Hypervalent Iodine-mediated Efficient Synthesis of Imidazoles

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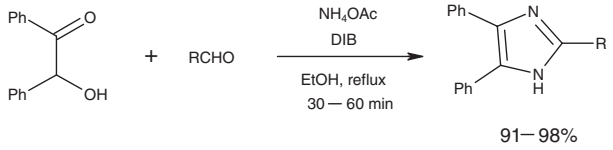
The condensation of an α-hydroxy ketone with an aldehyde and ammonium acetate in the presence of diacetoxy iodobenzene (DIB) produced the corresponding imidazole in excellent yield.

Hypervalent iodine-mediated organic syntheses have attracted considerable attention in recent years.[1] Various organoiodide(III) reagents have successfully been utilized in different organic transformations. Recently, we applied diacetoxy iodobenzene (DIB) for the synthesis of isoxazolines.[2] In continuation of our work on the application of this reagent, we have discovered that it can efficiently be employed for the synthesis of an imidazole derivative by treatment of an aldehyde with an α-hydroxy ketone and ammonium acetate (Scheme 1).

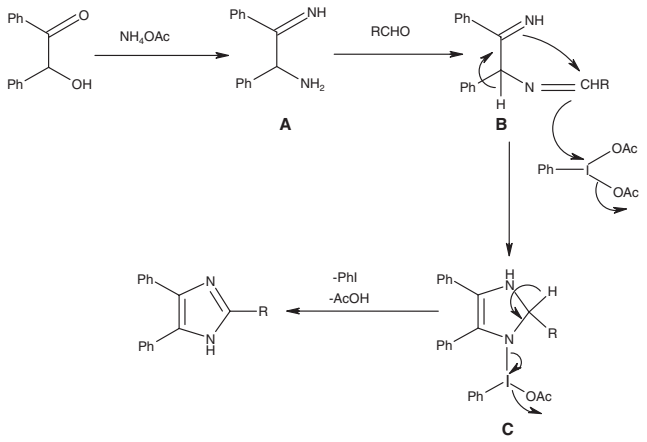
Imidazoles exhibit various interesting biological properties and many of them have been characterized as important therapeutic agents,[3] fungicides and herbicides,[4] and plant growth regulators.[5] They have also been applied in the synthesis of ionic liquids.[6] However, the methods for the synthesis of imidazoles starting from α-hydroxy ketones are limited.[7] Moreover, long reaction times, unsatisfactory yields, and applicability to only aromatic aldehydes are the disadvantages of many of the reported methods.

The present condensation mediated by DIB (Scheme 1) proceeded smoothly to afford the imidazoles in excellent yields (91–98%) (Table 1).[8] The conversion was complete within 30–60 min. Both aromatic and aliphatic aldehydes were equally utilized for the preparation of imidazoles. Aromatic aldehydes containing electron-donating as well as electron-withdrawing groups underwent the conversion facilely. The probable mechanism of the conversion is shown in Scheme 2.

The α-hydroxyketone reacts at first with NH_4OAc and its keto group is converted into =NH and the hydroxy group into $-NH_2$ to form the intermediate **A**. This intermediate reacts with an aldehyde to furnish the corresponding imine **B**. The cyclization of the imine subsequently takes place easily in the presence of DIB to produce **C**. The iodine of DIB attracks electrons of the double bond of the imine system of **B** followed by the loss of an –OAc group. The subsequent deattachment of PhI and AcOH from **C** affords the stable imidazole derivative. During the preparation of the imidazoles following the present method the formation of PhI was detected by direct comparision of the reaction mixture with an authentic sample of PhI by TLC



Scheme 1.



Scheme 2.

experiments.

In conclusion, we have demonstrated that an imidazole derivative can easily be synthesized in short reaction time and in excellent yield starting from an aldehyde (aromatic or aliphatic), and an α-hydroxy ketone using NH_4OAc in the presence of a hypervalent iodine reagent, DIB. A new useful application of this reagent is thus disclosed.

The authors thank CSIR and UGC, New Delhi for financial assistance.

References and Notes

Part 153 in the series "Studies on novel synthetic methodologies."

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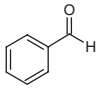
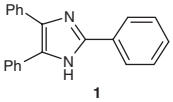
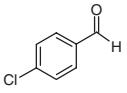
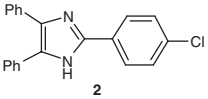
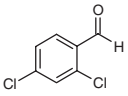
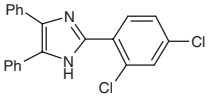
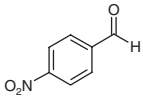
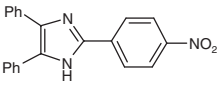
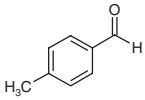
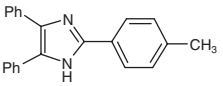
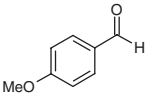
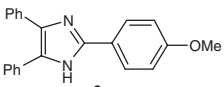
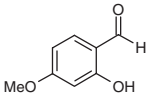
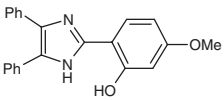
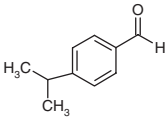
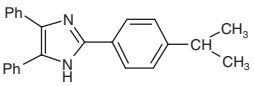
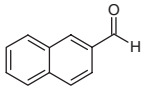
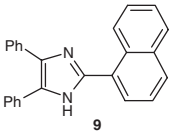
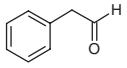
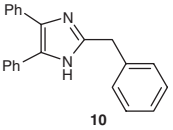
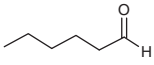
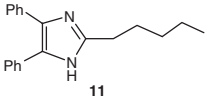
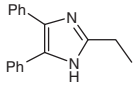
Table 1. Preparation of imidazoles from aldehydes and benzoin using DIB and NH_4OAc

Entry	Aldehyde	Product[a]	Time /min	Isolated yield /%
1		 **1**	30	98
2		 **2**	30	96
3		 **3**	30	95
4		 **4**	60	94
5		 **5**	30	98
6		 **6**	45	94
7		 **7**	45	92
8		 **8**	30	98
9		 **9**	45	96
10		 **10**	60	91
11		 **11**	60	94
12		 **12**	60	92

[a]The structures of the products were determined from spectral (^{1}H NMR and MS) data.

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8 General procedure for the synthesis of imidazole: A mixture of an aldehyde (0.5 mmol), benzoin (0.5 mmol), NH_4OAc (1.5 mmol), and DIB (0.5 mmol) in ethanol (5 mL) was refluxed for 30–60 min. The reaction was monitored by TLC. After completion, the mixture was cooled and the solvent was removed under reduced pressure. Saturated aq, $NaHCO_3$ (10 mL) was added and the mixture was extracted with EtOAc (3×10 mL). The extract was dried and concentrated. The residue was subjected to column chromatography (silica gel, hexane–EtOAc) to obtain pure imidazole derivative.

The spectral (^{1}H NMR and MS) data of some representative imidazoles are given below.

Compound 2: ^{1}H NMR (200 MHz, $CDCl_3$): δ 12.16 (1H, brs), 8.06 (2H, d, $J = 8.0$ Hz), 7.60–7.42 (4H, m), 7.40–7.06 (8H, m); FAB-MS: m/z 355, 353 $[M + Na]^+$.

Compound 4: ^{1}H NMR (200 MHz, $CDCl_3$): δ 12.68 (1H, brs), 8.39–8.21 (4H, m), 7.62–7.43 (4H, m), 7.42–7.10 (6H, m); FAB-MS: m/z 364 $[M + Na]^+$.

Compound 8: ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.01 (2H, d, $J = 8.0$ Hz), 7.56 (4H, d, $J = 8.0$ Hz), 7.38–7.20 (8H, m), 2.99 (1H, m), 1.25 (6H, d, $J = 7.0$ Hz); FAB-MS: m/z 361 $[M + Na]^+$.

Compound 10: ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.52–7.05 (16H, m), 4.04 (2H, s); FAB-MS: m/z 333 $[M + Na]^+$.

Compound 11: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.48–7.34 (4H, m), 7.30–7.09 (6H, m), 2.62 (2H, t, $J = 7.0$ Hz), 1.81–1.62 (2H, m), 1.40–1.24 (4H, m), 0.83 (3H, t, $J = 7.0$ Hz); FAB-MS: m/z 313 $[M + Na]^+$.

Published on the web (Advance View) September 22, 2007; doi:10.1246/cl.2007.1270