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The reaction of α-(aryl)-4-morpholineacetonitriles (masked aroyl anion equivalents) with *N*-protected 4(5)-bromo-5(4)-nitro-1*H*-imidazoles gave 4-aroyl-5-nitroimidazoles which were reduced to afford 4-aroyl-5-aminoimidazoles.

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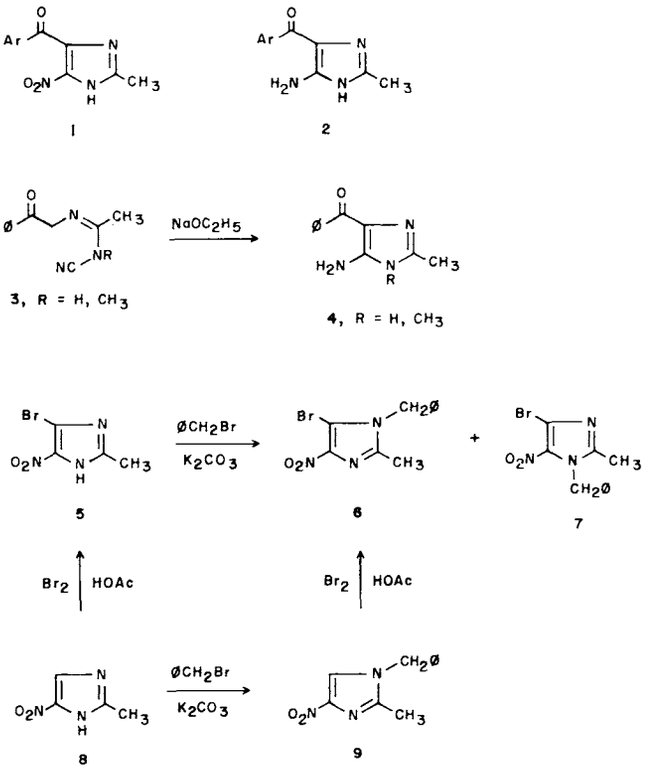
4-Aroyl-5-nitro-1*H*-imidazoles **1** and 4-aroyl-5-amino-1*H*-imidazoles **2** are potentially useful intermediates for the synthesis of imidazo-pyrimidines; however, routes to 4-aroyl-5-nitroimidazoles have not been reported. While there are a number of specific syntheses of 5-amino-imidazoles which contain cyano [1-3], alkoxycarbonyl [2,3], carboxamide [2] sulfonamide [4] and formyl [5] substituents at the 4-position, only one report [3] describes 5-amino-4-benzoyl derivatives **4** (R = H, CH_3) *via* cyclization of **3**.

Our interest in α-aryl-4-morpholineacetonitriles as aroyl anion equivalents [6-8] and the fact that such carbanions displace halogen from activated halobenzenes [7] (such as 4-fluoronitrobenzene) prompted us to study the reaction of 4-bromo-2-methyl-5-nitroimidazole (**5**) with aroyl anion equivalents. To avoid anion exchange with the NH of the imidazole **5**, a blocking group on the nitrogen is required. Since imidazoles unsubstituted on nitrogen were desired, we investigated the use of the benzyl group as a suitable removable blocking group. Reaction of 4-bromo-2-methyl-5-nitro-1*H*-imidazole (**5**) with benzyl bromide in the presence of potassium carbonate or *N*,*N*-diisopropylethylamine as base, gave a mixture (*ca* 1:1) of *N*-benzyl derivatives **6** and **7**. The higher melting 5-bromo-4-nitro isomer **6** could be crystallized directly from the reaction mixture in 40% yield and the mother liquors chromatographed to give the 4-bromo-5-nitro isomer **7**.

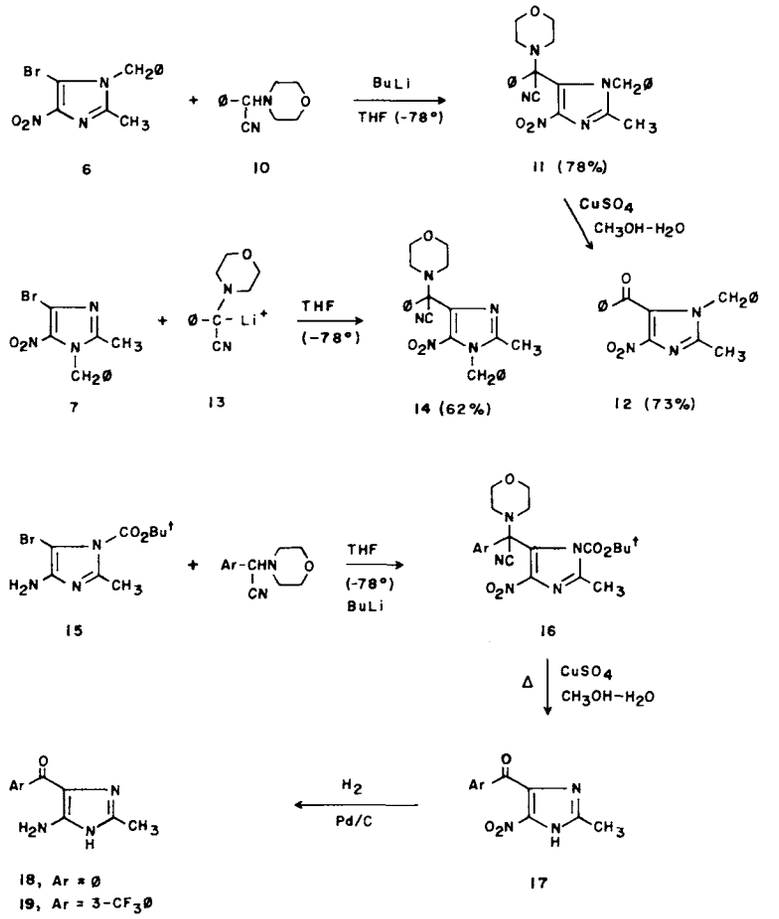
The assignment of structures to the isomers **6** and **7** is based on the following chemical and physical properties. Reaction of 2-methyl-5-nitro-1*H*-imidazole (**8**) with benzyl bromide under basic conditions is known to give 2-methyl-4-nitro-1-(phenylmethyl)-1*H*-imidazole (**9**), while benzyl tosylate (△ neat) affords the isomeric 2-methyl-5-nitro-1-(phenylmethyl)-1*H*-imidazole [9]. In addition, recent ^{13}C nmr studies of 4- and 5-nitroimidazoles [10,11] confirmed the structural assignment of **9** as a 1-substituted-4-nitro derivative. The reported ^1H nmr spectra of isomeric 1-methyl-4-nitro- and 1-methyl-5-nitroimidazoles show that the *N*-methyl group (δ *ca* 3.93) is deshielded when the nitro group is in the 5-position and thus the *N*-methyl group (δ *ca*, 3.75) in 4-nitroimidazoles occurs at higher field [12].



The CH_2 (δ 5.28) of the *N*-benzyl group in 4-nitro isomer **6** is at higher field (^1H nmr) while the CH_2 (δ 5.58) in the 5-nitro isomer **7** is deshielded. The ^{13}C nmr spectra of **6** and **7** confirm their structures since the chemical shifts fit with previous correlations [10]. The ^{13}C-2 for **6** and **7** are at δ 145.7 and δ 150.2 while the $^{13}CH_2$'s are at δ 48.81 and δ 49.78 respectively.

In addition, bromination of 1-benzyl-4-nitro derivative **9** afforded 1-benzyl-5-bromo-4-nitro derivative **6**. Reaction of **6** or **7** with the lithium salt of α-phenyl-4-morpholineacetonitrile (**10**) (THF, -78°) gave the expected products **11** and **14** in good yields. Acid hydrolysis to free the protected carbonyl group in **11** afforded the 5-benzoyl-2-methyl-4-nitro-1-(phenylmethyl)-1*H*-imidazole (**12**).

Rather than pursue the *N*-benzyl series of compounds, we investigated the *t*-Boc group as a potentially more



useful (readily removable) protecting group for the imidazole nitrogen. Reaction of 4-bromo-2-methyl-5-nitro-1*H*-imidazole (**5**) with di-*t*-butyl dicarbonate in pyridine gave, in high yield, a single isomer which was determined to have structure **15** by x-ray analysis. With the lithium salts of α-aryl-4-morpholineacetonitriles, the *N*-*t*-Boc derivative **15** gave products **16** in moderate to good yields (Table I). Deprotection of the masked carbonyl by acid hydrolysis was accomplished by heating with copper sulfate in aqueous methanol. These conditions [13,14,15,16] resulted in deprotection of the carbonyl group and loss of the *N*-*t*-Boc group to give derivatives **17** (Table II). Other hydrolysis conditions, such as dilute hydrochloric acid or aqueous acetic acid, failed to give cleanly the products **17** (Ar = Ph).

Several conditions are critical in these reactions. Generation of the lithium salts of α-aryl-4-morpholineacetonitriles can be conveniently carried out with butyllithium at -78° (rather than using LDA) provided the butyllithium is added slowly to keep the internal temperature of the mixture below -70°. In large scale runs (30-50 g) the yields of **16** (Ar = Ph) decreased dramatically in the absence of strict temperature control (probably due to the addition of butyllithium to the nitrile function. Better yields of **16** (Ar = Ph) are also obtained by slow addition of the lithium salt **13** (in THF at -78°) to a solution or suspension of **15** in THF at -78°C. Addition of *N*-*t*-Boc-4-nitro-5-bromoimidazole **15** to anion **13** may result in the anion attacking the *t*-Boc group. Evidence for this possibility was observed in the reaction of the *N*-*t*-Boc 4,5-dichloroimidazole **21** with anion **13**. The major product isolated (>50%) was **22** from acylation of the carbanion **13**.

Reduction of the nitro group in derivatives **17** (Ar = Ph, 3-CF_3Ph) with hydrogen and 10% palladium on car-

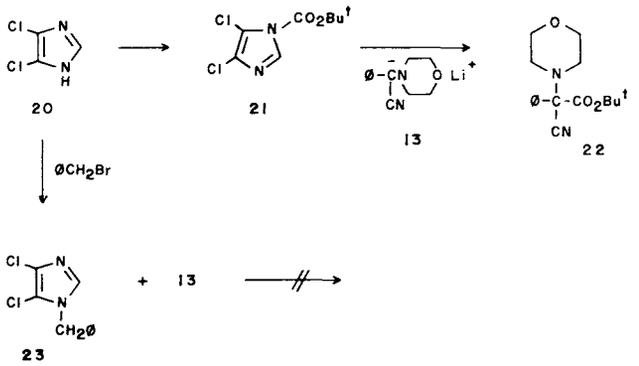
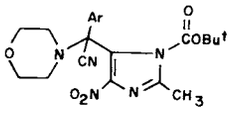


Table 1

1,1-Dimethylethyl 5- [(Aryl)-cyano-4-morpholinylmethyl]-2-methyl-4-nitro-1*H*-imidazole-1-carboxylates [a]



Ar	Yield %	Crystallization Solvent	mp, °C	Formula	Calcd.	Found
Ph	60	EtOAc-hexane	140-142	$C_{21}H_{25}N_5O_5$	C 59.0	C 58.7
					H 5.9	H 5.9
					N 16.4	N 16.4
3-CF_3-Ph	85	Et_2O-hexane	140-143	$C_{22}H_{24}F_3N_5O_5$	C 53.3	C 53.3
					H 4.9	H 4.8
					N 14.1	N 14.3
					F 11.5	F 11.4
3-CH_3-Ph	45	Et_2O-hexane	120 sinters 126-137 dec	$C_{22}H_{27}N_5O_5$	C 59.8	C 59.0
					H 6.2	H 6.0
					N 15.9	N 15.8
4-Cl-Ph	66	Et_2O-hexane	136-139	$C_{21}H_{24}ClN_5O_5$	C 54.6	C 54.6
					H 5.2	H 5.1
					N 15.2	N 15.0
					Cl 7.7	Cl 7.9
2-Cl-Ph	57	CH_2Cl_2-hexane	94 sinters 105-120 dec	$C_{21}H_{24}ClN_5O_5$	C 54.6	C 54.9
					H 5.2	H 5.3
					N 15.2	N 15.2
					Cl 7.7	Cl 7.7
3-Thienyl-	24	Et_2O-hexane	138 dec	$C_{19}H_{23}N_5O_5S$	C 52.6	C 52.6
					H 5.4	H 5.3
					N 16.2	N 6.1
					S 7.4	S 7.4

[a] All compounds were prepared according to procedure II in Experimental.

bon gave good yields of **18** and **19**. Reduction of **17** (Ar = Ph) with Raney nickel as catalyst gave **18** in 69% yield.

Attempts to displace chloride from 4,5-dichloro-1-(phenylmethyl)-1*H*-imidazole (**23**), prepared from 4,5-dichloroimidazole [17], with anion **13** (THF, -78°) failed, and more vigorous conditions were not investigated. This *N*-benzyl derivative **23** should be less reactive than the *N*-*t*-Boc derivative **21**; however, as discussed earlier, anion **13** attacks the *N*-*t*-Boc group of **21** preferentially.

In summary, we have extended the reactions of masked carbonyl anions to synthesize 4-aroyl-5-nitro-1*H*-imidazoles. Reduction of the nitro group then provides a route to 4-aroyl-5-amino-1*H*-imidazoles.

EXPERIMENTAL

All melting points were taken on a Mel-Temp® apparatus and are not corrected. Samples for analysis were dried *in vacuo* over Drierite® at 70° for 16-25 hours. ^1H NMR spectra were determined with a Varian FT 80 spectrometer and ^{13}C nmr were determined with a Nicolet NT 300WB spectrometer. Chemical shifts (δ) are in ppm relative to internal tetramethylsilane. Solvents were removed under reduced pressure by the use of a rotary evaporator. Magnesol® is the trade name for hydrous magnesium silicate.

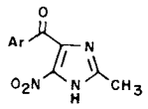
5-Bromo-2-methyl-4-nitro-1-(phenylmethyl)-1*H*-imidazole (**6**) and 4-Bromo-2-methyl-5-nitro-1-(phenylmethyl)-1*H*-imidazole (**7**).

A mixture of 1.13 g (5.5 mmoles) of 4-bromo-2-methyl-5-nitroimidazole (**5**), 1.2 g of *N*,*N*-diisopropylethylamine, 1.02 g (6.0 mmoles) of benzyl bromide in 30 ml of dioxane was stirred at room temperature for 18 hours. The mixture was concentrated under vacuum, the residue partitioned between dichloromethane and cold dilute hydrochloric acid. The organic layer was separated, washed with cold 1*N* sodium hydroxide, water, dried (sodium sulfate) and the solvent removed. The residual yellow oil was triturated with hexane to give 1.3 g (80%) of white crystals. Thin layer chromatography (silica gel) with dichloromethane as solvent showed two spots. Silica gel chromatography (dichloromethane) gave 0.37 of oil (front running component) which was crystallized from dichloromethane-hexane to afford 0.20 g of **7** as white crystals; ^1H nmr (deuteriochloroform): δ 2.50 (s, 3, CH_3), 5.58 (s, 2, -CH_2-), 6.90-7.20 (m, 2, Ph), 7.20-7.50 (m, 3, Ph), mp 102-105°. The slower moving component (0.61 g) was crystallized from dichloromethane-hexane to give 0.4 g of **6** as white crystals, mp 160-162°; ^1H nmr (deuteriochloroform): δ 2.43 (s, 3, CH_3), 5.28 (s, 2, -CH_2-), 6.95-7.20 (m, 2, Ph) 7.25-7.48 (m, 3, Ph). On larger scale runs (22.6 g, 0.11 mole), the higher melting isomer could be crystallized directly from the mixture with dichloromethane-hexane to give 13.2 g (41%) of **6** as white crystals, mp 160-162°. Chromatography of the mother liquors then afforded **7**.

Anal. **Calcd. for** $C_{11}H_{10}BrN_3O_2$ (Isomer **6**): C, 44.6; H, 3.4; N, 14.2; Br, 27.0. Found: C, 44.5; H, 3.4; N, 14.0; Br, 27.1. (Isomer **7**) Found: C, 44.8; H, 3.5; N, 14.2; Br, 27.0.

Table II

(2-Methyl-5-nitro-1*H*-imidazol-4-yl)(aryl)methanones

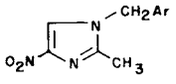


Ar	Yield %	Crystallization Solvent	mp, °C	Formula	Calcd.	Found
Ph	58 [a]	EtOAc-hexane	237-240	$C_{11}H_9N_3O_3$	C 57.1	56.8
					H 3.9	4.0
					N 18.2	18.1
3-CF_3-Ph	46 [b]	CH_3OH	239-241	$C_{12}H_8F_3N_3O_3$	C 48.2	48.0
					H 2.7	2.5
					N 14.0	14.0
					F 19.0	19.0
3-CH_3-Ph	55 [b]	CH_2Cl_2-CH_3OH-hexane	223-225	$C_{12}H_{11}N_3O_3$	C 58.8	58.7
					H 4.5	4.5
					N 17.1	17.0
4-Cl-Ph	48 [b]	CH_2Cl_2-CH_3OH-hexane	219-221	$C_{11}H_8ClN_3O_3$	C 49.7	49.7
					H 3.0	3.0
					N 15.8	15.8
					Cl 13.4	13.2
2-Cl-Ph	44 [b]	CH_3OH	198-200	$C_{11}H_8ClN_3O_3$	C 49.7	49.8
					H 3.0	2.9
					N 15.8	15.6
					Cl 13.4	13.4
3-Thienyl	40 [b]	CH_2Cl_2-hexane	235-237	$C_9H_7N_3O_3S$	C 45.6	45.3
					H 3.0	2.9
					N 17.7	17.7
					S 13.5	13.5

[a] Procedure III (A) in the Experimental. [b] Procedure III (B) in the Experimental.

Table III

1-(Arylmethyl)-2-methyl-4-nitro-1*H*-imidazoles [a]



Ar	Yield	Crystallization Solvent	mp, °C	Formula	Calcd.	Found
Ph	84	Et_2O-hexane	104-105	$C_{11}H_{11}N_3O_2$	C 60.8	60.8
					H 5.1	5.2
					N 19.4	19.3
4-F-Ph	77	CH_2Cl_2-hexane	107-109	$C_{11}H_{10}FN_3O_2$	C 56.2	56.3
					H 4.3	4.3
					N 17.9	18.0
					F 8.1	8.1
4-NO_2Ph	69	CH_2Cl_2-hexane	177-179	$C_{11}H_{10}N_4O_4$	C 50.4	50.3
					H 3.8	3.7
					N 21.4	21.3

[a] All compounds prepared according to procedure I in the Experimental.

Procedure I. 2-Methyl-4-nitro-1-(phenylmethyl)-1*H*-imidazole (**9**).

A mixture of 2.10 g (16.5 mmoles) of 2-methyl-5-nitroimidazole (**8**), 3.06 g (18.0 mmoles) of benzyl bromide, 3.0 g (21.7 mmoles) of potassium carbonate and 25 ml of dry *N,N*-dimethylformamide was stirred at room temperature for 18 hours and then poured onto crushed ice. The mixture was extracted with dichloromethane and the extracts washed with cold 1 *N* sodium hydroxide and water, dried (sodium sulfate) and the solvent removed. Trituration of the residual yellow oil with ether-hexane gave 3.0 g (84%) of off-white crystals, mp 100-103°. Recrystallization of a sample from dichloromethane-ether gave off-white crystals, mp 104-105°; ^{1}H nmr (deuteriochloroform): δ 2.40 (s, 3, CH_3), 5.14 (s, 2, -CH_2-), 7.05-7.5 (m, 5, Ph), 7.66 (s, 1, C_5-H); ^{13}C nmr (deuteriochloroform): δ (ppm) 12.81 (2-CH_3), 49.73 (-CH_2-), 122.43 (C_5), 145.02 (C_2), 145.39 (C_4); intensity of C_2/C_4 peak (2.45).

Anal. Calcd. for $C_{11}H_{11}N_3O_2$: C, 60.8; H, 5.1; N, 19.4. Found: C, 60.8; H, 5.2; N, 19.3.

5-Bromo-2-methyl-4-nitro-1-(phenylmethyl)-1*H*-imidazole (**6**).

A mixture of 1.08 g (5 mmoles) of **9**, 25 ml of acetic acid, 2 ml of dichloromethane and 1.25 g (7.8 mmoles) of bromine was heated on a steam bath for 75 hours. Cooling and scratching flask gave crystals which were filtered off and washed with hexane to give 1.0 g (68%) of **6** as white crystals, mp 156-161° (identical by ^{1}H nmr with an authentic sample). Recrystallization from dichloromethane-methanol-hexane gave white crystals, mp 159-161°.

5-(Cyano-4-morpholinylphenylmethyl)-2-methyl-4-nitro-1-(phenylmethyl)-1*H*-imidazole (**11**).

To a solution under argon of 1.21 g (6 mmoles) of α-phenyl-4-morpholineacetonitrile (**10**) in 50 ml of tetrahydrofuran chilled to -78° (dry ice-acetone) was added (dropwise) 5 ml of 1.55*M* butyllithium in hexane. To this chilled solution (after standing ½ hour) was added dropwise a solution of 1.48 g (5 mmoles) of **6** in 30 ml of dry THF. The mixture was stirred for 4 hours at -78° and then allowed to warm to room temperature and stand 8 hours. Several drops of acetic acid were added, followed by the addition of water. The mixture was extracted with dichloromethane and the extracts dried (Na_2SO_4), treated with activated carbon and concentrated to give 2.6 g of a yellow gum. Trituration with ether-hexane gave 1.63 g (78%) of cream colored crystals, mp 136-137°C. Recrystallization from ether-CH_2Cl_2 gave cream colored crystals, mp 149-150°C; ^{1}H NMR ($CDCl_3$) δ 2.15 (s, 3, CH_3), 2.35-2.65 (m, 4, -CH_2OCH_2-), 3.5-3.84 (m, 4, -CH_2N-CH_2-), 5.55 (s, 2, -CH_2-), 6.45-7.85 (m, 10, Ph). Further crystallization from acetone-hexane gave crystals mp 145-146°.

Anal. Calcd. for $C_{23}H_{23}N_5O_3$: C, 66.2; H, 5.6; N, 16.8. Found: C, 65.9; H, 5.5; N, 16.9.

4-(Cyano-4-morpholinylphenylmethyl)-2-methyl-5-nitro-1-(phenylmethyl)-1*H*-imidazole (**14**).

To a solution under argon of 1.21 g (6 mmoles) of α-phenyl-4-morpholineacetonitrile (**10**) in 50 ml of THF chilled to -78° was added (dropwise) 5 ml of 1.55 *M* butylithium in hexane. To this chilled solution (after standing 1 hour) was added dropwise (*via* needle under argon) a solution of 1.48 g (5 mmoles) of **7** in 30 ml of THF. The mixture was stirred at -78° for 4 hours and then allowed to warm to room temperature and stand 8 hours. Several drops of acetic acid were added and the mixture was concentrated under vacuum. The residue was partitioned between water and dichloromethane. The organic layer was separated, dried (sodium sulfate) and the solvent removed to give 2.0 g of yellow glass; (nmr spectrum identical with purified sample). Trituration with ether-hexane gave 1.3 g (62%) of solid which was crystallized from dichloromethane-ether-hexane to give 1.0 g (48%) of yellow crystals, mp 173-175°; ^{1}H nmr (deuteriochloroform): δ 2.50 (s, 3, CH_3), 2.45-3.0 (m, 4, -CH_2OCH_2-), 3.5-3.95 (m, 4, -CH_2N-CH_2-), 5.44 (s, 2, -CH_2-), 6.8-7.85 (m, 10, Ph).

Anal. Calcd. for $C_{23}H_{23}N_5O_3$: C, 66.2; H, 5.6; N, 16.8. Found: C, 65.8; N, 5.6; N, 16.8.

(2-Methyl-4-nitro-1-(phenylmethyl)-1*H*-imidazol-5-yl)phenylmethanone (**12**).

A mixture of 0.26 g (0.6 mmoles) of **11**, 6 ml of 0.1 *M* copper sulfate and 18 ml of methanol was heated on a steam bath for 18 hours. The mixture was diluted with water and extensively extracted with dichloromethane. The extracts were washed with water, dried (sodium sulfate) and concentrated to give 0.14 g (73%) of yellow gum (^{1}H nmr identical with pure material) which crystallized on standing. Chromatography on silica gel with hexane-acetone (7:3) as solvent gave product which was crystallized from hexane containing several drops of dichloromethane to afford 0.12 g (62%) of white crystals, mp 137°.

Anal. Calcd. for $C_{18}H_{15}N_3O_3$: C, 67.3; H, 4.7; N, 13.1. Found: C, 67.4; H, 4.7; N, 13.1.

1,1-Dimethylethyl 5-bromo-2-methyl-4-nitro-1*H*-imidazole-1-carboxylate (**15**).

A. To a solution of 2.06 g (0.01 mole) of **5** in 5 ml of pyridine was added 5.46 g (0.025 mole) of di-*t*-butyl dicarbonate. After 30 minutes at room temperature, the solution was diluted with hexane and filtered to give 2.9 g (95%) of yellow crystals, mp sinters 95°, melts 235°. Recrystallization from hexane gave 2.0 g (65%) of white crystals, mp sinters 109°, melts 269°; ^{1}H nmr (deuteriochloroform): δ 1.70 (s, 9, *t*-Bu), 2.63 (s, 3, CH_3).

Anal. Calcd. for $C_9H_{12}BrN_3O_4$: C, 35.3; H, 4.0; N, 13.7; Br, 26.1. Found: C, 35.5; H, 3.9; N, 13.8; Br, 26.1.

B. A suspension of 13.33 g (0.055 mole) of **5**, 12.0 g (0.093 mole) of *N,N*-diisopropylthylamine, 16.0 g (0.073 mole) of di-*t*-butyl dicarbonate, 1.0 g of 4-dimethylaminopyridine in 100 ml of dioxane was stirred at 22° for 18 hours. The mixture was concentrated under vacuum and the residue partitioned between 1*N* sodium hydroxide and dichloromethane. The organic was separated, washed with cold dilute hydrochloric acid, dried (sodium sulfate), and filtered through a short pad of hydrous magnesium silicate. The filtrate was concentrated to give 10.85 g of solid which was recrystallized from dichloromethane-hexane to give 9.2 g (55%) of off-white crystals, mp 265-268°.

Procedure II.

(A). 1,1-Dimethylethyl 5-(cyano-4-morpholinylphenylmethyl)-2-methyl-4-nitro-1*H*-imidazole-1-carboxylate (**16**, Ar = Ph).

A solution of 16.2 g (0.08 mole) of α-phenyl-4-morpholineacetonitrile (**10**) in 125 ml of dry tetrahydrofuran was cooled to -78° (dry ice-acetone) and 56.3 ml (0.09 mole) of 1.6 *M* butyllithium in hexane was added dropwise over 1 hour (internal temperature of reaction mixture kept below -70°). This solution was added to a stirred slurry under argon of 21.7 g (0.071 mole) of **15** in 200 ml of THF which had been cooled to -78° (dry ice-acetone). The addition was carried out dropwise over 2.5 hours while the internal temperature of the mixture was kept below -72°. The cooling bath was removed and, after one hour, the solution was diluted with dichloromethane. Several drops of acetic acid were added followed by addition of water. The organic layer was separated, and the aqeuous layer extracted with dichloromethane. The combined organic layer and extracts were dried (sodium sulfate) and concentrated to give 35 g of dark oil. Addition of ether and crystallization gave 18.3 g (60%) of cream crystals, mp 140-143°. Recrystallization of a sample from ethyl acetate-hexane gave cream crystals, mp 140-142°; ^{1}H nmr (deuteriochloroform): δ 1.58 (s, 9, *t*-Bu), 2.5 (s, 3, CH_3), 2.3-2.65 (m, 4, -CH_2-O-CH_2-), 3.5-3.75 (t, 4-CH_2NCH_2-), 7.4-7.95 (m, 5, Ph).

(B). 1,1-Dimethylethyl5-[(Cyano-4-morpholinyl)-(3-trifluoromethylphenyl)-methyl]-2-methyl-4-nitro-1*H*-imidazole-1-carboxylate (**16**, Ar = 3-CF_3Ph).

A solution of 10.8 g (0.04 mole) of α-(3-trifluoromethylphenyl)-4-morpholineacetonitrile in 125 ml of THF under argon was chilled to -78° and over 30 minutes was added 28 ml (0.045 mole) of 1.6 *M* butyllithium in hexane. After stirring for 2 hours at -78°, this solution was added dropwise (over 2.5 hours) to a chilled (-78°) slurry (under argon) of **15** in 150 ml of THF. The cooling bath was removed and after warming to room temperature (*ca* one hour), the mixture was diluted with dichloromethane and several drops of acetic acid were added. Cold water was added, the organic layer separated, and the aqueous layer extracted with dichloromethane. The organic layer and extracts were combined, dried (sodium

sulfate) and the solvent removed. The dark yellow oil (16.5 g) began to crystallize, ether was added and, after standing (16 hours), the mixture was filtered to give 14.8 g (85%) of cream colored crystals, mp 132-138°. Recrystallization of a sample by dissolving in small amount of dichloromethane, adding ether-hexane (1:1) and concentrating on a steam bath gave crystals, mp 140-143° (sinters 135°); ^{1}H nmr (deuteriochloroform): δ 1.58 (s, 9, *t*-Bu), 2.50 (s, 3, CH_3), 2.15-2.65 (m, 4, $-CH_2O-CH_2-$), 3.4-3.75 (m, 4, $-CH_2-NCH_2-$), 7.5-8.2 (m, 4, aromatic).

Procedure III.

(A). (2-Methyl-5-nitro-1*H*-imidazol-4-yl)phenylmethanone (**17**, Ar = Ph).

To a solution of 19.2 g (0.045 mole) of **16** (Ar = Ph) in 1.3 liters of methanol was added 450 ml of aqueous 0.1 *M* cupric sulfate. The mixture was heated (steam bath) for two hours, diluted with water, saturated brine and dichloromethane added. On stirring, solid separated and the mixture was filtered to give 6.7 g of brown solid. Trituration with hexane-ether gave 6.0 g (58%) of yellow crystals, mp 232-236°. A sample was recrystallized (2x) from ethyl acetate-hexane to give off-white crystals, mp 237-240°; ^{1}H nmr (deuteriochloroform): δ 2.48 (s, 3, CH_3), 7.44-8.0 (m, 5, Ph).

(B). (2-Methyl-5-nitro-1*H*-imidazol-4-yl)(3-trifluoromethylphenyl)methanone (**17**, Ar = 3-CF_3Ph).

A mixture of 7.49 g (0.03 mole) of cupric sulfate pentahydrate in 264 ml of water was diluted with 828 ml of methanol. The solution was stirred and heated on a steam bath while 12.0 g (0.024 mole) of **16** (Ar = 3-CF_3Ph) was added in small portions. The mixture was stirred and heated for two hours, filtered and the filter cake washed extensively with methanol. The filtrate was extracted with ethyl acetate (for other examples, dichloromethane was used). The extract was dired (sodium sulfate) and the solvent removed to give 3.3 g (46%) of tan crystals, mp 234-236°. Recrystallization from methanol with the aid of activated carbon gave 2.7 g (38%) of white crystals, mp 239-241°; ^{1}H nmr (deuteriochloroform): δ 2.50 (s, 3, CH_3), 7.47-8.15, (m, 4, aromatic).

(5-Amino-2-methyl-1*H*-imidazol-4-yl)phenylmethanone (**18**).

(A). A mixture of 3.0 g (0.013 mole) of **17** (Ar = Ph), 100 ml of ethanol and *ca* 300 mg of 10% Pd/C was shaken in a Parr hydrogenator under 30 lb of hydrogen for 5 hours. The mixture was filtered through a diatomaceous earth, the filtrate cake washed with ethanol and the filtrate concentrated to an oil. Addition of methanol and crystallization gave 2.0 g (76% of yellow crystals, mp 109-112° (Lit [3] mp 110-112°C); ^{1}H nmr (deuteriochloroform): δ 2.25 (s, 3, CH_3), 2.40 (s, broad, 2, NH_2), 7.25-7.9 (m, 5, Ph).

Anal. Calcd. for $C_{11}H_{11}N_3O$: C, 65.7; H, 5.5; N, 20.9. Found: C, 65.4; H, 5.5; N, 21.0.

(B). A mixture of 0.5 g (2.16 mmoles) of **17** (Ar = Ph), 2.0 g of Raney nickel, 1.5 g of anhydrous sodium sulfate and 50 ml of ethyl acetate was shaken in a Parr hydrogenator under 30 lb of hydrogen pressure for 18 hours. The mixture was filtered through diatomaceous earth, the filter cake washed with ethyl acetate and the filtrate concentrated. The residue crystallized and was recrystallized from methanol to give 0.30 g (69%) of cream colored crystals, mp 111-115°.

(5-Amino-2-methyl-1*H*-imidazol-4-yl)(3-trifluoromethylphenyl)methanone (**19**) and Hydrochloride of **19**.

(A). A mixture of 0.5 g (1.7 mmoles) of **17** (Ar = 3-CF_3Ph) in 50 ml of methanol and a catalytic amount of 10% Pd/C was shaken in a Parr hydrogenator under 30 lb of hydrogen pressure for four hours. The mixture was filtered through diatomaceous earth, the filter cake washed with methanol and the filtrate concentrated.

The residue was one spot by tlc (silica gel) with ethyl acetate-methanol (9:1) as solvent. The residue was dissolved in dichloromethane, anhydrous hydrochloric acid added, followed by addition of ether. Filtration gave 0.2 g (38%) of off-white crystals, mp 208-210°; ^{1}H nmr (d_6-DMSO): δ 2.50 (s, 3, CH_3), 7.5-8.25 (m, 4, aromatic), 13.1 (s − broad, NH).

Anal. Calcd. for $C_{12}H_{10}F_3N_3O\cdot HCl$: C, 47.2; H, 3.6; N, 13.8; F, 18.7; Cl, 11.6. Found: C, 46.8; H, 3.5; N, 14.0; F, 18.5; Cl, 11.6.

(B). A 1.45 g (4.85 mmoles) sample of **17** (Ar = 3-CF_3Ph) was hydrogenated as described above to give 1.3 g of a yellow gum. The gum in 2-propanol was treated with activated carbon, filtered and the filtrate diluted with ether. Chilling gave 1.0 g (76%) of yellow crystals, mp 80-84°; ^{1}H nmr (deuteriochloroform): δ 2.35 (s, 3, CH_3), 5.45 (s − broad, 2, NH), 7.55-8.10, (m, 4, aromatic), ethyl ether solvate 2.2 (t), 3.42 (q).

Anal. Calcd. for $C_{12}H_{10}F_3N_3O.Et_2O$: C, 55.97; H, 5.87; N, 12.24; F, 16.60. Found: C, 54.56; H, 5.47; N, 12.32; F, 16.95.

1,1-Dimethylethyl 4,5-Dichloro-1*H*-imidazole-1-carboxylate (**21**).

To a solution of 13.7 g (0.10 mole) of 4,5-dichloro-1*H*-imidazole (**20**) [17] in 100 ml of pyridine was added 21.8 g (0.1 mole) of di-*t*-butyl dicarbonate. After 10 minutes, the mixture was poured into water and extracted with dichloromethane. The extracts were washed with cold dilute hydrochloric acid, dried (sodium sulfate) and then filtered through a pad of hydrous magnesium silicate. Concentration of the filtrate gave an oil which crystallized to give 23.5 g (99%) of off-white crystals, mp 50-54°. Recrystallization of a sample from dichloromethane-hexane gave white crystals, mp 54-55°.

Anal. Calcd for $C_8H_{10}Cl_2N_2O_2$: C, 40.5; H, 4.3; N, 11.8; Cl, 29.9. Found: C, 40.2; H, 4.1; N, 11.6; Cl 29.0.

4,5-Dichloro-1-(phenylmethyl)-1*H*-imidazole (**23**).

A mixture of 7.53 g (55 mmoles) of 4,5-dichloroimidazole (**20**) 12.0 g (93 mmoles) of *N,N*-diisopropylethylamine, 10.2 g (60 mmoles) of benzyl bromide in 150 ml of dioxane was stirred at room temperature for 6 days and the volatile components removed under vacuum. The residue was partitioned between dichloromethane and 0.1*N* hydrochloric acid, the organic layer separated, washed with cold hydroxide and dried (sodium sulfate). The organic layer was filtered through a pad of hydrous magnesium silicate and the filtrate concentrated to give 14.0 g of yellow oil which was crystallized from ether-hexane to afford 9.9 g of off-white crystals, mp 56-59°. Recrystallization of a sample from ether-hexane gave white crystals, mp 58-60°.

Anal. Calcd. for $C_{10}H_6Cl_2N_2$: C, 53.4; H, 2.7; N, 12.4; Cl, 31.5. Found: C, 53.4; H, 3.5; N, 12.2; Cl, 31.1.

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