

A NOVEL SYNTHESIS OF 2,4,5-TRIARYLIMIDAZOLES

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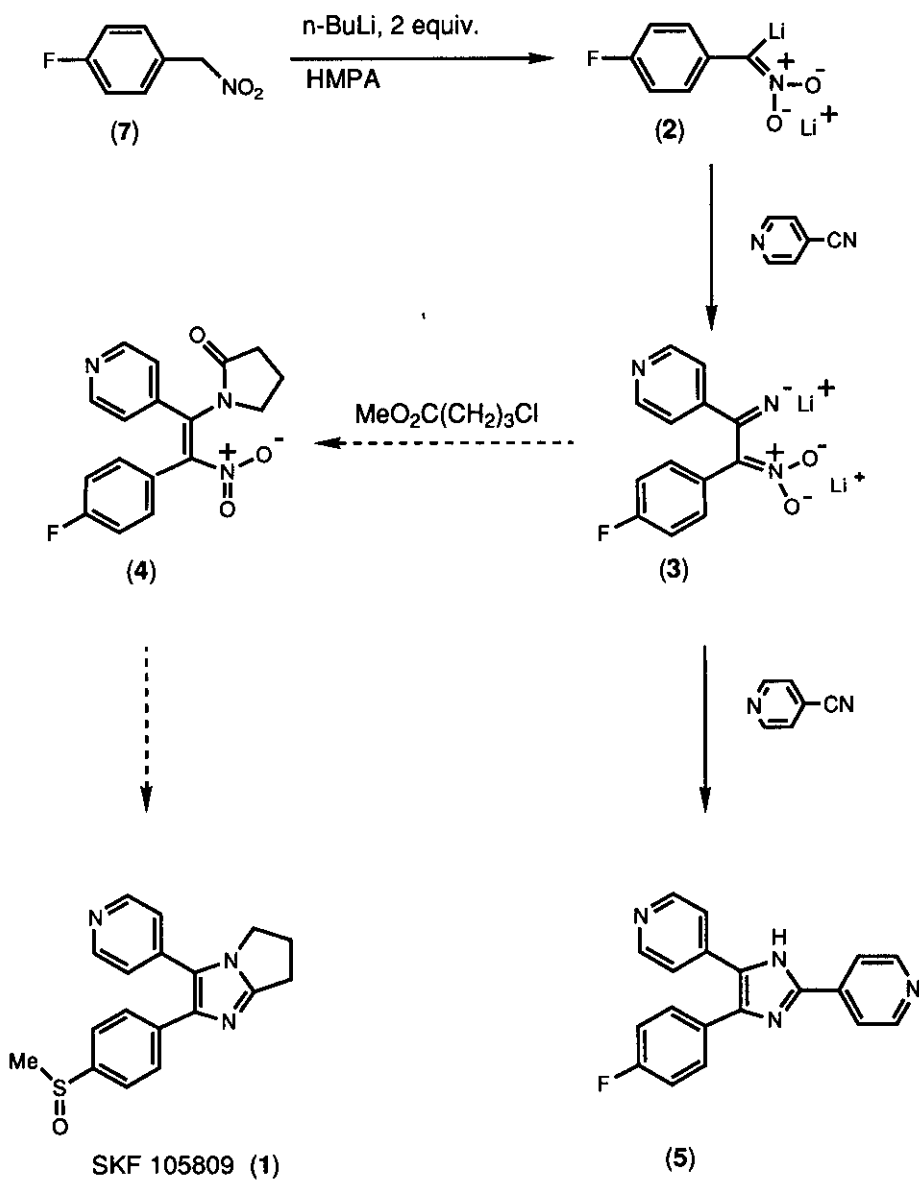
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Abstract - Aryl cyanides were reacted with α , α -dilithioarylnitromethanes to form 2,4,5-triarylimidazoles in good yield. An unusual cyclisation - elimination mechanism is proposed for this reaction.

As part of a research program to discover new synthetic routes to therapeutic agents of interest to SmithKline Beecham we investigated new approaches to 4,5-diarylimidazoles e.g. SK&F 105809 (**1**) (Scheme 1). Diarylimidazoles of this type have been shown to be inhibitors of enzymes in both the leukotriene and prostaglandin biosynthetic pathways and are therefore candidates as drugs for the treatment of inflammatory diseases e.g. asthma and arthritis.¹

This paper describes a novel and rapid method to prepare 2,4,5-triarylimidazoles which was discovered during an unsuccessful approach to SK&F 105809 (see Scheme 1). We hoped to extend some methodology originally described by Seebach *et al.* where he prepared dilithionitronate species of type (**2**) by treatment of nitroalkanes with two equivalents of *n*-butyllithium in THF in the presence of HMPA.² These dianions alkylate at carbon and are significantly more reactive towards aldehydes, ketones and esters than their monolithio analogues.³ Although the reaction with aryl cyanides was not disclosed we considered that this impressive enhancement in reactivity would cause the dianion to react with 4-cyanopyridine to give imine dianion (**3**) (Scheme 1). We hoped that this intermediate could be quenched with methyl 4-chlorobutyrate to give pyrrolidinone (**4**), an advanced intermediate to SK&F 105809 (**1**). In fact when the reaction of nitronate dianion (**2**) with one equivalent of 4-cyanopyridine was attempted and then quenched with methyl 4-chlorobutyrate the only product isolated was triarylimidazole (**5**) in 35% yield. Clearly the intermediate (**3**) had reacted further with the aryl nitrile to give triarylimidazole (**5**) *via* a hitherto unknown cyclisation - elimination process.

Unsymmetrical 2,4,5-triarylimidazoles of this type are quite difficult to prepare using known literature methods.⁴ Many⁵ have been made using the Davidson⁶ modification of the Radziszewski⁷ imidazole synthesis but unfortunately the unsymmetrical benzil starting materials required for this reaction are difficult to make. 2,4-Diphenyl-5-(3-pyridyl)imidazole was prepared in 47% yield by the reaction of 1,3-diphenyl-2-azaallyllithium with 3-cyanopyridine.⁸ Other unsymmetrical triarylimidazoles have been made by the treatment of 2,4,6-triaryl-4H-1,3,5-thiadiazines with triethylamine.⁹



Scheme 1

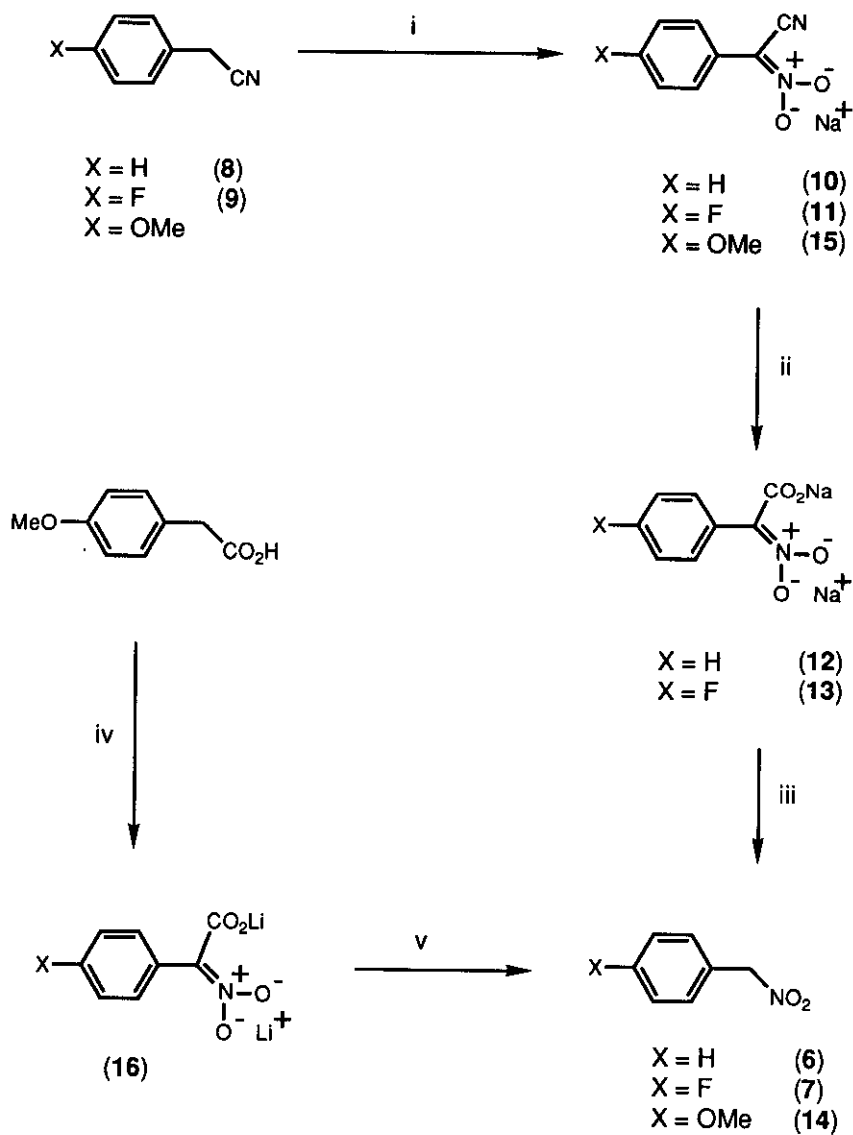
The novel reaction between nitrodianion (2) and 4-cyanopyridine therefore provides a direct and valuable alternative synthesis of triarylimidazole (5). The scope of this reaction using aryl nitromethanes and aryl cyanides with different substituents was subsequently explored and the results are detailed below.

Arylnitromethanes (6) and (7) were readily prepared using the method of Black and Babers.¹⁰ Hence, nitration of benzyl cyanides (8) and (9) with methyl nitrate in ethanolic sodium ethoxide gave (10) and (11) in 76% and 100% yields, respectively. Hydrolysis of the nitrile group with boiling aqueous sodium hydroxide gave salts (12) and (13) which were decarboxylated with concentrated hydrochloric acid. Thus (6) and (7) were obtained in 55% and 70% yields from benzyl cyanides (8) and (9), respectively. A modification of this procedure was necessary to prepare (14) as attempts to hydrolyse nitrile (15) with boiling aqueous sodium hydroxide resulted in formation of a complex mixture of products. Treatment of *p*-methoxyphenylacetic acid with three equivalents of LDA followed by methyl nitrate afforded nitrocarboxylate (16). This was decarboxylated using aqueous acetic acid to give (14) in 87% overall yield (Scheme 2).

The α,α -dilithio *p*-fluorophenyl nitronate anion (2) was formed from (7) in THF (50 ml per gram of substrate) and HMPA (3.0 equivalents) using 2.1 equivalents of *n*-butyllithium at -80°C . Treatment of this solution with 2.1 equivalents of benzonitrile afforded imidazole (17) in 66% yield. Addition of HMPA after the butyllithium only gave a yield of 43%. Use of more than 2.1 equivalents of butyllithium or benzonitrile did not improve yields further. Use of higher concentrations caused a lowering of the yield. No further optimisation was attempted. The preferred conditions thus found for imidazole (17) were subsequently used for the synthesis of imidazoles (18) - (25) (Scheme 3). Best yields were obtained with *p*-methoxyphenyl nitromethane (14); this presumably reflects the enhanced nucleophilicity of the dianion due to the presence of the electron donating 4-methoxy substituent. Conversely only a small difference was observed between the chemistry of phenyl nitromethane (6) and the electron deficient *p*-fluorophenyl nitromethane (7). Of the three electrophiles, benzonitrile gave the best results and 4-methoxybenzonitrile the poorest. Although 4-trifluoromethylbenzonitrile would be expected to be the most reactive nitrile, lower yields were obtained for the corresponding imidazoles. This could be due to the occurrence of competing alkylation side reactions but this was not investigated.

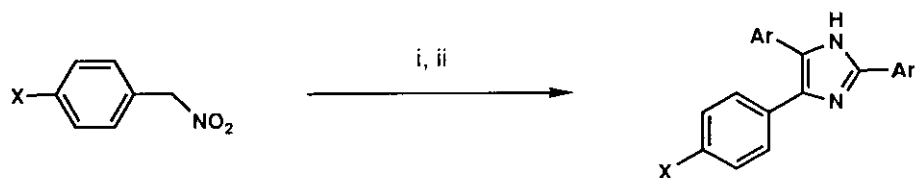
The proposed mechanism for imidazole formation is shown in Scheme 4. Presumably once intermediate (27) has added to a second mole of nitrile, the newly formed intermediate (29) can cyclise to (30) and then eliminate nitrite to give the appropriately substituted imidazole. Thus the nitro group serves a dual role as activating and leaving group.

A further extension of this methodology was investigated in an attempt to prepare triarylimidazoles bearing three different aryl groups. Thus two different aryl cyanides were added stepwise to a THF-HMPA solution of dianion (2) (Scheme 5). The major product isolated was indeed the expected 4-fluorophenyl-5-phenyl-2-(4-pyridyl)imidazole (26). In addition imidazole (17) was isolated in 13% yield and a trace of imidazole (5) was obtained. The formation of (17) in fact gave us some indication of the reactivity of the initial addition product (27) since this intermediate clearly reacted with further benzonitrile even though only one equivalent was used (see Scheme 4). This suggests that benzonitrile adds at a similar rate to (27) as it does to (28). This small difference in reactivity limited the observed yield of (26) to a modest 31%. However, potentially the method does represent a very direct route to triarylimidazoles with three different aryl groups.



Reagents: i) NaOEt, EtOH, MeONO₂; ii) NaOH (aq.), reflux; iii) HCl (aq.) (conc.), -5°C - 0°C; iv) LDA, 3.0 equiv., -70°C, MeONO₂; v) AcOH, H₂O.

Scheme 2

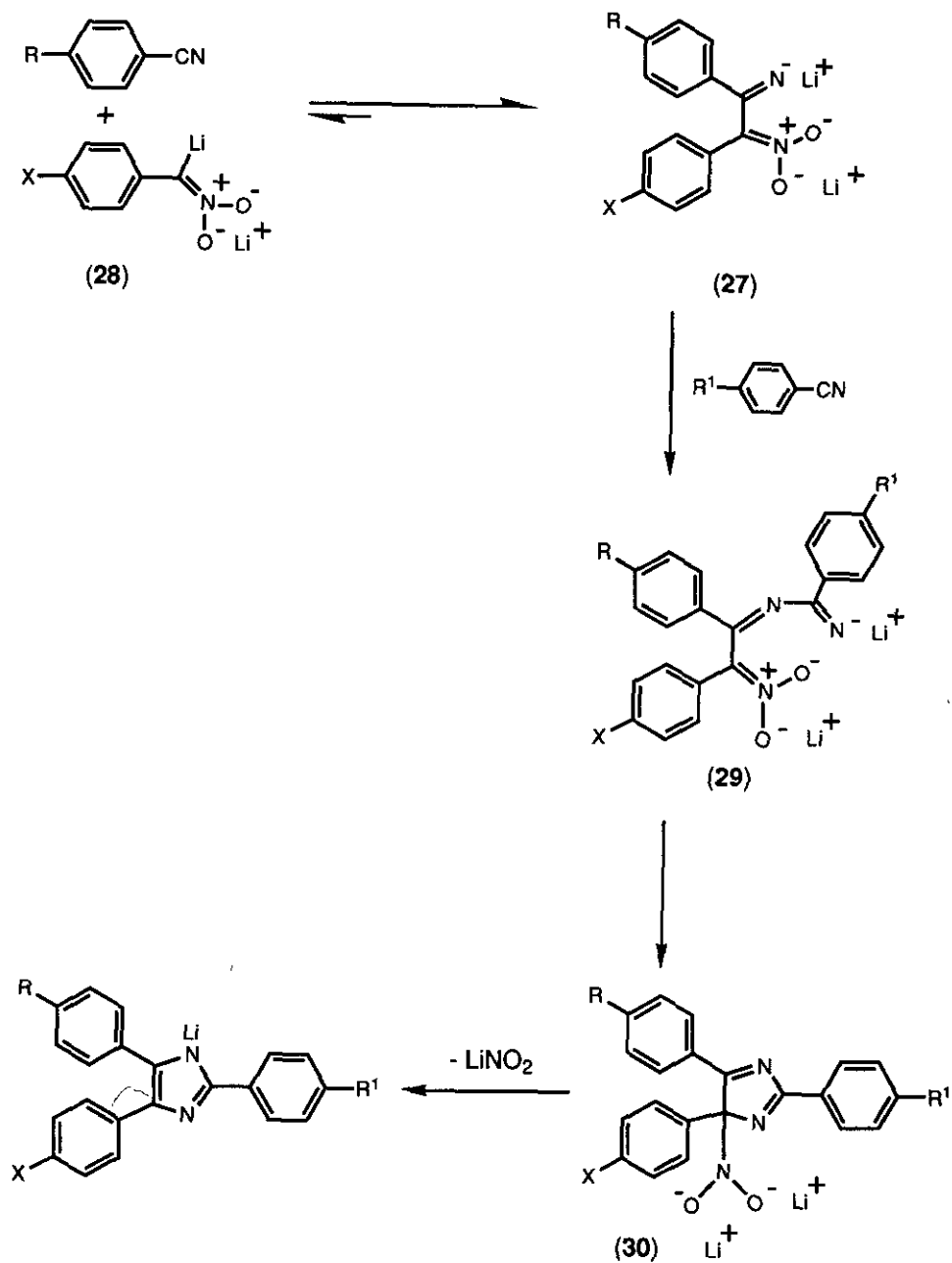


Reagents: i) n-BuLi, 2.1 equiv., -80°C - -20°C, THF, HMPA; ii) ArCN, 2.1 equiv., -70°C - room temperature, 18 h.

X	Ar		Yield (%)
F		(17)	67
F		(18)	41 ^a
F		(19)	10
H		(20)	64
H		(21)	39 ^a
H		(22)	- ^b
OMe		(23)	60
OMe		(24)	62
OMe		(25)	15

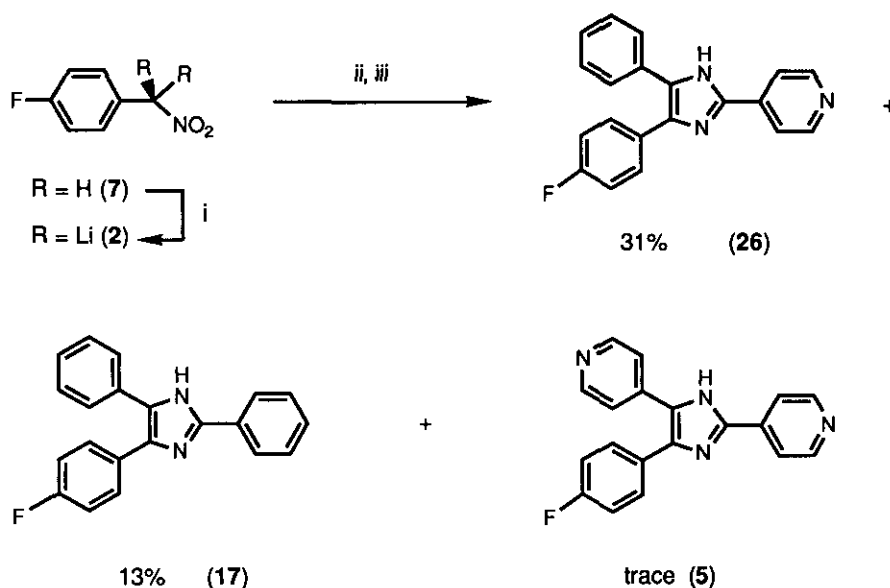
a. Solution assay of the crude product by hplc. b. Although a characteristic fluorescent product was detected by tlc a pure sample was not isolated.

Scheme 3



Scheme 4

In conclusion the examples illustrated show that this novel chemistry provides an opportunity to prepare a large number of 2,4,5-triarylimidazoles in a rapid and efficient way. The chemistry works especially well when the aromatic ring of the arylnitromethane dianion contains electron donating substituents.



Reagents: i) *n*-BuLi, 2.1 equiv., THF, HMPA, -70°C - -10°C , 60 min; ii) benzonitrile, 1.0 equiv., -80°C - -20°C , 40 min, -20°C - room temperature, 20 min; iii) 4-cyanopyridine, 1.0 equiv., -80°C - room temperature, 16 h

Scheme 5

EXPERIMENTAL

Melting points were measured with a Buchi MP apparatus and are uncorrected. Elemental analyses were performed using a Control Equipment Corporation 440 instrument. Ir spectra were recorded on a Perkin Elmer 781 spectrophotometer. 270 MHz ^1H Nmr spectra were recorded on a Jeol JNM-GX 270 FT spectrometer. 400 MHz ^1H nmr and ^{13}C nmr spectra were recorded on a Jeol GSX-400 spectrometer. Chemical shifts are reported as parts per million downfield shift from TMS as internal standard. Mass spectra and accurate mass measurements were recorded on a VG 70-250 - SEQ mass spectrometer. Hplc was performed using a Technicol Kromasil 5C18 column with methanol : water - 9:1 as eluant; flow rate 1.0 ml/min; uv-detection at 226 nm. Response factors were calculated for imidazoles (18) and (21) using reference standards of high purity.

Phenylnitromethane (6) and 4-Fluorophenylnitromethane (7).

These compounds were prepared according to the literature method.¹⁰

4-Methoxyphenylnitromethane (14)

To a solution of diisopropylamine (101 ml, 0.723 mol) in THF (400 ml) was added n-butyllithium (289 ml of a 2.5 M solution in hexane, 0.723 mol) at -20°C. The solution was stirred for 30 min at -20°C before it was cooled to -60 - -70°C and 4-methoxyphenylacetic acid (40.0 g, 0.241 mol) was added in 80 ml THF. The resultant bright yellow cloudy mixture was stirred at -30 - -40°C for 45 min before it was cooled to -60°C and methyl nitrate (22.3 ml, 0.338 mol) was added. The yellow colour was quenched and a white precipitate formed. This suspension was stirred for 45 min at -30 - -40°C and then for 2 h at room temperature. The solid was filtered under nitrogen and washed with ether (2 x 200 ml). Hence lithium 2-(4-methoxyphenyl)-2-nitro-2-lithioacetate (16) was obtained; δ_{H} (270 MHz, DMSO-d₆, 40°C) 3.70 (3H, s), 6.75 (2H, d, $J = 8.0$ Hz) and 7.50 (2H, d, $J = 8.0$ Hz). The solid was dissolved in water (1.0 l) and treated with acetic acid (20.0 ml). The resultant cloudy solution was extracted with ether (2 x 400 ml). The aqueous layer was treated with further acetic acid (6.0 ml) and extracted with further ether (2 x 400 ml). This process was repeated until all the product had been extracted. The combined organic extracts were dried (Na₂CO₃) and concentrated to leave a clear orange liquid. Hence 4-methoxyphenylnitromethane (14) (35.5 g, 89%) was obtained; bp 100°C/0.5 mm; ν_{max} (thin film) 2950, 1600, 1540, 1500, 1360, 1300, 1240, 1170 and 1010 cm⁻¹; δ_{H} (270 MHz, CDCl₃) 3.95 (3H, s), 5.45 (2H, s) 7.05 (2H, d, $J = 8.0$ Hz) and 7.50 (2H, d, $J = 8.0$ Hz).

General procedure for 2,4,5-triarylimidazoles

To a solution of aryl nitromethane (10.0 mmol) in THF (50 ml per gram of substrate) was added HMPA (5.2 ml, 30.0 mmol). The solution was cooled to -80°C before n-butyllithium (8.4 ml of a 2.5 M solution in hexane, 21.0 mmol) was added. The resultant solution was stirred for 100 min and was allowed to warm gradually to -20°C over this time. The reaction mixture was then re-cooled to -70°C before the aryl cyanide (21.0 mmol) was added in THF (2 ml per gram of substrate). The reaction was allowed to warm to room temperature and was stirred for 18 h before it was worked up.

4-(4-Fluorophenyl)-2,5-diphenylimidazole (17)

The THF solution was concentrated *in vacuo* and the residue was chromatographed on silica gel using ether : hexane - 2:8 - 3:7 as eluant. Hence the title compound was obtained as a white crystalline solid (1.36 g, 67%); mp 256 - 257°C (from ether-hexane). Anal. Calcd for C₂₁H₁₅N₂F: C, 80.23; H, 4.81; N, 8.91 : M^+ 314.1219. Found; C, 79.79; H, 4.85; N, 8.69; M^+ , 314.1212. ν_{max} (KBr) 3430, 3000, 1520, 1480, 1410 and 1210 cm⁻¹; δ_{H} (CDCl₃, 400 MHz) 7.03 (2H, t, $J = 8$ Hz), 7.30 - 7.60 (10H, m) and 7.92 (2H, d, $J = 8$ Hz); δ_{C} (CDCl₃, 100.40 MHz) 114.6, 114.8, 125.2, 126.8, 127.8, 127.9, 128.0, 128.1, 129.3, 129.4, 130.0, 146.0 and 161.4 ($^1J_{\text{CF}} = 244$ Hz); m/z 314 (M^+) and 183.

4-(4-Fluorophenyl)-2,5-di(4-trifluoromethylphenyl)imidazole (18)

Solution assay of crude product in the reaction mixture by hplc = 41%. The THF solution was concentrated *in vacuo* and the residue taken up in water (400 ml). The aqueous mixture was extracted with ether (3 x 200 ml) and the combined organic layers were dried (Na₂SO₄) and concentrated. The brown oily residue was chromatographed on silica gel using ether : hexane - 3 : 7 as eluant. Hence the crude product was obtained as an orange solid (1.16 g, 37%), and this was recrystallised; mp 216 - 218°C (from ether-hexane); HRms calcd for

$C_{23}H_{13}N_2F_7$: 450.0967, found 450.0976. ν_{max} (KBr) 3450, 3010, 1640, 1500, 1160, 1130 and 1070 cm^{-1} ; δ_H (400 MHz, DMSO- d_6 , 40°C) 7.20 (0.6H, t, $J = 8$ Hz), 7.35 (1.4H, t, $J = 8$ Hz), 7.60 (2H, m), 7.65 - 7.80 (4H, m), 7.85 (2H, d, $J = 8$ Hz) and 8.30 (2H, d, $J = 8$ Hz); m/z 450 (M^+), 251, 183, 157 and 107. Hplc retention time = 6.71 min.

4-(4-Fluorophenyl)-2,5-di(4-methoxyphenyl)imidazole (19)

The THF solution was concentrated *in vacuo* and the residue was chromatographed on silica gel using ether : hexane - 1:1 as eluant to give the title compound (510 mg, 10%); mp 178 - 180°C (from ether-hexane); HRms calcd for $C_{23}H_{19}N_2O_2F$: 374.1431, found 374.1429. ν_{max} (KBr) 3500, 2900, 1600, 1500, 1250, 1050 cm^{-1} ; δ_H (400 MHz, DMSO, 40°C) 3.80 (3H, s), 3.82 (3H, s), 6.98 (2H, d, $J = 8$ Hz), 7.06 (2H, d, $J = 8$ Hz), 7.20 (2H, t, $J = 8$ Hz), 7.43 (2H, d, $J = 8$ Hz), 7.55 (2H, dd, $J = 8$ Hz and $J = 8$ Hz) and 8.01 (2H, d, $J = 8$ Hz); δ_C (67.80 MHz, $CDCl_3$) 55.2, 113.9, 114.0, 115.0, 115.3, 121.8, 123.8, 127.3, 128.7, 129.3, 129.5, 129.6, 130.8, 131.6, 145.9, 159.0, 160.2 and 161.9 ($C-F$, $^1J_{CF} = 247$ Hz); m/z 374 (M^+) and 359.

2,4,5-Triphenylimidazole (20)

The THF solution was concentrated *in vacuo* and the residue was chromatographed on silica gel using ether : hexane : triethylamine - 3.0 : 7.0 : 0.1 followed by methanol as eluant. The methanol fraction was concentrated *in vacuo* and the residue was treated with water (ca. 200 ml). The product which precipitated was filtered, washed with water, (ca. 20 ml) and was dried *in vacuo* to give the title compound (1.42 g, 64%); mp 272 - 273°C (from ether - hexane), (lit.,⁹ 275 - 277°C), δ_H (DMSO- d_6 , 40°C, 270 MHz) 7.20 - 7.65 (13H, m) and 8.10 (2H, d, $J = 7$ Hz).

4-Phenyl-2,5-di(4-trifluoromethylphenyl)imidazole (21)

Solution assay of the crude product in the reaction mixture by hplc = 39%. The THF solution was concentrated *in vacuo* and the residue was chromatographed on silica gel using ether : hexane - 3 : 7 as eluant. Hence the crude product was obtained as an oily solid (1.34 g). This was recrystallised from ether-hexane to give an analytically pure sample; mp 235 - 237°C (from ether-hexane); Anal. Calcd for $C_{23}H_{14}N_2F_6$: C, 63.89; H, 3.26; N, 6.48; M^+ , 432.1061. Found; C, 63.83; H, 3.41; N, 6.44; M^+ , 432.1024. ν_{max} (KBr) 3440, 3060, 1620 and 1340 cm^{-1} ; δ_H (400 MHz, DMSO- d_6 , 90°C) 7.35 - 7.50 (3H, m) 7.55 (2H, d, $J = 7$ Hz), 7.65 (2H, d, $J = 8$ Hz), 7.75 (2H, d, $J = 8$ Hz), 7.80 (2H, d, $J = 8$ Hz) and 8.30 (2H, d, $J = 8$ Hz); δ_C (67.80 MHz, $CDCl_3$); 123.6 (F_3C^- , $^1J_{CF} = 272$ Hz), 123.7 (F_3C^- , $^1J_{CF} = 270$ Hz), 124.5, 124.8, 125.2, 127.1, 127.4, 128.0, 129.0 ($-C-CF_3$, $^2J_{CCF}$, 32 Hz), 131.2, 132.4, 133.1, 133.7, 137.0 and 144.6; m/z 432 (M^+), 233 and 165. Hplc retention time = 6.77 min.

4-(4-Methoxyphenyl)-2,5-diphenylimidazole (23)

The THF solution was concentrated *in vacuo*. The residue was then taken up in water (200 ml) and extracted with ether (2 x 200 ml). The combined organic extracts were dried (Na_2SO_4) and concentrated to leave a thick orange oil. The oil was chromatographed on silica gel using ether : hexane - 1:1 as eluant to give the title compound (1.78 g, 60%) as a white powder; mp 225-226°C (from ether-hexane). (lit.,⁴ 224 - 226°C).

4-(4-Methoxyphenyl)-2,5-di(4-trifluoromethylphenyl)imidazole (24)

The THF solution was diluted with ether (250 ml) and washed with water (2 x 100 ml). The aqueous layer was acidified to pH 4 with acetic acid and then extracted with ether (2 x 200 ml). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to leave a thick red oil. This oil was chromatographed on silica gel

using ether : hexane : triethylamine - 40 : 59 : 1 as eluant to give the title compound (2.69 g, 62%) as a pale yellow solid; mp 207 - 209°C (from ether-hexane). Anal. Calcd for $C_{24}H_{16}N_2OF_6$: C, 62.34; H, 3.49; N, 6.06. Found ; C, 62.32; H, 3.53; N, 6.16; ν_{max} (KBr) 3450, 3000, 1610, 1580, 1320, and 1130 cm^{-1} ; δ_H (400 MHz, DMSO- d_6 , 40°C) 3.75 (0.7H, s), 3.80 (2.3H, s), 6.95 (0.5H, d, $J = 8$ Hz), 7.05 (1.5H, d, $J = 8$ Hz), 7.50 (2H, d, $J = 8$ Hz), 7.65 (1.5H, d, $J = 8$ Hz), 7.75 (0.5H, d, $J = 8$ Hz), 7.80 (2H, d, $J = 8$ Hz), 7.85 (2H, d, $J = 8$ Hz), 8.30 (2H, d, $J = 8$ Hz) and 13.00 (1H, s); δ_C (CDCl₃, 100.4 MHz) 55.1, 114.1, 123.1, 123.8 (F₃C - $^1J_{CF} = 272$ Hz), 124.0 (F₃C - $^1J_{CF} = 270$ Hz), 125.1, 125.4, 125.8, 127.7, 128.8 (F₃C - C, $^2J_{CCF} = 33$ Hz), 130.2 (F₃C - C, $^2J_{CCF} = 33$ Hz), 132.6, 136.4, 145.6 and 159.5; m/z 462 (M^+).

2,4,5-Tri(4-methoxyphenyl)imidazole (25)

The THF solution was diluted with ether (200 ml) and acidified with acetic acid. This mixture was then washed with water (2 x 300 ml) and the combined aqueous layers were extracted with ether (200 ml). The combined organic extracts were dried (Na₂SO₄) and concentrated *in vacuo* to afford a red oil which was chromatographed on silica gel using ether : hexane - 7 : 3 as eluant. Hence the title compound (563 mg, 15%) was obtained as a yellow crystalline solid; mp 88 - 94°C (from ether-hexane). (lit.,¹¹ 82°C. lit.,⁴ 183 - 185°C).

2-(4-Pyridyl)-4-(4-fluorophenyl)-5-phenylimidazole (26)

To a solution of 4-fluorophenylnitromethane (7) (500 mg, 3.22 mmol) in THF (25 ml) was added HMPA (1.68 ml, 9.67 mmol). The solution was cooled to -70°C and *n*-butyllithium (2.71 ml of a 2.5 M solution in hexane, 6.78 mmol) was then added. The resultant solution was stirred at -70 - -10°C for 60 min before it was cooled to -80°C and benzonitrile (329 μ l, 3.23 mmol) was then added. The reaction mixture was stirred at -80 - -20°C for 40 min and then at -20°C - room temperature for 20 min. After this time the temperature was lowered to -80°C and 4-cyanopyridine (335 mg, 3.22 mmol) in THF (3.0 ml) was added. The reaction mixture was allowed to warm to room temperature and was stirred for 16 h. After this period the reaction mixture was concentrated to dryness *in vacuo* and the residue was chromatographed on silica gel using ethyl acetate as eluant. Hence: (a) 4-(4-fluorophenyl)-2,5-diphenylimidazole (17) (130 mg, 13%) was obtained as a fluffy white crystalline solid which had identical spectroscopic properties to the sample previously prepared; (b) 2-(4-pyridyl)-4-(4-fluorophenyl)-5-phenylimidazole (26) (310 mg, 31%) was obtained as an off white crystalline powder; mp 291°C (decomp.) (from dichloromethane) ; HRms calcd for $C_{20}H_{14}N_3F$: 315.1172, found 315.1171. ν_{max} (nujol mull) 1670, 1610, 1510, 1220, 1150 and 1130 cm^{-1} ; δ_H (400 MHz, CD₃ OD) 6.95 (2H, t, $J = 8$ Hz), 7.27 (3H, m), 7.40 (4H, m), 7.88 (2H, d, $J = 5$ Hz) and 8.50 (2H, d, $J = 5$ Hz) ; δ_C (100.4 MHz, CDCl₃) 114.5, 114.8, 119.3, 127.2, 127.5, 127.8, 129.5, 137.2, 142.7, 148.8 and 161.8 (F-C, $^1J_{CF} = 261$ Hz); m/z 315 (M^+) ; and (c) 2,5-di(4-pyridyl)-4-(4-fluorophenyl)imidazole (5) (trace) was obtained as a mixture with HMPA ; δ_H (270 MHz, CDCl₃) 7.10 (2H, t, $J = 8$ Hz), 7.50 - 7.60 (4H, m), 8.20 (2H, d, $J = 6$ Hz) 8.50 (2H, d, $J = 5$ Hz) and 8.65 (2H, d, $J = 6$ Hz); m/z 316 (M^+).

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Received, 12th October, 1993