Synthesis of 4,5-disubstituted imidazoles

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Introduction of a triphenylmethyl group on the nitrogen of imidazole-4,5-dicarboxylic acid esters or 4,5-dihydroxymethylimidazole resulted in deactivation of the functional group adjacent to the protecting group and allowed reactions to take place preferably or exclusively on the other functional group. Thus, dimethyl 1-triphenylmethylimidazole-4,5-dicarboxylate (**2**), on treatment with hydrazine and methylamine produced methyl 4-hydrazinocarbonyl-1-triphenylmethylimidazole-5-carboxylate (**3***a*) and methyl 4-methylaminocarbonyl-1-triphenylmethylimidazole-5-carboxylate (**3***b*), respectively. Reduction of **2** with lithium borohydride gave methyl 4-hydroxymethyl-1-triphenylmethylimidazole-5-carboxylate (**4***a*). Treatment of 4,5-dihydroxymethyl-1-triphenylmethylimidazole (**5***a*), with trimethylacetyl chloride and with acetic anhydride afforded 5-hydroxymethyl-4-trimethylacetoxymethyl-1-triphenylmethylimidazole (**6***a*), and 4-acetoxymethyl-5-hydroxymethyl-1-triphenylmethylimidazole (**6***c*), respectively. Oxidation of **5***a* with activated manganese dioxide produced the monoaldehydes **9** and **10** in a ratio of 11:1. A new mild process for deprotection of *N*-triphenylmethylimidazoles, compatible with acid sensitive groups in the molecule, is reported. The synthesis of several 4,5-disubstituted imidazoles is also described.

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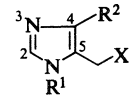
L'introduction d'un groupe triphénylméthyle sur l'azote des esters de l'acide imidazoledicarboxylique-4,5 ou du dihydroxyméthyl-4,5 imidazole, provoque la désactivation du groupe fonctionnel voisin du groupe protecteur et induit des réactions préférentielles ou exclusives au niveau de l'autre groupe fonctionnel. Dans ces conditions, le triphénylméthyl-1 imidazoledicarboxylate-4,5 de méthyle réagit avec l'hydrazine ou la méthylamine pour donner soit l'hydrazinocarbonyl-4 triphenylméthyl-1 imidazolecarbonylate-1 de méthyle (**3***a*) ou le méthylaminocarbonyl-4 triphenylméthyl-1 imidazole carboxylate-5 de méthyle (**3***b*). Le composé **2**, en présence de borohydrure de lithium, conduit à l'hydroxyméthyl-4 triphénylméthyl-1 imidazolecarboxylate-5 de méthyle (**4***a*). Le dihydroxyméthyl-4,5 triphenylméthyl-1 imidazole (**5***a*) réagit avec le chlorure de triméthylacétyle ou l'anhydride acétique pour donner soit l'hydroxyméthyl-5 triméthylacetoxyméthyl-4 triphénylméthyl-1 imidazole (**6***a*) ou l'acétoxyméthyl-4 hydroxyméthyl-5 triphénylméthyl-1 imidazole (**6***c*). L'oxydation du composé **5***a* par le dioxyde de manganèse fournit les monoaldéhydes **9** et **10** dans un rapport de 11:1. On rapporte une nouvelle méthode de déprotection douce des *N*-triphénylméthylimidazoles qui est compatible avec les groupes sensibles aux acides. On décrit également la synthèse de plusieurs imidazoles substitués en positions 4 et 5.

[Traduit par le journal]

In a research project directed toward the syntheses of novel histamine H-2 receptor antagonists as potential antiulcer agents, structurally related to cimetidine (1), 4,5-disubstituted imidazoles of the general structure **1** were needed as intermediates.

Most syntheses of 4,5-disubstituted imidazoles are based on ring closure of α-diketones, α-hydroxy-, α-halogeno- or (under reducing conditions) α-oximinoketones. All these suffer from deficiencies such as difficulties in the syntheses of starting materials and low yields. Furthermore, the applicability of these processes is limited to the syntheses of products that can survive the vigorous conditions involved in the ring-closing step (2). It seemed of interest to investigate the possibility of an alternative synthesis which would utilize viable sources of starting materials with a preformed imidazole ring. This paper describes the synthesis of 4,5-heterodisubstituted imidazoles from the readily available dimethyl 4,5-imidazole dicarboxylate (**1**) and from 4,5-dihydroxymethyl imidazole (**5***b*).



1

R^1 = H; R^2 = CO_2CH_3, CH_2OH, CN, CHO, $CONHCH_3$, $CONHNH_2$, CH=CHCN; X = Cl, Br

The ester groups in **1** and the hydroxymethyl groups in **5***b* are chemically equivalent and therefore chemical modifications of these molecules invariably yield symmetrically disubstituted products. It appeared to us that the presence of a bulky triphenylmethyl group at the 1-position of dimethyl imidazole-4,5-dicarboxylate (compound **2**) would hinder reactions on the neighboring ester at C-5, thus permitting reactions to take place preferentially at the other ester group. For similar reasons, the reactivities of the hydroxymethyl groups in the protected diol **5***a* were expected to be influenced by the presence of the triphenylmethyl group.

The reactions of the protected ester **2** with nucleophiles are shown in Scheme 1. Treatment of dimethyl imidazole-4,5-dicarboxylate (3) with tri-

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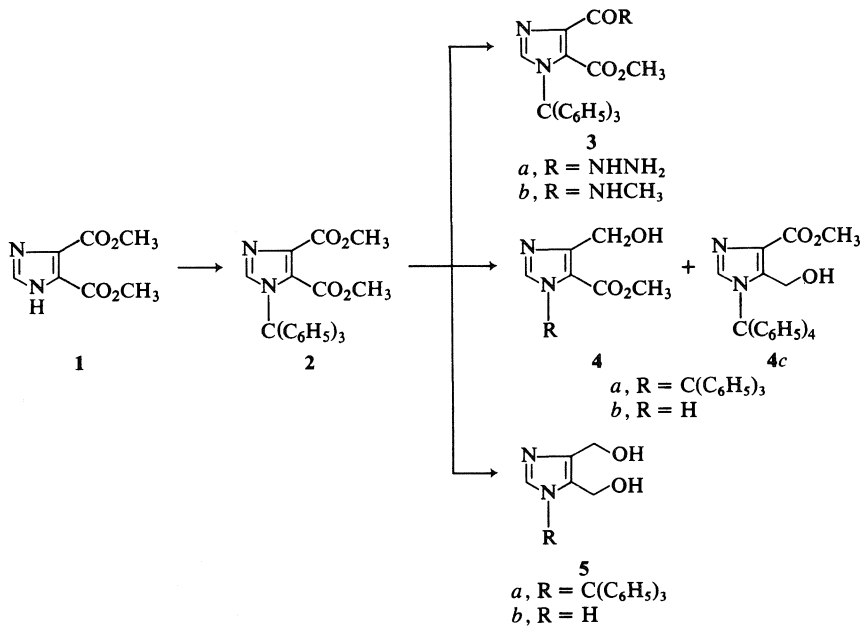


SCHEME 1

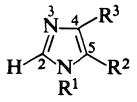
phenylmethyl chloride in dimethylformamide in the presence of triethylamine (4, 5) provided a 93% yield of dimethyl 1-triphenylmethylimidazole-4,5-dicarboxylate (**2**). When **2** was treated with a large excess of hydrazine (24 equiv.) in ethanol, the monohydrazide **3***a* was obtained in 94% yield. It is pertinent to note that similar reaction with the unprotected diester **1** yielded exclusively imidazole-4,5-dicarboxylic acid dihydrazide (6). Reaction of **2** with a large excess of methylamine in tetrahydrofuran–ethanol solvent mixture was also regiospecific and produced the monoamide **3***b*, exclusively. It was also possible to reduce one of the ester groups in **2** and produce the corresponding monoester. Thus, treatment of **2** with lithium borohydride in diglyme gave a 62% yield of the monoesters **4***a* and **4***c* in a ratio of 10:1, which upon removal of the triphenylmethyl group yielded the monoester **4***b*.

That the triphenylmethyl group in **3***a*, **3***b*, and **4***a* was correctly assigned to the nitrogen atom adjacent to the carboxymethyl group was supported by ^{1}Hmr spectroscopy. The methyl groups of dimethyl imidazole-4,5-dicarboxylate (**1**) experienced the same chemical shift and appeared as a singlet at δ 3.8 (see Table 1). In compound **2**, the methyl groups appeared as sharp singlets at δ 3.87 (same region as in **1**) and 3.17. Due to the shielding influence of the triphenylmethyl group these resonance peaks were assigned to the methyl protons of the carboxymethyl groups at C-4 and C-5, respectively. The ^{1}Hmr spectra of **3***a*, **3***b*, and **4***a* revealed that the sharp singlet at lower field (δ 3.8) had disappeared, while the singlet at higher field (δ 3.1–3.2) remained. Thus, the carboxymethyl group of these products must be adjacent to the triphenylmethyl group.

4,5-Dihydroxymethyl-1-triphenylmethylimidazole (**5***a*) was also found to be a viable intermediate for the synthesis of 4,5-heterodisubstituted imidazoles. The triphenylmethyl group in **5***a* appreciably decreased the reactivity of the adjacent hydroxyl group thus allowing reactions to take place preferably at the other hydroxyl group. Although the blocked diol **5***a* could be obtained from **5***b* by reaction with triphenylmethyl chloride, the difficulties involved in the preparation of **5***b* (7) by reduction of **1** with lithium aluminum hydride (mainly because of the extremely low solubilities of **1** in the permissible solvents) makes this process less desirable. It was found more convenient to prepare **5***a* by reduction of the diester **2** with lithium aluminum hydride in tetrahydrofuran. The high solubilities of **2** in THF and ether and the easily removable protective group makes this process attractive for the synthesis of **5***b* on a preparative scale.

It was possible to protect one of the hydroxyl groups in **5***a* while the other remained free for subsequent reactions (Scheme 2). Thus, treatment of **5***a* with trimethylacetyl chloride and with acetic anhydride produced the monoesters **6***a* (79%) and **6***c* (90%), respectively. When **6***a* was treated with thionyl chloride the chloride hydrochloride **7** was

TABLE 1. Nuclear magnetic resonance spectra of certain imidazole derivatives[a]

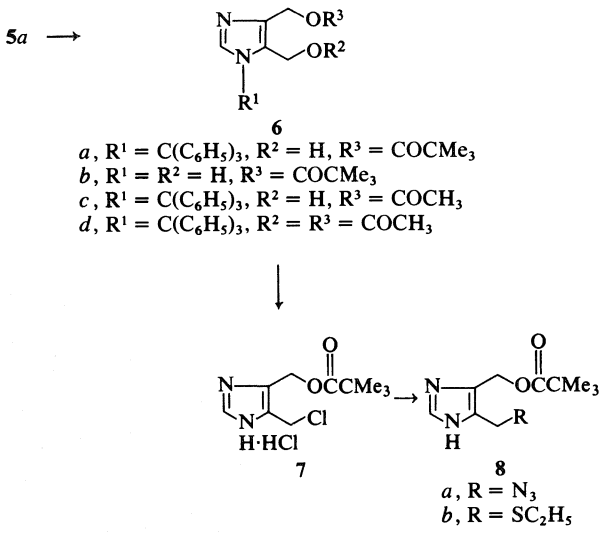


Compound	H-2	R^1	R^2	R^3	Solvent
1	(7.93)	H	CO_2CH_3 (3.83)	CO_2CH_3 (3.83)	DMSO-d_6
2	(7.55)	Tr[c] (7.1–7.5)	CO_2CH_3 (3.17)	CO_2CH_3 (3.87)	$CDCl_3$
3a	[b]	Tr (7.1–7.5)	CO_2CH_3 (3.0)	$CONHNH_2$	DMSO-d_6
3b	[b]	Tr (7.1–7.5)	CO_2CH_3 (3.20)	$CONHCH_3$ (2.91, d, J = 5)	$CDCl_3$
4a	[b]	Tr (7.1–7.4)	CO_2CH_3 (3.17)	CH_2OH (4.83)	$CDCl_3$
4b	(7.62)	H	CH_2OH (4.65)	CO_2CH_3 (3.87)	DMSO-d_6, D_2O
5a	[b]	Tr (7.2–7.5)	CH_2OH (3.95)	CH_2OH (4.65)	$CDCl_3$
5b	(7.7)	H	CH_2OH (4.63)	CH_2OH (4.63)	D_2O
6a	[b]	Tr (7.1–7.5)	CH_2OH (4.0)	$CH_2O-\overset{O}{\overset{\|}{C}}-CMe_3$ (5.15) (1.18)	$CDCl_3$
6b	(7.43)	H	CH_2OH (4.7)	$CH_2O\overset{O}{\overset{\|}{C}}CMe$ (5.03) (1.1)	$CDCl_3$
6c	[b]	Tr (7.1–7.5)	CH_2OH (4.6, d, J = 6)	$CH_2O\overset{O}{\overset{\|}{C}}-CH_3$ (5.13) (2.08)	$CDCl_3$
6d	[b]	Tr (7.1–7.5)	$CH_2O\overset{O}{\overset{\|}{C}}CH_3$ (4.53) (1.63)	$CH_2O\overset{O}{\overset{\|}{C}}CH_3$ (5.07) (2.07)	$CDCl_3$
9	[b]	Tr (7.1–7.5)	CH_2-OH (3.95, d, J = 6) (4.75, t, J = 6)	CHO (10.0)	$CDCl_3$
10	[b]	Tr (7.1–7.5)	CHO (9.3)	CH_2OH (4.75, d, J = 6) (4.20, t, J = 6)	$CDCl_3$

[a]Recorded at 60 MHz. Values expressed as ppm (δ). All spectra appeared as sharp singlets, unless otherwise noted. The coupling constants are recorded in Hz.
[b]Appeared in the region 7.1–7.5 together with the aromatic protons.
[c]Tr = $C(C_6H_5)_3$.

obtained in good yield (83.5%). Treatment of **7** with sodium azide in aqueous ethanol afforded a 91% yield of the azide ***8a***. The reaction of **7** with sodium ethanethiolate in water gave a good yield (75%) of the thioether ***8b***.

Oxidation of the diol ***5a*** with activated manganese dioxide (8) in boiling chloroform, conditions similar to those previously employed by Kelley and co-workers for the oxidation of an analogous product (5), gave a mixture of the isomeric monoaldehydes **9** and **10** in which compound **9** was the predominant isomer (92%). Several transformations of **9** giving rise to a variety of 4,5-heterodisubstituted imidazoles are apparent (Scheme 3). Thus, the reaction of **9** with ammonia in methylene chloride in the presence of activated manganese dioxide (8), a process described by Gilman (9), gave rise to the cyanocompound **11**. Treatment of **11** with thionyl chloride afforded **12** which on reaction with sodium 2-aminoethanethiolate produced **13**.



SCHEME 2

Extension of the side chain in **9** was possible by reaction of **9** and diethylcyanomethylphosphonate (10) giving rise to a mixture of the olefins **14** and **15** in a ratio of 2:1.

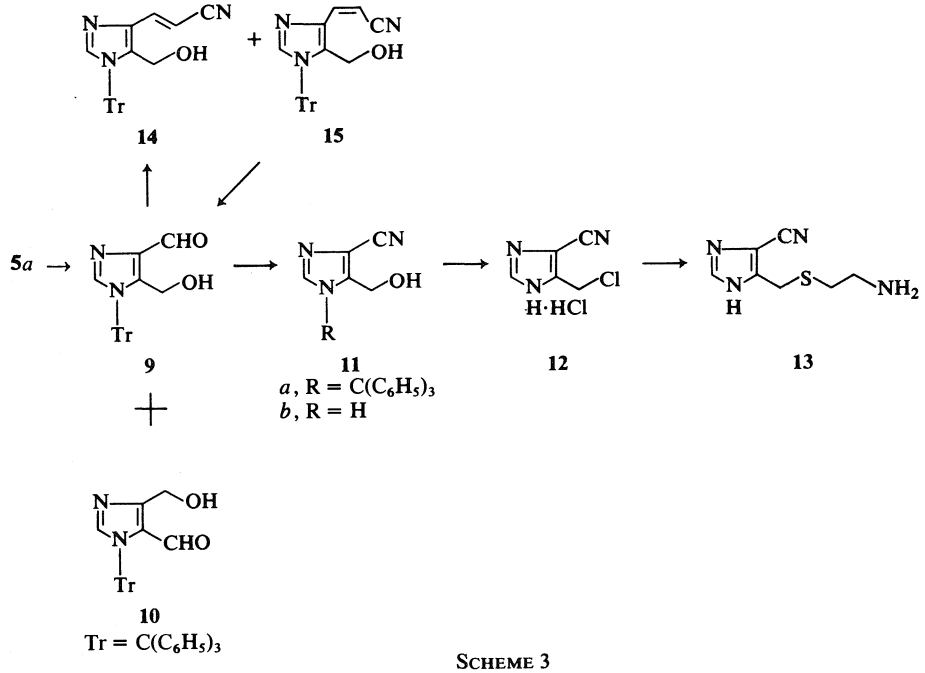
The assignment of structures for compounds **6***a*, **6***c*, and **9** as having the hydroxymethyl group next to the nitrogen atom carrying the triphenylmethyl group was made on the basis of ^{1}Hmr studies. Examination of Table 1 reveals that the methylene groups in 4,5-dihydroxymethylimidazole (**5***b*) experience the same chemical shift and appear as a sharp singlet at δ 4.63. In 4,5-dihydroxymethyl-1-triphenylmethylimidazole (**5***a*), the methylene group at C-4 resonated in the same field as those in **5***b* and appeared as a singlet at δ 4.65 whereas the methylene group at C-5 was shifted to higher field and appeared as a singlet at δ 3.95. The ^{1}Hmr spectra of **6***a*, **6***c*, and **9** revealed that the sharp singlet for the methylene of the hydroxymethyl group at δ 4.65 had disappeared, while the singlet in the region of δ 3.95 remained.

Excellent results were obtained in deblocking *N*-triphenylmethylimidazoles (i.e., compound **11***a*) using dilute hydrochloric acid solutions as has already been reported (4, 5). However, equally good results were obtained by simply refluxing ethanolic solutions of blocked imidazoles in the presence of water and a small amount of acetic acid. This process is compatible with acid-sensitive groups in the molecule. Compounds **4***b*, **5***b*, and **6***b* were prepared by this method in high yields.

In summary, we have shown that the commercially available imidazole-4,5-dicarboxylic acid can be conveniently converted to valuable and otherwise not easily accessible 4,5-disubstituted imidazoles by simple chemical processes.

Experimental

The infrared spectra were recorded on a Unicam SP-200G grating ir spectrophotometer. The ^{1}Hmr spectra were determined on a Varian EM 360 spectrometer using tetramethylsilane (for solutions other than deuterium oxide) and sodium 4,4-di-



SCHEME 3

methyl-4-silapentane-1-sulfonate (for solutions of deuterium oxide) as internal standards. Melting points are uncorrected and were determined on an electrothermal melting point apparatus. The analyses were performed by Micro-Tech Laboratories, Skokie, IL. Thin layer chromatography (tlc) was carried out on pre-coated silica gel plates (E. Merck F-254). Reaction yields refer to products which showed a single spot on tlc plates.

*Dimethyl imidazole-4,5-dicarboxylate (**1**)*

This compound was prepared by a described procedure (3*b*). Recrystallization twice from water provided pure sample, mp 206–207°C. (lit., (3*a*), mp 200–202°C).

*Dimethyl 1-triphenylmethylimidazole-4,5-dicarboxylate (**2**)*

This compound was prepared according to the procedure described in the literature (4, 5) for the synthesis of *N*-triphenylmethylimidazoles. Thus, a mixture of dimethyl imidazole-4,5-dicarboxylate (11.0 g, 60 mmol), dry triethylamine (10.4 mL, 78 mmol), and dry dimethylformamide (75 mL) was blanketed with nitrogen and stirred at room temperature. To this mixture was added 19.5 g (70 mmol) of triphenylmethyl chloride in one lot. Soon after the addition, a white precipitate was formed; to facilitate stirring an additional 40 mL of dimethylformamide was added. The reaction was monitored by tlc on silica plates using 5% methanol in methylene chloride as eluent and was complete after 2 h. After stirring for an additional 2 h, the reaction mixture was poured over a mixture of crushed ice and water (600 mL). The solids were collected and washed with water. The partly dried product was dissolved in methylene chloride and the solution washed several times with water to eliminate unreacted diester **1**, dried, and evaporated. The residue was dissolved in $CHCl_3$ (50 mL), the solution diluted with petroleum ether (100 mL, bp 30–60°C), and the resultant solution allowed to crystallize at room temperature. The solids were collected by filtration to give 19.5 g of **2**, mp 202–205°C. The mother liquor was evaporated at reduced pressure and the residue was recrystallized from the same solvent system as above to provide an additional 4.5 g of **2** which were combined with the first crop to a total of 24 g (93%); ir (Nujol): 1720 cm^{-1}. *Anal.* calcd. for $C_{26}H_{22}N_2O_4$: C 73.22, H 5.19, N 6.57; found: C 73.24, H 5.52, N 6.57.

*Methyl 4-hydrazinocarbonyl-1-triphenylmethylimidazole-5-carboxylate (**3**a)*

To a stirred suspension of **2** (0.5 g, 1.18 mmol) in ethanol (2 mL) was added 0.9 mL (0.91 g, 28.4 mmol) of anhydrous hydazine and the reaction mixture stirred at room temperature for 40 min. Removal of the solvent by evaporation and recrystallization of solid residue from ethanol yielded 0.47 g (94%) of **3***a*, mp 240–242°C (decomp.); ir (Nujol): 3300, 1720, 1670, 1620, 1570 cm^{-1}. *Anal.* calcd. for $C_{25}H_{22}N_4O_3$: C 70.40, H 5.20, N 13.14; found: C 70.15, H 5.16, N 13.18.

*Methyl 4-methylaminocarbonyl-1-triphenylmethylimidazole-5-carboxylate (**3**b)*

A solution of **2** (1.0 g, 2.34 mmol) in tetrahydrofuran–ethanol solvent mixture (1:1, 45 mL) was saturated with methylamine (gas) and the reaction mixture stirred at room temperature for 48 h. The reaction was monitored by tlc on silica plates using ether–benzene (1:1) as eluent; after 48 h, the spot for **2** (R_f 0.4) disappeared and a new spot of R_f 0.24 (**3***b*) appeared. The reaction mixture was evaporated at reduced pressure. The solid residue was dissolved in acetone–chloroform mixture (1:10) and filtered through a pad of silica (4 cm long × 3.5 cm id) and the silica washed with the same solvent mixture (50 mL). The combined filtrate and washings were evaporated, the residue triturated with acetone–ether (1:2, 15 mL) and the crystalline material collected to give 0.85 g (85%) of **3***b* mp 211–213°C; ir (Nujol): 3380 (NH), 1730, 1680, 1570 cm^{-1}. *Anal.* calcd. for $C_{26}H_{23}N_3O_3$: C 73.30, H 5.44, N 9.87; found: C 73.09, H 5.34, N 9.78.

*Methyl 4-hydroxymethyl-1-triphenylmethylimidazole-5-carboxylate (**4**a)*

To a solution of sodium borohydride (0.57 g, 15 mmol) in dry diglyme (25 mL) was added anhydrous lithium bromide (1.3 g, 15 mmol) and the suspension was placed under a slow stream of nitrogen and stirred at room temperature for 30 min. To this mixture was added the diester **2** (2.13 g, 5 mmol) and the reaction mixture stirred at 25°C for 7 h, stored at 0°C overnight, and then stirred at 25°C for 5 h more. The reaction mixture was poured into cold water (200 mL) and the precipitate collected by filtration and washed with water. The solids were dissolved in methylene chloride, the solution extracted with water, dried, and evaporated to give 1.8 g of a syrup. Analysis of this product on tlc (silica, 10% MeOH–CH_2Cl_2) showed one major spot of R_f 0.51 (**4***a*) and three minor spots of R_f 0.46 (diol), 0.62, and 0.77 (**2**). The crude product was chromatographed on Alumina Act. II (Alumina Fluka for chromatography type 507C) (column size 13 × 1.8 cm id). Elution with ether–benzene (1:1) mixture removed the unreacted diester (0.32 g); subsequent elution with 2% methanol in methylene chloride gave 1.2 g (62%) of product which on tlc showed a major spot for **4***a* and a minor one of R_f 0.62 (presumably the isomer of **4***a*). Further elution with 4% methanol in methylene chloride gave 0.2 g of the diol **5***a*.

The major fraction (**4***a* plus isomer) without further purification was used in the next reaction. A sample was recrystallized from 80% ethanol to afford **4***a*, mp 162–163°C; ir ($CHCl_3$): 3300, 1720 cm^{-1}. *Anal.* calcd. for $C_{25}H_{22}N_2O_3$: C 75.35, H 5.54, N 7.03; found: C 75.28, H 5.53, N 7.05.

*Methyl 4(5)-hydroxymethylimidazole-5(4)-carboxylate (**4**b)*

A solution of **4***a* (0.6 g) in 80% ethanol (10 mL) and glacial acetic acid (0.5 mL) was stirred under reflux for 45 min. Removal of the solvent by evaporation *in vacuo* left a solid which was partitioned between water (10 mL) and ether–hexane mixture (1:1, 10 mL). The organic phase containing triphenyl carbinol was separated and discharged; the aqueous phase was evaporated under reduced pressure to give 0.21 g (90%) of **4***b*. Recrystallization from ethanol yielded the analytical sample, mp 171–172°C. *Anal.* calcd. for $C_6H_8N_2O_3$: C 46.15, H 5.16, N 17.94; found: C 46.13, H 5.16, N 17.95.

*4,5-Dihydroxymethyl-1-triphenylmethylimidazole (**5**a)*

Dimethyl 1-triphenylmethylimidazole-4,5-dicarboxylate (58 g, 0.136 mol) was added in small portions to a stirred mixture of 9 g (0.237 mol) of lithium aluminum hydride in 1 L of dry tetrahydrofuran at 0°C under a nitrogen atmosphere. After the addition was completed (30 min) the cooling bath was removed and stirring was continued at room temperature for 3 h. The reaction mixture was cooled to 0°C and treated successively with 60 mL of water, 60 mL of 15% aqueous sodium hydroxide, and 60 mL of water. It was then filtered and the inorganic salts were washed with tetrahydrofuran. The combined filtrate and washings were evaporated under reduced pressure. The residue was dissolved in methylene chloride, the solution was washed with water, dried, and evaporated to give 38 g (75%) of **5***a*, mp 192–193°C; on tlc (silica, 10% methanol – methylene chloride), this product showed a single spot of R_f 0.4. *Anal.* calcd. for $C_{24}H_{22}N_2O_2$: C 77.81, H 5.99, N 7.56; found: C 77.84, H 6.15, N 7.44.

In a larger scale experiment, the yield of **5***a* was 85%.

*4,5-Dihydroxymethylimidazole (**5**b)*

To a solution of **5***a* (1 g, 2.7 mmol) in 80% ethanol (10 mL) was added glacial acetic acid (0.5 mL) and the solution was refluxed

for 1.5 h. Removal of the solvent *in vacuo* left a solid residue which was partitioned between water and ether. The ether phase containing triphenyl methanol was separated and discharged; the aqueous phase was evaporated to dryness at reduced pressure to give 0.33 g (98.5%) of crystalline **5***b*. Recrystallization from ethanol afforded the analytical sample, mp 165–166°C (lit. (7) mp 162–163°C).

*5-Hydroxymethyl-4-trimethylacetoxymethyl-1-triphenylmethylimidazole (**6**a)*

To a suspension of **5***a* (29.6 g, 80 mmol) in dry methylene chloride (250 mL) was added 8.3 g (124 mmol) of dry pyridine and the mixture, protected from moisture, was cooled in an ice bath while stirring. A solution of 10.25 g (85 mmol) of trimethylacetyl chloride in 100 mL of methylene chloride was added dropwise. After the addition was completed (10 min), the reaction solution was stirred at room temperature for 2.5 h and then stored at 0°C overnight. The reaction mixture was washed with water (3 × 200 mL), dried, and evaporated under reduced pressure to give a syrup which on tlc (silica, 10% acetone in methylene chloride) showed one major spot for **6***a* (R_f 0.45), a minor spot for unreacted **5***a* (R_f 0) and three other unidentified minor spots (R_f 0.62, 0.82, and 0.92). This product was dissolved in acetone – methylene chloride solvent mixture (1:10, 200 mL) and the solution filtered through a pad of silica (10 cm × 4 cm id) and the silica bed washed with the same solvent system (200 mL). By this treatment, the unreacted **5***a* was removed. The filtrate and washings were combined and evaporated to give 31 g of crystalline product. Recrystallization from benzene (70 mL) – petroleum ether (175 mL, bp 90–120°C) afforded 21.6 g (59.5%) of **6***a*, mp 157–159°C. The mother liquor was evaporated and the residue was chromatographed on silica using acetone–chloroform solvent mixture (1:10) as eluent to provide an additional 7 g of **6***a*. The two crops were combined to a total yield of 28.6 g (79%); ir ($CHCl_3$): 3580, 1720 cm^{-1}. *Anal.* calcd. for $C_{29}H_{30}N_2O_3$: C 76.62, H 6.65, N 6.16; found: C 77.03, H 6.49, N 6.16.

*4(5)-Hydroxymethyl-5(4)-trimethylacetoxymethylimidazole (**6**b)*

To a solution of **6***a* (2.0 g, 4.4 mmol) in 80% ethanol (20 mL) was added glacial acetic acid (1 mL) and the resultant solution was heated under reflux for 1 h and then evaporated to dryness at reduced pressure. The residue was chromatographed on a wet column of silica (12 cm × 1.8 cm id) using 5% methanol in chloroform as eluent to give 0.89 g (95%) of **6***b* as a syrup which crystallized on standing. This product showed on tlc (silica, 10% MeOH – CH_2Cl_2) a single spot of R_f 0.2. Recrystallization from methylene chloride – ether solvent mixture afforded the analytical sample, mp 97–99°C: ir ($CHCl_3$): 3200, 1720 cm^{-1}. *Anal.* calcd. for $C_{10}H_{16}N_2O_3$: C 56.59, H 7.60, N 13.20; found: C 56.55, H 7.62, N 13.15.

*4-Acetoxymethyl-5-hydroxymethyl-1-triphenylmethylimidazole (**6**c)*

To a suspension of **5***a* (0.925 g, 2.5 mmol) in 5 mL of methylene chloride was added 0.4 mL (5 mmol) of dry pyridine and 0.3 mL (3.2 mmol) of acetic anhydride and the mixture stirred at room temperature for 3 h. Methylene chloride (50 mL) was added and the resultant solution was washed with water (3 × 50 mL), dried, and filtered. Removal of the solvent *in vacuo* gave 1.0 g of solids which on tlc (silica, 10% acetone in chloroform) showed a major spot of R_f 0.23 (**6***c*) and two minor spots of R_f 0 and 0.4 (**5***a*). This product was purified by column chromatography on silica using acetone–chloroform mixture (1:3) as eluent to provide 0.92 (90%) of crystalline **6***c*. Recrystallization from ethanol afforded the analytical sample, mp 192–193°C; ir ($CHCl_3$): 3580, 3460, 1727 cm^{-1}. *Anal.* calcd. for $C_{26}H_{24}N_2O_3$: C 75.70, H 5.86, N 6.79; found: C 75.60, H 5.85, N 6.80.

*5(4)-Chloromethyl-4(5)-trimethylacetoxymethylimidazole hydrochloride (**7**)*

A mixture of **6***a* (5.0 g, 11 mmol) and thionyl chloride (25 mL) was stirred at 23°C for 10 min and then heated under reflux for 30 min. Removal of the excess thionyl chloride *in vacuo* left a syrupy residue which partly solidified on trituration with ether (50 mL). The ether was removed by evaporation. The residue was dissolved in 95% ethanol (5 mL), the solution was diluted with ether (60 mL) and allowed to crystallize at room temperature. The crystalline product was collected, washed with ether, and dried to give 2.15 g (83.5%) of **7**, mp 275–280°C (decomp.); ^{1}Hmr (CD_3OD–CD_3COCD_3) δ: 1.2 (s, 9H, CMe_3), 5.03 (s, 2H, CH_2Cl), 5.37 (s, 2H, CH_2O), 9.17 (s, 1H, H-2). *Anal.* calcd. for $C_{10}H_{15}ClN_2O_2 \cdot HCl$: C 44.96, H 6.04, N 10.49, Cl 26.14; found: C 44.81, H 5.94, N 10.47, Cl 25.60. In a larger scale experiment, the yield of **7** was 90%.

*5(4)-Azidomethyl-4(5)-trimethylacetoxymethylimidazole (**8**a)*

To a solution of sodium azide (0.52 g, 8 mmol) in 4 mL of aqueous ethanol (50%) was added a solution of **7** (0.534 g, 2 mmol) in 2 mL of 90% ethanol. After stirring at room temperature for 18 h the reaction mixture was diluted with water (10 mL) and extracted with methylene chloride (4 × 10 mL). The combined extracts were washed with water, dried, and evaporated to give 0.45 g (91%) of **8***a* as a syrup which crystallized on trituration with ether. This product showed on tlc (silica, 5% MeOH – CH_2Cl_2) a single spot of R_f 0.35. Recrystallization from ether afforded the analytical sample, mp 88.5–89°C; ir (Nujol): 2100 (N_3) 1730 cm^{-1} (CO); ^{1}Hmr ($CDCl_3$) δ: 1.17 (s, 9H, $COMe_3$), 4.43 (s, 2H, CH_2N_3), 5.13 (s, 2H, CH_2O), 7.70 (s, 1H, H-2). *Anal.* calcd. for $C_{10}H_{15}N_5O_2$: C 50.62, H 6.37, N 29.52; found: C 50.26, H 6.42, N 29.63.

*4(5)-Ethylthiomethyl-5(4)-trimethylacetoxymethylimidazole (**8**b)*

Ethanethiol (0.6 mL, 8 mmol) was added to 1 mL of 4 *N* aqueous sodium hydroxide and the solution was placed under a nitrogen atmosphere and cooled in an ice bath. To this solution was added 0.534 g (2 mmol) of **7** and the reaction mixture was stirred at room temperature for 2 h. The solvent was removed by evaporation and the residue partition between water and methylene chloride. The organic phase after drying was evaporated to dryness, and the residue was chromatographed on silica gel (10 g) using 5% methanol in methylene chloride as eluent to give 0.396 g (75%) of **8***b* as an oil; ir (neat): 1710 cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 1.17 (s, 9H CMe_3), 1.20 and 2.50 (t and q for SCH_2CH_3), 3.80 (s, 2H, CH_2S—), 5.10 (s, 2H, CH_2O), 7.67 (s, 1H, H-2). The hydrochloride salt of **8***b* had mp 147–149°C. *Anal.* calcd. for $C_{12}H_{20}N_2O_2 \cdot HCl$: C 49.22, H 7.23, N 9.57; found: C 49.18, H 7.19, N 10.15.

*4-(5-Hydroxymethyl-1-triphenylmethyl)imidazolecarboxaldehyde (**9**) and 5-(4-hydroxymethyl-1-triphenylmethyl)imidazolecarboxaldehyde (**10**)*

The procedure described by Kelley and co-workers (5) for the synthesis of 4-(*N*-triphenylmethyl)imidazole carboxaldehyde was used as follows. A mixture of 29.2 g (73.5 mmol) of **5***a* and 47 g (540 mmol) of activated manganese dioxide (8) and 1 L of dry and ethanol-free chloroform was refluxed with mechanical stirring for 1.5 h. Fresh manganese dioxide (47 g) was added and refluxing continued for an additional 1.5 h. The hot reaction mixture was filtered through a Celite pad and the solids were washed with chloroform (300 mL). The combined filtrate and washings were evaporated *in vacuo* and the residue was triturated with ether (100 mL). The solids were collected to give 25 g of crude product which on tlc (silica, 10% acetone – $CHCl_3$) showed 3 spots of R_f values 0.50 (major, **9**), 0.23 (minor, **10**), and 0. The crude product was chromatographed on a silica column

(700 g), eluted successively with methylene chloride, 5% acetone – methylene chloride, and 10% acetone – methylene chloride to give 17.9 g (62%) of crystalline **9**. The analytical sample obtained by recrystallization from methylene chloride had mp 177.5–178.5°C; ir ($CHCl_3$): 3350, 1675 cm^{-1}. *Anal.* calcd. for $C_{24}H_{20}N_2O_2$: C 78.24, H 5.47, N 7.60; found: C 77.85, H 5.60, N 7.43. Further elution of the column with 1:1 acetone – methylene chloride solvent mixture gave 1.6 g (5.5%) of the isomer **10**, mp 160–164°C; ir ($CHCl_3$); 3350, 1660 cm^{-1}. *Anal.* calcd. for $C_{24}H_{20}N_2O_2$: C 78.24, H 5.47, N 7.60; found: C 77.39, H 5.50, N 7.58.

*4-Cyano-5-hydroxymethyl-1-triphenylmethylimidazole (**11**a)*

A described general procedure (9) was used as follows. To a solution of 1.3 g (3.36 mmol) of **9** in 60 mL methylene chloride was added 2.6 g molecular sieves (type 4A) and the mixture was stirred at room temperature. Ammonia (gas) was bubbled into the reaction mixture for 10 min then 2.6 g of activated manganese dioxide (8) was added and the mixture was stirred at room temperature for 2 h while the bubbling of ammonia was maintained. The reaction mixture was filtered and the solids were washed with methylene chloride (50 mL). The combined filtrate and washings were evaporated to give 1.3 g of an oil which crystallized from methylene chloride – ether mixture to give 0.52 g of **11***a*, mp 170–172°C. From the mother liquor, after evaporation and crystallization of the residue as above, an additional 0.17 g of **11***a* was obtained. The two crops were combined to a total yield of 0.69 g (48%); ir (Nujol): 3350, 2240 cm^{-1}; ^{1}Hmr ($CDCl_3$–CD_3OD) δ: 7.4 (m, 16H, ArH and H-2), 3.85 (s, 2H, CH_2). *Anal.* calcd. for $C_{24}H_{19}N_3O$: C 78.88, H 5.24, N 11.50; found: C 78.28, H 5.24, N 11.55.

*4(5)-Cyano-5(4)-hydroxymethylimidazole hydrochloride (**11**b)*

To a solution of **11***a* (2.14 g, 5.45 mmol) in methanol (25 mL) was added 2.5 *N* hydrochloric acid (4, 5) (12 mL) and the resulting solution was heated at 40°C for 1 h and then evaporated under reduced pressure. The solid residue was dissolved in water (15 mL) and the solution extracted with ether (2 × 20 mL). The aqueous phase was evaporated to dryness to give 0.82 g (94%) of **11***b* as a solid. Recrystallization from an ethanol–ether solvent mixture afforded the analytical sample mp 180–182°C; ir (Nujol): 2200 (CN) cm^{-1}; ^{1}Hmr (DMSO-d_6) δ: 4.98 (s, 2H, CH_2O), 8.04 (s, 1H, H-2). *Anal.* calcd. for $C_5H_5N_3O$·HCl: C 37.63, H 3.16, N 26.33; found: C 37.52, H 3.18, N 26.22.

*5(4)-Chloromethyl-4(5)-cyanoimidazole hydrochloride (**12**)*

A mixture of 1.6 g (4.4 mmol) of **11***a* and 35 mL of thionyl chloride was refluxed for 20 h. The reaction mixture was evaporated to dryness and flashed with chloroform (3 × 20 mL). The residue was extracted with ether (3 × 45 mL) and methylene chloride (25 mL) and the organic extracts were discharged. The solid product was collected to give 0.44 g (56%) of **12**; ir (Nujol): 2600, 2220 cm^{-1}; ^{1}Hmr (D_2O) δ: 8.83 (s, 1H, H-2), 4.95 (s, 2H, CH_2). *Anal.* calcd. for $C_5H_4N_3Cl$·HCl: C 33.73, H 2.83, N 23.61; found: C 33.54, H 2.81, N 23.62.

*4(5)-Cyano-5(4)-[(2-aminoethyl)thiomethyl]imidazole (**13**)*

To a solution of 2 *N* sodium ethoxide in ethanol (7 mL) was added a solution of 0.785 g (5 mmol) of 2-aminoethanethiol hydrochloride in 7 mL of ethanol and the mixture was placed under a nitrogen atmosphere and stirred at −10°C for 25 min. To this mixture was added dropwise over a period of 15 min a solution of 0.63 g (3.5 mmol) of **12** in 7 mL ethanol. After the addition of **12** was completed, the cooling bath was removed and the reaction mixture stirred at room temperature for 4 h. Removal of the solvent by evaporation left a residue which was purified by chromatography on a column of Rexyn 102 resin (NH_4^+ form, 10 cm long × 2 cm id). The column was eluted successively with water (50 mL), 0.1 *N* ammonium hydroxide (50 mL), and 0.2 *N* ammonium hydroxide (50 mL). The fractions of eluent containing the product were combined and evaporated to give 0.25 g (42.5%) of **13** as a syrup. This product showed on tlc (silica, ammonia–methanol–water, 0.5:9:0.5) a single spot of R_f 0.7; ^{1}Hmr (D_2O) δ: 7.66 (s, 1H, H-2), 3.90 (s, 2H, CH_2S), 2.86 (m, 4H, SCH_2CH_2N). *Anal.* calcd. for $C_7H_{10}N_4S$: C 46.13, H 5.53, S 17.59; found: C 46.09, H 5.49, S 17.49.

*Preparation of compounds **14** and **15***

A mixture of 0.811 g of 50% sodium hydride – oil suspension (16.9 mmol) and 20 mL of dry benzene was cooled in an ice bath while stirring under an atmosphere of nitrogen. To this mixture was added dropwise 1.43 mL (8.85 mmol) of diethylcyanomethylphosphonate and, after the addition was completed, the mixture stirred at 0°C for 5 min. This solution was transferred into a dropping funnel and added dropwise to a stirred solution of 2.96 g (8.05 mmol) of the aldehyde **9** in 260 mL of dry benzene at 45°C. After the addition was completed, the reaction mixture was stirred at 45°C for 20 min under a nitrogen atmosphere. After cooling to room temperature, the reaction solution was washed with brine (200 mL), the organic phase separated, and the aqueous phase extracted with chloroform (50 mL). The combined extracts were washed with brine, dried, and evaporated to give 1.9 g (61%) of a syrup. This product showed on tlc (silica, ether) two spots of R_f 0.38 (*trans*-isomer **14**) and 0.23 (*cis*-isomer **15**). The ratio of *trans*- to *cis*-isomer in the mixture was 2:1 as determined by ^{1}Hmr. The two isomers were separated by chromatography on a column of silica gel (150 g) eluted successively with ether, ether – methylene chloride mixture (1:1), and methylene chloride. The *trans*-isomer **14** had mp 171–172°C; ir ($CHCl_3$): 3570 (OH), 2220 (CN), 1620 (C=C) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 7.53 (d, 1H, C=CH, J = 16 Hz), 7.3 (m, 16H, ArH and H-2), 6.00 (d, 1H, C=CH, J = 16 Hz), 4.06 (d, 2H, CH_2OH, J = 6 Hz on exchange with D_2O gives a singlet), 1.45 (t, 1H, OH, J = 6 Hz, disappears on exchange with D_2O). *Anal.* calcd. for $C_{26}H_{21}N_3O$: C 79.77, H 5.40, N 10.73; found: C 79.69, H 5.39, N 10.79. The *cis*-isomer **15** had mp 181–182°C; ir ($CHCl_3$): 3570 (OH), 2220 (CN), 1625 (C=C) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 7.24 (m, 17H, ArH, H-2 and *CH*=CHCN), 5.24 (d, 1H, C=*CH*CN, J = 11.8 Hz), 4.07 (s, 2H, CH_2OH). *Anal.* calcd. for $C_{26}H_{21}N_3O$: C 79.77, H 5.40, N 10.73; found; C 79.78, H 5.41, N 10.80.

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