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FUNCTIONAL MASKING OF CARBONYL GROUP BY 1-METHYL-1H-IMIDAZOL-2-YL MOIETY

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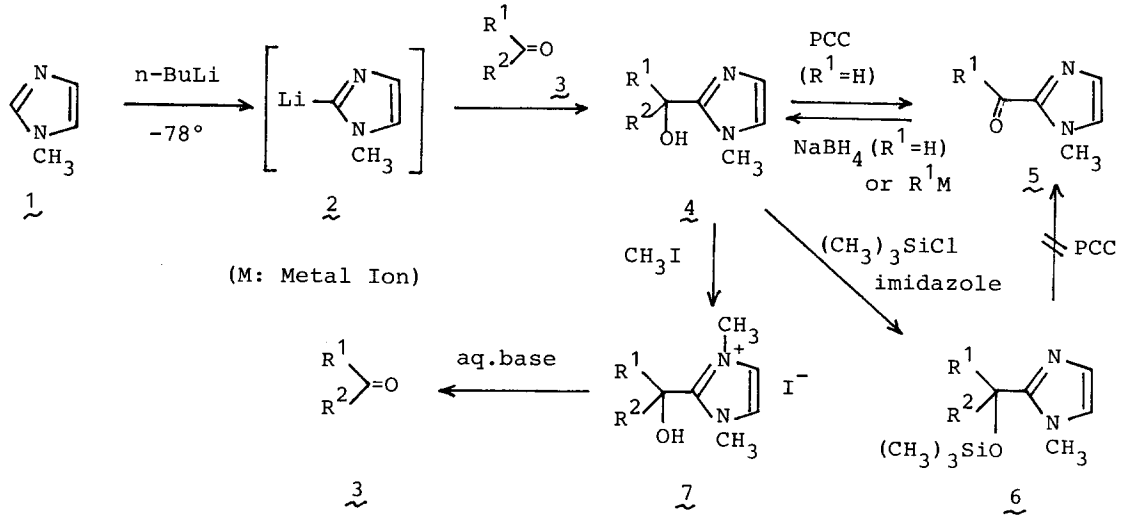
Abstract: Easily obtained 1-methyl-2-(1'-hydroxyalkyl)-1H-imidazoles (4) were found to be a new type of masked form for carbonyl group which could survive under various severe conditions. The corresponding carbonyl compounds (3) were easily reproduced by quarternization of the imidazole (4) with CH_3I followed by aqueous basic treatment. 2-Acyl-1H-imidazoles (5) were convertible to aldehydes or ketones (3) by using the present methodology.

2-Acyl-1H-imidazole derivatives (5) have never been studied so much while 1-acyl-1H-imidazole derivatives have been well applied in the organic preparations as one of the active acyl sources[2]. The authors would like to report here a useful new type of protected form, R-C(OH)-C=N-CH=CH-N-CH_3, for carbonyl group which could be derived from 1-methyl-2-acyl-1H-imidazole (5).

Treatment of 1-methyl-2-lithio-1H-imidazole (2) with carbonyl compound (3) easily gave 1-methyl-2-(1'-hydroxyalkyl)-1H-imidazole (4)[3], which could also be prepared from 1-methyl-2-acyl-1H-imidazole (5)[4] by reduction with $NaBH_4$ or



Scheme 1

additive alkylation with alkyllithium or Grignard reagent. Most of these preparations proceeded in high yields (more than 80%).

The authors found that the N-methiodides (7) of the 1-methylimidazol-2-alkanol (4) were easily converted to the corresponding carbonyl compounds (3) by stirring a two-layers mixture consisting of the methiodide (7), appropriate organic solvent (e.g. EtOAc, C_6H_6, $^iPr_2O$) and excess of 10% K_2CO_3 aq. (Method-A). The K_2CO_3 aq. could be replaced by slight excess of 0.2N-NaOH aq. containing more than four equivalents of sodium 6-aminocaproate as a trapping agent of aldehyde which was added in order to prevent self-aldol condensation of the product in the aqueous phase[5] (Method-B). The Method-A is recommended for producing ketones or aromatic aldehydes, and the Method-B for producing aromatic or aliphatic aldehydes[6].

TYPICAL PROCEDURE FOR METHOD-A: A suspension of 1 methyl-2-(1'-hydroxy-1'1'-diphenyl)methyl-1H-imidazole (4e, 1.32 g) in a mixture consisting of iodomethane (5 ml) and ethyl acetate (25 ml) was refluxed for 2 hr followed by evaporation of the volatile portions[7]. Benzene (5 ml) and 10% K_2CO_3 (10 ml) were added to the crystalline residue and the mixture was warmed at 60° under stirring and N_2 atmosphere for 2 hr. Evaporation of the organic layer gave a crystalline residue, which was distilled under vacuum to afford an almost pure benzophenone. Yield, 0.88 g (96.6 %).

TYPICAL PROCEDURE FOR METHOD-B: A solution of 1-methyl-2-(1'-hydroxy-3',7'-dimethyloct-6-en-1-yl)-1H-imidazole (4b, 2.36 g)[8] in ethyl acetate (25 ml) was refluxed for 2 hr in the presence of iodomethane (5 ml) followed by evaporation of the volatile portions[7] to give a crystalline residue, to which 6-amino-1-caproic acid (5.24 g), 1N-NaOH (50 ml) and benzene (20 ml) were added and the two-layers solution was stirred at 80° under N_2 atmosphere for 5 hr. The mixture was acidified with 10% HCl and extracted with benzene. The organic solvent was evaporated after drying to afford an almost pure citronellal, which was distilled under vacuum. Yield, 1.15 g (74.5 %).

Stabilities of the imidazole moiety under various conditions were checked by using 4c as a sample and the compound (4c) almost survived under the following severe conditions commonly required for removal of other protecting groups: 1N-KOH/CH_3OH/70°/7hr; 20% H_2SO_4/70°/7hr; H_2/5% Pd-C/C_2H_5OH/1 atm./r.t./18hr; $NaBH_4$/CH_3OH/r.t./20hr; $LiAlH_4$/THF/r.t./N_2/20hr; CF_3COOH/r.t./24hr; Al_2O_3/CH_3OH/10hr. Although 4c was oxidized with pyridinium chlorochromate (PCC) to give the ketone (5c) in more than 60% yield, the corresponding O-trimethylsilylated compound (6c) was inactive toward the oxidizing reagent[9].

Requiring activation step for demasking seems to be a new concept in the organic synthesis and to be somewhat biomimetic because preactivation with cofactors is often observed in the enzymatic reactions[10,11].

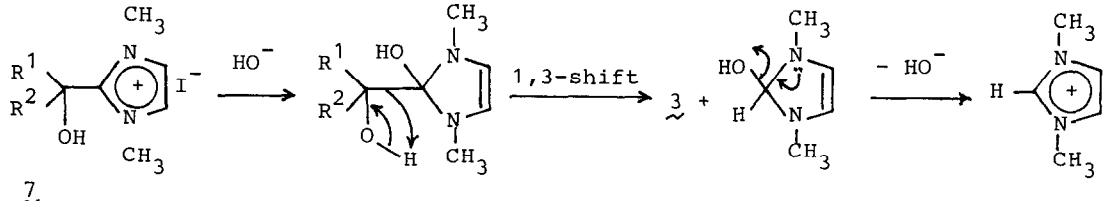
Isolation of the imidazole counterpart from the reaction mixture of the Method-A or the Method-B was unsuccessful probably because of its high solubility in water or instability in such aqueous basic medium. The authors had been

TABLE 1. REPRODUCTION OF CARBONYL GROUP BY METHOD-A AND METHOD-B

Entry	Substrate	R^1	R^2	Method	Yield (%)[a]
1	4a	n-hexyl	H	B	83.9
2	4b	$Me_2C=CH(CH_2)_2CHMeCH_2-$	H	B	79.0 (74.5)[c]
3	4c	$3,4-(OCH_2O)-C_6H_4-$	H	A	92.8
4	4c	$3,4-(OCH_2O)-C_6H_4-$	H	B	47.1
5	4d	cyclohexyl	H	B	84.8
6	4e	C_6H_5-	C_6H_5-	A	quant. (96.6)[c]
7	4f	C_6H_5-	CH_3-	A	quant.
8	4g	n-hexyl	CH_3-	A	quant.
9	4h	n-butyl	C_6H_5-	A[b]	quant.
10	4i	$R^1,R^2 = -C_6H_4-CH_2CH_2CH_2-$		A	quant.
11	4j	8-methoxybenzo-(b)furan-2-yl	CH_3-	A	quant.

a: These were obtained by GLC analyses using an internal standard. b: Me_2SO_4 was used instead of CH_3I. c: Isolated yield (5 - 10 mmole scale experiment).

aware that the methiodide of 4h decomposed slowly in hot organic solvent in the presence of a small amount of water to give valerophenone. Thus the methiodide of 4h was heated by prolonged refluxing (3 days) in 90% ethanol to give valerophenone (86% yield) and evaporation of the mother liquor also gave hygroscopic crystals (mp 90° in a sealed tube, 63% yield) which could be identified as 1,3-dimethyl-1H-imidazolium iodide by comparison with a pure sample prepared from 1 and CH_3I. Therefore the reaction mechanism of the present cleaving reaction is suggested as follows.



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1,3-Dithiane and O-protected gem-cyanohydrine moieties can be regarded as "functional protecting groups" because their active hydrogen atom is replaceable with electrophiles[12]. On the other hand, the present protected form (4) can also be considered to be functional in the case of R^1=H because the hydrogen atom can be substituted with nucleophile via ketone (5). Therefore the present procedure will provide a different and useful route to prepare ketones and aldehydes. The present methodology[10] will not provide us only further little advantages such as easy separation of the basic product (4 or 5) from neutral

by-products and relatively easy crystallization of 4 (or its salt)[7], 5 (or its salt) or 7, but combinating applications with other methodologies will also give us further benefits on syntheses of more complex molecules. Several applications are under investigation[13,14].

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2) H.A.Staab, Angew. Chem. Int. Ed. Engl., 74, 351 (1962); H.A.Staab and W.Rohr, "Newer Method of Organic Chemistry" (edited by Foerst), vol.V, p 61 (1968, Academic Press, New York); S.Ohta and M.Okamoto, J. Syn. Org. Chem. Jpn., 41, 38 (1983).
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4) 2-Acyl-1H-imidazole derivatives were easily obtained by treating 1H-imidazole or 1-alkyl-1H-imidazole with acyl halides in the presence of base (see ref. 3b and 3d). See also: M.D.Nair, V.Sudarsanam, and J.A.Desai, Indian J. Chem., Sect. B, 21B, 1027 (1982); E.Regel and K.H.Buechel, Justus Liebigs Ann. Chem., 1977, 145.
5) Under the reaction condition of the method-B, aldol condensation product was not detected in the reaction mixture.
6) S.Ohta and M.Okamoto, Chem. Pharm. Bull. (Tokyo), 28, 1917 (1980).
7) In many cases the residue (methiodide) was crystalline. In the Table 1, only methiodide of 4b was not crystalline, but the hydrochloride of 4b was crystallized (mp 105°).
8) Viscous oil (bp 132° at 3 mmHg). It was prepared by treating citronellal with 1-methyl-2-lithio-1H-imidazole in THF at -78°.
9) Hypochloric acid (HClO) also oxidized 4c and 4e to give piperonal and benzophenone, respectively, in high yields, but in the case of 4f a considerable amount of α-chloroacetophenone (about 15%) was obtained accompanying with acetophenone (about 80%), so this procedure must be further improved for general applications.
10) We wish to call such type of protection "locked protection" (4 = locked form ; CH_3I = key; 7 = delocked but closed form; 3 = opened form).
11) Acetal and ketal forms have been well-known to be very stable under basic conditions while they can be easily deprotected by treating with acid. This simplicity for cleavage is disadvantageous at the same time because such compounds can not be treat with acid except of removing the protection (see: T.W.Green, "Protective Groups in Organic Synthesis", John Wiley & Sons, New York, 1981); J.F.W.McOmie, "Protctive Groups in Organic Chemistry", Plenum Press, London, 1973.
12) J.C.Stowell, "Carbanion in Organic Syntheses", John Wiley & Sons, New York, 1979.
13) Cleavage of 1-methyl-2-(1'-hydroxy-3'-phenylprop-2'-en-1'-yl)-1H-imidazole to cinnamaldehyde by the Method-A or Method-B was unsuccessful.
14) All new compounds, appeared in this communication, gave satisfying values in their elemental micro-analyses.

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