An Easily Introduced and Removed Protecting Group for Imidazole Nitrogen: A Convenient Route to 2-Substituted Imidazoles

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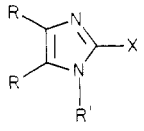
Orthoamides (3–5) prepared from imidazoles and triethyl or trimethyl orthoformate are rapidly metalated at −40 °C in THF or ether to give the corresponding 2-lithio anion which reacts with a variety of electrophiles. The dialkoxymethyl protecting group is readily hydrolyzed under neutral or acidic conditions at room temperature, giving the 2-substituted 1*H*-imidazole 1 (R = H, X = COOH, n-C_4H_9, $COCH_3$, $CHOHC_6H_5$, $C(CH_3)OH$-2-pyridyl, 9-hydroxyfluorenyl, 1-hydroxycyclohex-2-enyl, $C(OH)(C_6H_5)_2$; R = CH_3, R′ = H, X = CHO) and the tris(2-imidazolyl)phosphines (R = H, CH_3, $CH(CH_3)_2$). A mechanism for the deprotection of **3** is proposed.

The syntheses of 1*H*-2-substituted-imidazoles (**1**) can be approached from several directions. Classical methods



1, R′ = H
2a, R′ = $CH(OEt)_2$; X = H
2b, R′ = $CH(OEt)_2$; X = Li
3, R = H = X; R′ = $CH(OEt)_2$
4, R = CH_3; X = H; R′ = $CH(OEt)_2$
5, R = $CH(CH_3)_2$; X = H; R′ = $CH(OCH_3)_2$

involve the construction of the ring with the 2-substituent in place (e.g., Radziszewski and Weidenhagen syntheses).[1] Recent syntheses are based on the substitution of the parent imidazole and include addition of isocyanates at high temperature[2] and photochemical rearrangement of the 1 isomer[3] although these are of limited synthetic utility. More commonly, N-protected imidazoles are lithiated at C-2 by treatment with n-butyllithium,[4] and the corresponding anion is added to electrophilic reagents. For the most part, however, deprotection of the imidazole nitrogen involves acidic, basic, or reductive conditions, and problems are often encountered in either the lithiation or addition step. For example, while *N*-benzylimidazoles can be readily prepared and the benzyl group removed,[5,6] the lithiation step has been reported to give benzyl deprotonation as well as deprotonation at C-2.[7] *N*-Alkoxymethyl groups direct the lithiation to C-2, but their removal requires strong acid reflux,[7] and the yields of isolated products are modest[7] to nil.[8] The *N*-tosyl group is easily introduced[9] and removed,[10] but the nucleophilicity of the C-2 anion is low.[11]

Finally, the trityl group has recently been shown to be a useful protecting group for imidazole itself,[12] the yields of 2-substituted products being good to excellent starting from the N-protected form.[12a] The method appears to be fairly general; however, the conditions reported for deprotection require refluxing acidic alcohol media and may preclude its applicability for very acid-sensitive products.[13]

During the course of our work on imidazole-containing enzyme models, we required an N-protecting group which could be easily inserted and if necessary be removed under completely neutral conditions. The diethoxymethyl function in orthoamide **2a** meets these requirements since it is readily hydrolyzed under neutral or acid conditions in a few minutes. In addition, metalation of **2a** with n-BuLi at −40 °C in THF or ether gives only **2b** in less than 5 min, and the latter anion is an effective nucleophile, reacting with a variety of electrophilic agents to give good yields of 2-substituted imidazoles after hydrolysis.

The protected imidazoles (**2a**) are prepared by heating a mixture of the imidazole with an excess of triethyl orthoformate in the presence of an acid catalyst with continuous removal of the alcohol produced.[11b] While we have not attempted to maximize yields, using a 1:4 ratio of imidazole–orthoformate routinely gives 80% yields of purified **2a**. NMR analysis of the reaction mixture shows only starting material and product, with no discernible disubstitution. The method is also applicable to the more sterically hindered 4,5-dimethyl- and 4,5-diisopropylimidazoles, both **4** and **5** being obtained in good yield. 4,5-Diisopropylimidazole appears to be particularly hindered; N-protection with trityl[11c] fails in our hands and the orthoamide derived from triethyl orthoformate is obtained in only low yield, starting material being mostly

(1) See *Chem. Heterocycl. Compd.* **1953**, *1*.

(2) Papadopoulos, E. P. *J. Org. Chem.* **1977**, *42*, 3925.

(3) Iwasaki, S. *Helv. Chim. Acta.* **1976**, *59*, 2738. This procedure also gives the 4 isomer.

(4) Shirley, D. A.; Alley, P. W. *J. Am. Chem. Soc.* **1957**, *79*, 4922.

(5) Jones, R. G. *J. Am. Chem. Soc.* **1949**, *71*, 383.

(6) The *N*-benzyl group can be removed by hydrogenolysis using H_2/Pd/C: Lown, J. W.; Tracy, M., private communication.

(7) Tang, C. C.; Davalian, D.; Huang, P.; Breslow, R. *J. Am. Chem. Soc.* **1978**, *100*, 3918.

(8) Roe (*J. Chem. Soc.* **1963**, 2195) reports that a variety of *N*-(methoxymethyl)imidazole-containing species was stable to refluxing 6 N HCl.

(9) Sakakibara, S.; Fujii, T. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 1466.

(10) van der Eijk, J. M.; Nolte, R. J. M.; Zwikker, J. W. *J. Org. Chem.* **1980**, *45*, 547.

(11) (a) Curtis, N. J., unpublished observations. (b) A referee has suggested that the use of *p*-toluenesulfonic acid catalysis renders the method seriously limited in generality for acid-sensitive materials. On the following grounds, this appears not to be a problem: initial experiments were done with *no* acid catalyst present and the orthoamides formed, albeit in a longer time. Subsequent experiments utilized formic acid catalysis, but because of its volatility it was removed as the alcohol distilled. *p*-Toluenesulfonic acid was finally adopted as a nonvolatile catalyst. The question about acid strength is a moot point since any strong acid catalyst in this medium will have its strength leveled to that of the corresponding imidazolium ion. (c) Khalaj, A., unpublished observations.

(12) (a) Kirk, K. L. *J. Org. Chem.* **1978**, *43*, 4381. Unfortunately, one cannot compare the relative merits of the trityl and dialkoxymethyl methods in *overall* yield since no conditions for synthesis of *N*-tritylimidazole nor yield from imidazole were reported. (b) Giesemann, H.; Oelschlägel, A.; Pfau, H. *Chem. Ber.* **1960**, *93*, 576.

(13) When tris(*N*-(ethoxymethyl)imidazol-2-yl)phosphine was refluxed with HCl analogously to the procedure quoted in ref 7, P–C bond cleavage occurred, giving imidazole as the product: Brown, R. S., unpublished observation.

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recovered. The less bulky dimethoxymethyl group is, however, readily introduced. Using an analogous procedure to that which gave **3** we were unable to isolate the corresponding orthoamide of benzimidazole in useful yield.

The metalation reactions are carried out in dry ether or THF at −40 °C, depending upon the solubility of the anion produced, and after 15 min the electrophilic agent is introduced and the reactions are allowed to come to room temperature overnight. The optimum conditions were not determined, but it is apparent from the appearance of precipitates and color changes that the reaction is not instantaneous in some cases.

The deprotection and workup procedures depend upon the sensitivity of the product. For instance, acid-sensitive phosphines **17b**, **19b**, and **20b**[13] were isolated by stirring the crude reaction product (the tris N-protected analogues of **17b**, **19b**, and **20b**) at 25 or 56 °C in 5–10% aqueous acetone. Within a few minutes, crystals of the phosphines (**17b** and **19b**) appeared, the hydrolysis being complete in a few hours. The mildness of the hydrolysis conditions is further exemplified by the preparation of the sensitive[14] imidazole-2-carboxylic acid **8b**. The isolated yield of 60% (49% from imidazole) is significantly better than reported routes[15] and the method is simple (see Experimental Section).

For those products for which it is not necessary to maintain a nonacidic environment, the product imidazole is conveniently obtained by first extracting the reaction mixture with aqueous HCl, neutralizing the acid extracts with solid $NaHCO_3$, and extracting the neutral aqueous mixture with $CHCl_3$. Deprotection accompanies the acid extraction.

While the isolated, overall yields were generally good, in cases where there is an acidic hydrogen present on the electrophile the yields are lower, presumably due to proton abstraction by the 2-lithio anion.[16]

The deblocking of **3** was followed by NMR in D_2O at 40 °C. Hydrolysis is complete in less than 30 min, no significant "pH" change is observed ("pH" maintained at ~7), and the initial products are imidazole, ethanol, and ethyl formate. Solvolysis of **3** was also monitored by NMR in methanol-d_4 and was found to be complete in a few hours, the products being only ortho ester and imidazole. Thus, nonaqueous removal of the *N*-dialkoxymethyl group is feasible.

Although it requires more kinetic analysis, the deprotection appears mechanistically interesting. Of the three possible mechanisms summarized in Scheme I, eq 2 can be eliminated (at least in D_2O) since no formic acid is produced before the free imidazole (**1**) is liberated; formic acid does appear in the reaction mixture later but at the expense of ethyl formate. Inspection of the NMR aromatic region during hydrolysis of **3** in D_2O shows a transient multiplet[17] indicative of some imidazole other than **3** or **1**, which we tentatively ascribe to **7**. On this basis, it would appear that eq 3 is likely in H_2O (D_2O), although clearly more conclusive proof is required and is being sought.

On the other hand, since deprotection of **3** in methanol-d_4 produced only imidazole and ortho ester, the mechanism for product formation must be similar to that

Table I. Preparation and Properties of 2-Substituted Imidazoles from 3, 4, and 5

starting imidazole	electrophile	product formula[a]	isolated yield, %	mp, °C or bp, °C (torr)	recryst solvent	NMR ($CDCl_3$), δ
3	CO_2[b] (**8a**)	$-CO_2H$ (**8b**)	60	172–174 dec[c,d]		7.57[e] (s)
3	*n*-C_4H_9I[f] (**9a**)	$-n$-C_4H_9 (**9b**)	84	93 (0.02)	*q*	0.8–2.0[g] (m, 7 H), 2.78 (t, 2 H), 6.98 (s, 2 H)
3	$CH_3CON(CH_3)_2$[h] (**10a**)	$-COCH_3$ (**10b**)	80	136–137[i]	PhH/CH_3OH	2.58[j] (s, 3 H), 7.30 (s, 2 H)
3	C_6H_5CHO[f] (**11a**)	$-CHOHC_6H_5$ (**11b**)	77	205–206[k]	*r*	5.86[j] (s, 1 H), 6.95 (s, 2 H), 7.2–7.6 (m, 5 H)
3	$CH_3COC_5H_4N$[f] (**12a**)	$-C(CH_3)OHC_5H_4N$ (**12b**)	64	136–137	$CHCl_3/CH_3OH$	6.92[j] (s, 2 H), 7.1–7.9 (m, 3 H), 8.5 (m, 1 H)
3	fluorenone[f] (**13a**)	-9-hydroxyfluorenyl (**13b**)	84	203–204[c]	$CHCl_3/CH_3OH$	6.83[l] (s, 2 H), 7.1–8.1 (m, 9 H)
3	cyclohex-2-enone[f] (**14a**)	1-hydroxycyclohex-2-enyl- (**14b**)	49	177–178	ether/CH_3OH	1.6–2.3[j] (m, 6 H), 5.7–6.1 (m, 2 H), 6.93 (s, 2 H)
3	$(C_6H_5)_2CO$[f] (**15a**)	$-C(OH)(C_6H_5)_2$ (**15b**)	72	195–197[m]	C_2H_5OH	6.5[l] (s, 1 H, br), 6.94 (s, 2 H), 7.1–7.6 (m, 10 H)
3	$(CH_3CH_2OCH_2SCH_2)_2CO$[n] (**16a**)	$-C(OH)(CH_2SCH_2OCH_2CH_3)_2$ (**16b**)	36	100–101	ether/$CHCl_3$	1.19[g] (t, 3 H), 3.30 (s, 4 H), 3.56 (q, 4 H), 4.53 (s, 4 H), 7.00 (s, 2 H)
3	PCl_3[o] (**17a**)	P/3 (**17b**)	36	229–231	CH_3OH	7.24[l] (s)
4	$HCON(CH_3)_2$[h] (**18a**)	$-CHO$ (**18b**)	82	164–165	ether/CH_3OH	2.30[g] (s, 6 H), 9.63 (s, 1 H)
4	PCl_3[o] (**17a**)	P/3 (**19b**)	46[p]	255–257	acetone/CH_3OH	1.93[l] (s)
5	PCl_3[o] (**17a**)	P/3 (**20b**)	55	185–187.5	ethanol/H_2O	1.22[j] (d, 36 H), 3.00 (m, 6 H)

[a] New compounds had satisfactory combustion analyses (±0.3% C, H, N) and gave exact-mass molecular ions. [b] 400% excess solid CO_2. [c] Dependent on rate of heating. [d] Lit.[5] mp 163–164 °C dec. [e] D_2O. [f] 20% excess. [g] $CDCl_3$. [h] 50% excess. [i] Lit.[3] mp 137–137.5 °C. [j] CD_3OD. [k] Mp 199–201 °C: Sonn, A.; Grief, P. *Chem. Ber.* **1933**, *66*, 1900. [l] Me_2SO-d_6. [m] Mp 189–190 °C: Rohr, W.; Swoboda, R.; Staab, H. A. *Chem. Ber.* **1968**, *101*, 3494–8. [n] Ratio of imidazole-ketone is 2:1. Synthesis and utility of this molecule to be published. [o] Ratio of imidazole–PCl_3 is 3:1. [p] Monohydrate. [q] Distilled. [r] Precipitated on concentration.

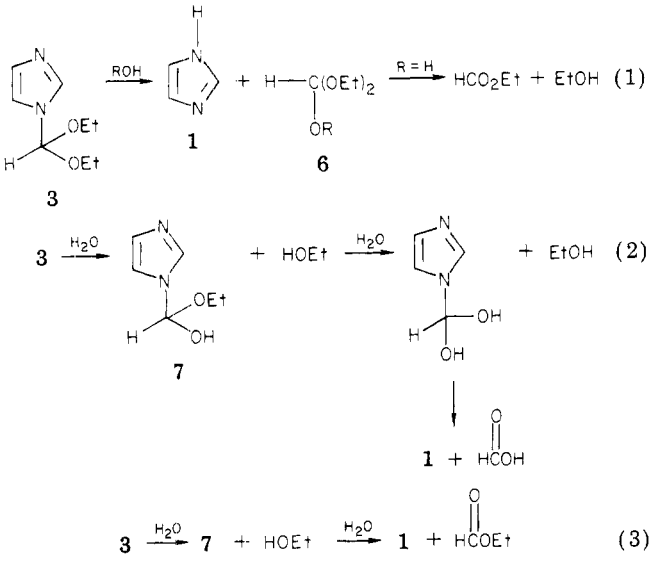
(14) 2-Imidazolecarboxylic acid is reported (ref 5) to decarboxylate on heating.

(15) From ref 5 and 2, the isolated yields were reported as 31% and 24%, respectively.

(16) For example, the reaction of the protected 4,5-dimethylimidazolate with cyclopentanone gave no addition.

(17) The imidazole 4,5-hydrogens of **3** appear at δ 7.23 (relative to HOD at δ 4.80), while those for imidazole itself are at δ 7.11, and the transient multiplet is centered at δ 7.08.

Scheme I



in eq 1 in this medium, with the reaction stopping at a mixed ortho ester (6, R = CD_3).[18]

Experimental Section

Imidazole 3.[19] Imidazole (12.8 g, 0.2 mol), 118.4 g (0.8 mol) of triethyl orthoformate, and 1 g of *p*-toluenesulfonic acid were heated at 130 °C until no more ethanol was distillable from the reaction mixture. The excess orthoformate was removed in vacuo, 1 g of solid Na_2CO_3 was added, and the residue was fractionally distilled to give 28.2 g of **3** (82%) as a colorless oil: bp 52 °C (0.02 torr); NMR ($CDCl_3$) δ 1.22 (t, 6 H), 3.59 (q, 4 H), 6.06 (s, 1 H), 7.1 (m, 2 H), 7.7 (m, 1 H).

Imidazole 4.[19] From 4,5-dimethylimidazole[20] in an analogous fashion to **3** was prepared **4** in 77% isolated yield: bp 82–87 °C (0.5 torr); NMR ($CDCl_3$) δ 1.22 (t, 6 H), 2.13 (s, 3 H), 2.17 (s, 3 H), 3.57 (q, 4 H), 5.90 (s, 1 H), 7.57 (s, 1 H).

Imidazole 5.[19] 4,5-Diisopropylimidazole[20] (10 g, 0.067 mol), 27 g (0.25 mol) of trimethyl orthoformate and 0.2 g of *p*-toluenesulfonic acid were refluxed in 100 mL of toluene until 100 mL of distillate had been collected over 6 h. The mixture was cooled and 2.7 g of starting imidazole was recovered by filtration. The filtrate was fractionally distilled to give 8.8 g (84% based on recovered starting material) of **5** as a colorless viscous oil: bp 96–100 °C (0.5 torr); NMR ($CDCl_3$) δ 1.26 (d, 6 H), 1.30 (d, 6 H), 3.33 (s, 6 H), 2.80–3.43 (m, 2 H), 5.86 (s, 1 H), 7.61 (s, 1 H).

Preparation of Lithium Anions of 3–5. To 50 mL of dry THF or ether kept under N_2 at −40 °C and containing 0.02 mol of either **3**, **4**, or **5** was added via syringe 0.02 mol of *n*-BuLi in hexane such that the temperature did not rise above −35 °C. After the addition, the pale yellow solution was left for 15 min at −40 °C before use.

Imidazole-2-carboxylic Acid (8b). To 0.02 mol of the lithium anion of **3** (prepared as above) was added 5 g of crushed solid CO_2. After the solution was stirred for 15 min, 1 mL of H_2O was added to the mixture which was left to warm to room temperature overnight. The resultant precipitate was separated, dissolved in 5 mL of water, cooled in ice, and acidified to pH 3 with 10% HCl. The precipitate was rapidly filtered since decarboxylation appeared to occur (see Table I).

2-*n*-Butylimidazole (9b). *n*-C_4H_9I (2.73 mL, 0.024 mol) was added via syringe to the lithium anion of **3** (prepared in dry THF as above) over 5 min at −40 °C. After the mixture warmed to room temperature overnight, 50 mL of ether was added, and the mixture was extracted with 0.1 N HCl (4 × 50 mL). The acid extract was neutralized (solid $NaHCO_3$) and extracted with $CHCl_3$ (6 × 100 mL). Removal of solvent in vacuo yielded an oil which after Kügelrohr distillation gave 84% **9b** as a colorless oil which gelled on cooling (Table I).

Imidazol-2-yldiphenylmethanol (15b). This was prepared similarly to **9b** except that the benzophenone was added to the lithium anion of **3** in 20 mL of dry THF, and the product was recrystallized from ethanol to give 72% of **15b** as white crystals. Compounds **10b**, **11b**, **12b**, **13b**, and **14b** were similarly prepared (Table I).

1,3-Bis[(ethoxymethyl)thio]-2-(2-imidazolyl)propan-2-ol (16b). A solution of **16a** (7.14 g (0.03 mol)) in 30 mL dry ether was added over 30 min to 0.06 mol of the lithium anion of **3** in 150 mL of dry ether at −60 °C. After being stirred at −60 °C for 1 h and warming to 0 °C, the reaction mixture was quenched by the addition of 20 mL of H_2O. The ether layer was separated and the aqueous layer was extracted with ether (2 × 50 mL). Solvent was removed from the combined ether layers and the residue was hydrolyzed with 50% aqueous ethanol (100 mL). After 4 h, the ethanol was removed in vacuo, and the residue was extracted with $CHCl_3$ (3 × 100 mL). The product, which contained unreacted imidazole, was purified by acidification–reneutralization, as outlined for **9b**, and recrystallized from ether/$CHCl_3$ to give a 36% yield of white crystals (Table I).

Tris(4,5-dimethylimidazol-2-yl)phosphine (19b). To the lithium anion of **4** (0.05 mol in 300 mL of dry ether) was added 2.28 g (0.0167 mol) of freshly distilled PCl_3. The resulting white slurry was allowed to stir and warm overnight. In the morning, 100 mL of concentrated NH_4OH was cautiously added and the resulting mixture stirred for 15 min. The ether layer was separated and dried over Na_2SO_4, and the solvent was removed in vacuo. The residue was stirred with 110 mL of 10:1 acetone–H_2O at reflux for 5 h and cooled to −20 °C, and the product was filtered and recrystallized from acetone/methanol (see Table I).

17b and **20b** were prepared similarly except that the deblocking for the former did not require heating.

Registry No. 1 (R = R′ = X = H), 288-32-4; 1 (R = Me; R′ = X = H), 2302-39-8; 1 (R = $CH(CH_3)_2$; R′ = X = H), 74482-96-5; **2b** (R = H; R′ = $CH(OEt)_2$; X = Li), 74482-97-6; **2b** (R = Me; R′ = $CH(OEt)_2$; X = Li), 74482-98-7; **2b** (R = $CH(CH_3)_2$; R′ = $CH(OCH_3)_2$; X = Li), 74482-99-8; **3**, 61278-81-7; **4**, 74483-00-4; **5**, 74483-01-5; **6** (R = Et), 122-51-0; **8a**, 124-38-9; **8b**, 16042-25-4; **9a**, 542-69-8; **9b**, 50790-93-7; **10a**, 127-19-5; **10b**, 53981-69-4; **11a**, 100-52-7; **11b**, 22098-62-0; **12a**, 1122-62-9; **12b**, 74483-02-6; **13a**, 486-25-9; **13b**, 74483-03-7; **14a**, 930-68-7; **14b**, 74498-47-8; **15a**, 119-61-9; **15b**, 5228-76-2; **16a**, 74483-04-8; **16b**, 74483-05-9; **17a**, 7719-12-2; **17b**, 74483-06-0; **18a**, 68-12-2; **18b**, 10111-08-7; **19b**, 74483-07-1; **20b**, 74483-08-2; trimethyl orthoformate, 149-73-5; butyllithium, 109-72-8.

(18) From the NMR spectrum of the products, one cannot tell whether significant alkoxy exchange of the ortho ester with solvent had occurred.

(19) Although the *N*-(dialkoxymethyl)imidazoles are quite moisture sensitive, they can be successfully stored in stoppered vials for long periods.

(20) 4,5-Dimethyl- and 4,5-diisopropylimidazoles were prepared by the method of Bredereck and Theilig (*Chem. Ber.* **1953**, *86*, 88).