A Facile Route to Imidazol-4-yl Anions and Their Reaction with Carbonyl Compounds

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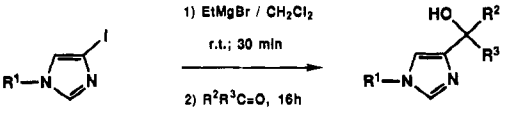
Summary: Treatment of N-protected 4-iodoimidazoles 1–3 in CH_2Cl_2 solution with an ethereal solution of ethylmagnesium bromide generates the corresponding imidazol-4-yl anions, which react with carbonyl compounds to give carbinols 4–14 in 60–83% yield.

Imidazolyl anions are readily generated on C-2,[1] but generation of the thermodynamically less stable C-4(5) anions, in the absence of blocking groups at C-2,[1,2] is much more difficult. Many biologically important molecules, for example histidine, H_2-antagonists,[3] and agricultural fungicides,[4] contain imidazole rings bearing alkyl substituents at the 4(5)-position. Consequently, a facile and versatile route to imidazol-4(5)-yl anions would have important synthetic applications.

One obvious method of generating such anions is via metal–halogen exchange with a 4(5)-haloimidazole. However, such an approach is complicated by the potentially very rapid equilibrium between the C-4(5) and C-2 anions.[5,6] Nonetheless, this route has been followed by several groups with varying degrees of success.[1,5–8] For example, Kirk[6] showed that treatment of 4-iodo-1-trityl-imidazole (1) with *n*-butyllithium, followed by addition of an electrophile, yielded mixtures of 4- and 2-substituted imidazoles, enriched in the former. El Borai et al.[7] refluxed 4-iodo-1-methylimidazole with EtMgBr in ether then replaced the solvent with benzene. Addition of triethylorthoformate yielded the imidazol-4-yl diethylacetal derivative in 57% yield. Katritzky et al.,[8] in the most general procedure to date, treated 4(5)-bromoimidazole with 2 equiv of *tert*-butyllithium at −78 °C to yield the 1,4-dianion. Quenching with a variety of electrophiles yielded 4-substituted products in 22–64% yield. Interestingly, these workers were unable to isolate secondary carbinols from reactions with aldehydes due to a spontaneous oxidation to give ketones.

In this paper, we disclose a procedure for the facile generation of imidazol-4-yl anions at ambient temperature by addition of EtMgBr to the N-protected 4-iodoimidazoles 1–3. These anions were reacted with a variety of aldehydes or ketones to give the carbinols 4–14 in 60–83% yield (Table I). Our method is compatible with a variety of N-protecting groups and completely suppresses formation of 2-alkylated imidazoles. It offers significant advantages over Katritzky's dianion approach[8] in terms of experimental facility, higher yields, and the easy isolation of products containing secondary hydroxyl groups.



1 R^1 = CPh_3

2 R^1 = SO_2NMe_2

3 R^1 = $SO_2(CH_2)_2SiMe_3$

4 - 14

The starting materials 1–3 were synthesized in >83% yield from readily available 4(5)-iodoimidazole[9] using standard N-protection procedures.[2,4,6,10] In a typical procedure, a 3 M solution of EtMgBr (1.1 equiv) in diethyl ether was added to a 0.25 M solution of the N-protected iodoimidazole 1–3 (2 mmol) in dry CH_2Cl_2 at ambient temperature. After 30 min the aldehyde or ketone (1.1 equiv) was added, and the mixture was left overnight (16 h). Half-saturated NH_4Cl solution was then added, and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography of the residue yielded the (4-hydroxyalkyl)imidazoles 4–14 as detailed in Table I.[11] The allylic alcohol 6 is an intermediate in a recently published synthesis of the antitumoural alkaloid girolline.[12]

It is noteworthy that the solvent of choice for these reactions is dichloromethane. In the case of the trityl-protected iodoimidazole 1, THF can also be used as solvent, albeit with some lowering in yield (Table I, entries 1 and 5). However, with the dimethylsulfamoyl-protected iodoimidazole 2, the use of CH_2Cl_2 is essential to prevent formation of 2-alkylated products. Presumably, the greater covalent character of the organomagnesium intermediate in the noncomplexing solvent CH_2Cl_2 means that is is less susceptible to equilibration. The use of Grignard reagents in CH_2Cl_2 (in the absence of other complexing metals) is still relatively uncommon.[13,14] This is somewhat surprising

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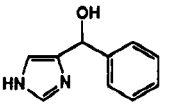
Table I. Reaction of Imidazol-4-yl Anions with Carbonyl Compounds in CH_2Cl_2

starting material	product	R^1	R^2	R^3	isolated yield (%)
1	4	CPh_3	Me	H	83 (66[a])
1	5	CPh_3	Ph	H	79
1	6	CPh_3	$CH{=}CH_2$	H	60
1	7	CPh_3	$(CH_2)_3CO_2Me$	H	63
1	8	CPh_3	4Cl-C_6H_4	4Cl-C_6H_4	69 (53[a])
2	9	SO_2NMe_2	Me	H	80
2	10	SO_2NMe_2	Ph	H	83
2	11	SO_2NMe_2	$(CH_2)_2CH{=}CMe_2$	H	83
2	12	SO_2NMe_2	Ph	Ph	82
2	13	SO_2NMe_2	$-(CH_2)_4-$		77
3	14	$SO_2(CH_2)_2$-$SiMe_3$	Ph	H	66

[a] Yield using THF as reaction solvent.

since its use is often accompanied by enhanced results when compared with those obtained in ethereal solvents.[13] We are aware of only one other example of a metal–halogen exchange reaction being performed in dichloromethane.[14]

The trityl,[6,12] dimethylsulfamoyl,[2,4] and [2-(trimethylsilyl)ethyl]sulfonyl[10] protecting groups are removable under a variety of conditions, so that our procedure represents a general method for preparing 4(5)-alkylated NH-imidazoles. For example, treatment of the *N*-trityl-imidazoles **5** and **8** with aqueous 60% CF_3CO_2H at ambient temperature for 1 h yielded the carbinols **15** (84% yield) and **16** (83% yield); both were isolated as their trifluoroacetate salts. The secondary alcohol **15** was also obtained



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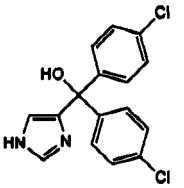

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by refluxing the dimethylsulfamoylimidazole **10** overnight in 10% sulfuric acid or with an equimolar amount of $LiAlH_4$ in THF (98% and 64% yield, respectively). (Arylhydroxymethyl)imidazoles related to **15**, but with substituents in the aryl ring, exhibit antihypertensive and antiulcerogenic properties,[15] and the tertiary alcohol **16** is a good inhibitor of the P-450 enzyme aromatase.[16]

Finally, it is noted that the reactivity of the magnesio-imidazol-4-yl anions generated via our procedure can be modified by the addition of other metal salts (e.g., $ZnCl_2$, CuCN), so that reaction with a wide variety of noncarbonyl containing electrophiles is also possible.[17]

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A Highly Stereoselective Synthesis of Aryl 2-Deoxy-β-glycosides via the Mitsunobu Reaction

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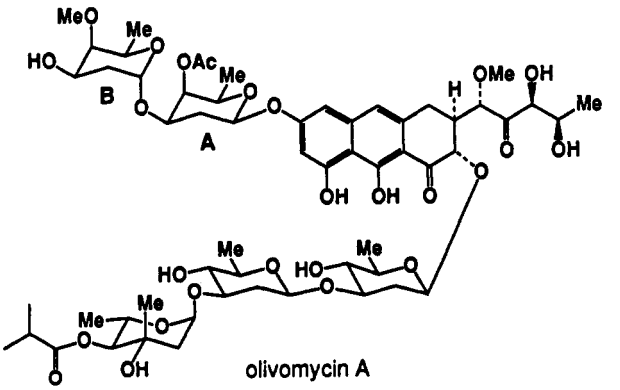
Summary: A highly stereoselective (6.5–>20:1) synthesis of aryl 2-deoxy-β-D-glycosides is described. This method involves the Mitsunobu coupling of phenols and 2α-(thiophenyl)- or 2α-(selenophenyl)-α-D-pyranoses **3–6**, **18**, and **19** followed by Bu_3SnH reduction of the PhS- and PhSe-groups.

In continuation of our studies on the synthesis of olivomycin A[1] we required an efficient glycosidation method for establishing the 2-deoxy-β-D-glycosidic linkage between the aglycon, olivin, and the AB disaccharide.[2,3] 2-Deoxy-β-glycosides have been synthesized with good stereoselectivity via the silver silicate mediated glycosylations of alcohols and 2-deoxypyranosyl bromides.[4] However, application of this method to the glycosylation of phenols



has led, at best, to 3:1 mixtures of β/α aryl glycosides.[4b,5] Other successful strategies[6] for the synthesis of β-2-deoxy

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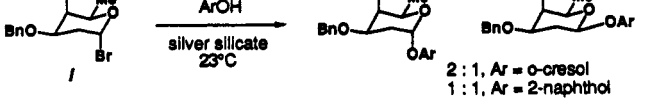

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