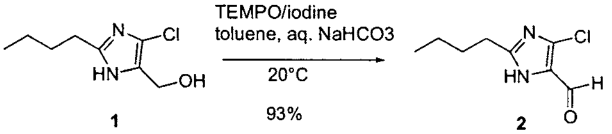
ABSTRACT



Chemoselective alcohol oxidations using catalytic TEMPO and stoichiometric iodine as the terminal oxidant were studied. Iodine was compared to other positive halogens as the terminal oxidant and shown to be superior in cases of electron-rich and heteroaromatic rings. The new conditions were successfully applied to an important intermediate (2) in the synthesis of Losartan.

Chemoselective oxidations of functional groups remain a challenge in organic synthesis.[1] In addition to the sometimes formidable chemoselectivity issues, the safety, cost, and environmental factors further complicate the use of some established oxidants, and these factors amplify in importance with the scale of the reaction. The oxidation of alcohols to carbonyl compounds using TEMPO, stoichiometrically or catalytically with a stoichiometric reoxidant, have been extensively reported in the literature.[2−12] These conditions successfully solve many of the demands of oxidation reactions. However, the high cost and availability of TEMPO on large scale have driven the development of the variety of stoichiometric oxidants. Herein we report our studies of iodine as a stoichiometric terminal oxidant of TEMPO.

The oxidation of the imidazole alcohol **1** with stoichiometric manganese dioxide was initially used for the synthesis of aldehyde **2** for Merck's anti-hypertensive Losartan.[13] However, these conditions proved to be unacceptable for a manufacturing environment.[14] TEMPO oxidations were

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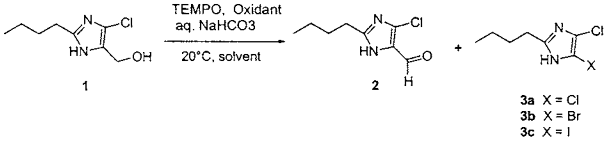
studied for this transformation, but initial attempts under standard conditions gave no desired product. Principally, electrophilic aromatic substitution *ipso* to the hydroxymethylene occurred with positive chloride or bromide reagents, resulting in dihalogenated imidazoles **3a** or **3b**, respectively.[15] In contrast to positive bromine and chlorine, iodine will not easily undergo electrophilic halogenation reactions.[16] However, iodine has been reported to react stoichiometrically with amines in the literature to give iminium or nitrosonium species.[17] We therefore speculated it would be inert to imidazole **1** yet reactive with TEMPO in a catalytic manner. Results of these experiments compared to other oxidants with imidazole **1** are shown in Table 1. Various chlorinating and brominating reagents gave only traces of desired product with the major product **3a**,**b** containing halogen. Oxone was slow to react and gave only small amounts of **2** as a minor product among several other. In contrast to these reagents, I_2 gave a high yield of **2** in several hours at room temperature with no **3c** observed.

Table 1. TEMPO-Catalyzed Oxidation of Imidazole Alcohol

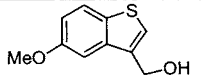
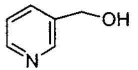


Entry	Oxidant	Solvent	Yield[a] 2	Yield 3 (a-c)
1	2 eq Br_2	Toluene	Trace	<50%
2	1 eq Br_2	Toluene	Trace	80%
3	1.1 eq NBS	Toluene	Trace	85%
4	1 eq NCS	Toluene	Trace	85%
6	**2 eq. I_2**	Toluene	**93%**	ND

[a] Assay yields calculated by HPLC using an external reference standard.

Iodine was an effective oxidant for simple substrates as well as other troublesome substrates. Table 2 lists examples tested with these oxidation conditions. The conditions are general for a variety of substrates including electron-rich, electron-poor, and heteroaromatic (entries 1−7). In the case of cinnamyl alcohol, about 5% of the iodinated double bond was observed and was therefore lower than IBDA (ref 8) because of this side reaction. A saturated alcohol, cyclohexanol, gave an 85% yield of cyclohexanone.

Table 2. Oxidation of Alcohols with Iodine as a Terminal Oxidant and Catalytic TEMPO

Entry	Alcohol	Solvent	Yield[a]
1	Benzyl alcohol	Toluene	96%
2	p-methoxybenzyl alcohol	Toluene	95%
3	p-nitrobenzyl alcohol	Toluene	90%
4	Cinnamyl alcohol	Toluene	85%
5		Toluene	92%
6		CH_2Cl_2	86%
7	cyclohexanol	CH_2Cl_2	85%

[a] Assay yields calculated by HPLC using an external reference standard.

The electon-rich benzothiophene alcohols (entries 5 and 6) gave large amounts of chlorinated ring products when bleach was used as the terminal oxidant with catalytic TEMPO. Attempted oxidation using sodium tungstate and peroxide gave only sulfoxide product.[18] With the current conditions, no sulfur oxidation or ring-iodination was observed. When I_2 was used as a terminal oxidant, however, a high yield of desired aldehyde was obtained.

Representative Oxidation. 2-(*n*-Butyl)-5-chloro-4-imidazolemethanol (750 mg, 3.98 mmol) was charged into a 100-mL round-bottom flask equipped with a magnetic stir bar. The solid was then slurried in toluene (10 mL) at 20 °C. An aqueous solution of sodium bicarbonate (1.00 g, 11.94 mmol in 10 mL of deionized water) was prepared and charged into the toluene slurry at 20 °C. Solid iodine (2.02 g, 7.96 mmol) was then charged in one portion to the alcohol followed by solid TEMPO (62 mg, 0.398 mmol). The reaction mixture was then aged overnight (16 h) at 20 °C. The batch was cooled to 5 °C and diluted with ethyl acetate (10 mL). The batch was quenched at 5 °C by adding an aqueous solution of sodium sulfite (501 mg sodium sulfite in 5 mL if DI water). The quenched reaction mixture was transferred to a separatory funnel (rinsed with additional ethyl acetate, 10 mL and DI water, 10 mL), and the aqueous layer was cut away. The organic layer was then washed with 10 mL of saturated aqueous potassium bicarbonate followed by 10 mL of brine. The washed organic layer was then diluted to 50 mL. The organic layer was then dried over sodium sulfate and concentrated in vacuo to a volume of 10 mL. A mechanical stir bar was added, and the solution was further concentrated by a stream of nitrogen to a volume of 5 mL. The batch was seeded with title aldehdye (50 mg), and the slurry was aged at 20 °C for 30 min. The batch was then cooled to 5 °C and aged for 30 min. The solids were isolated

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(15) Characterization data for **3b**: ^{1}H NMR (399.87 MHz, $CDCl_3$) δ 11.4 (br s, 1H), 2.74 (t, $J = 8$ Hz, 2H), 1.67 (pentet, $J = 8$ Hz, 2H), 1.34 (sextet, $J = 8$ Hz, 2H), 0.87 (t, $J = 7$ Hz, 3H); ^{13}C NMR (100.55 MHz, $CDCl_3$) δ 149.1, 122.5, 100.4, 30.5, 28.6, 22.2, 13.7. Anal. Calcd for $C_7H_{10}BrClN_2$: C, 35.40; H, 4.24; N, 11.79. Found: C, 35.88; H, 4.21; N, 11.81. LR MS calcd 235.9, found 235.9.

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by filtration, and the cake was washed with cold toluene (3 mL). The solids were dried in vacuo to provide aldehyde (690 mg).

In conclusion, iodine was found to be a novel terminal oxidant for TEMPO. This oxidant combination gave high yields of aldehydes for numerous alcohols, including sensitive ones that were not amenable to bleach oxidations. In addition, the oxidation was applied to the preparation of the commercially important Losartan aldehyde **2**. These mild conditions may be useful for a variety of other substrates that cannot tolerate strong reoxidants.

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