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Synthesis of the 8-Aminoquinoline Antimalarial 5-Fluoroprimaquine

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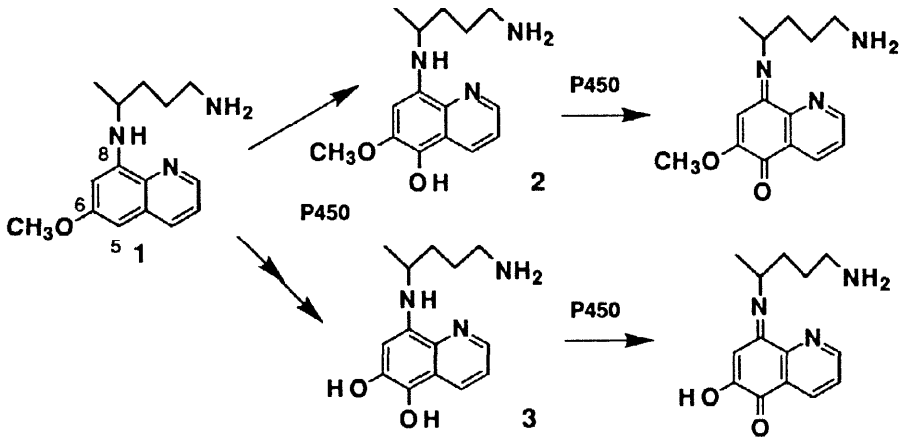
Abstract: Several approaches to the synthesis of 5-fluoro-6-methoxy-8-nitroquinoline **5**, the key intermediate required for the synthesis of 5-fluoroprimaquine, were investigated. In one approach, 5-chloro-6-methoxy-8-nitroquinoline was synthesised and treated with a variety of nucleophilic sources of fluoride. In another approach, electrophilic substitution of 6-methoxy-8-nitroquinoline with (N-fluorosulfonimide, NFSI) was investigated. The final approach to **5** involved a modified Skraup reaction of 5-fluoro-4-methoxy-2-nitroaniline which gave the required intermediate in 30% yield.

Introduction

Primaquine, **1**, an 8-aminoquinoline antimalarial, plays a unique role in the treatment of malaria in that it is the only drug capable of eliminating the persistent liver forms of the parasite responsible for relapses in *Plasmodium vivax* and *Plasmodium ovale* infections.[1] The clinical usefulness of primaquine is limited, however, by its toxic side-effects which include methaemoglobinaemia and in certain circumstances haemolytic anaemia.[2-7] The observed side-effects of primaquine are generally accepted to result from oxidative metabolism to a number of potentially toxic metabolites (Scheme 1). In particular ring-hydroxylated metabolites such as 5-hydroxy primaquine **2** and 5,6-dihydroxyprimaquine **3** have been shown to be significantly more effective than primaquine in oxidising haemoglobin and depleting reduced glutathione (GSH) in human erythrocytes.[6-8]



Scheme 1. Oxidative Metabolism of Primaquine to Potentially Toxic Quinonimine Metabolites

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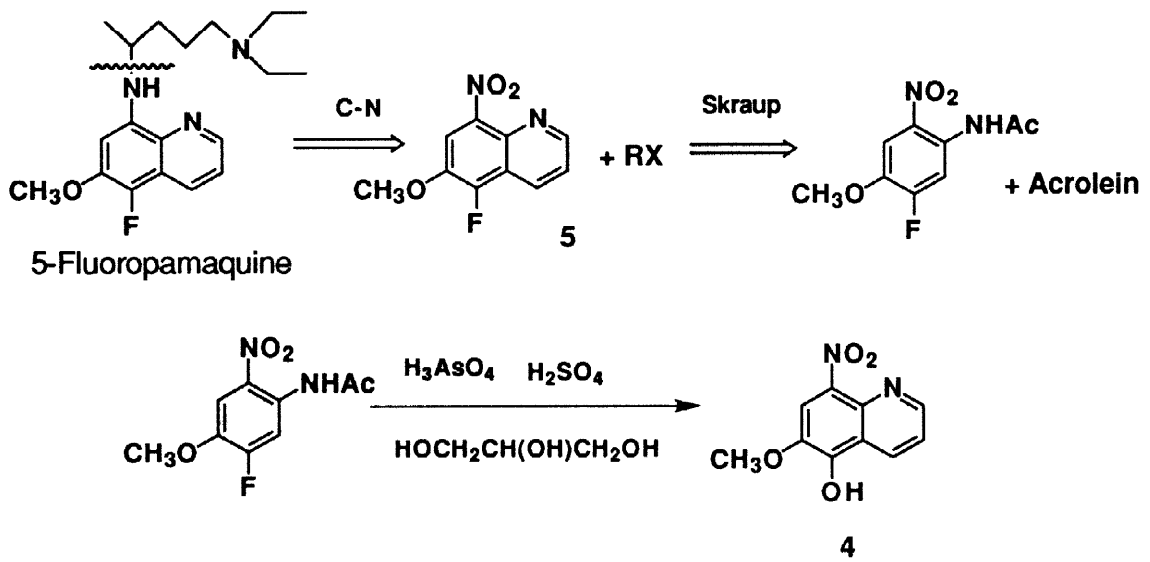
These latter effects can be attributed to the corresponding quinonimine derivatives [9,10] (Scheme 1) which together with hydrogen peroxide are the main products of the fast autoxidation undergone by these metabolites at neutral pH.[11] Since 5-hydroxylation results in the formation of potentially toxic quinonimine metabolites, we have attempted to block this pathway by introduction of fluorine at this position. Previous approaches [12] to the related 5-fluoropamaquine failed, since the key intermediate in this synthesis is 5-fluoro-6-methoxy-8-nitroquinoline **5**. Attempts to prepare this compound via the Skraup reaction of 5-fluoro-4-methoxy-2-nitroacetanilide gave 5-hydroxy-6-methoxy-8-nitroquinoline **4** (Scheme 2). The 8-nitro substituent activates the fluorine atom at position 5 towards nucleophilic displacement and, under the reaction conditions employed, almost complete replacement of the fluorine by hydroxyl occurs.

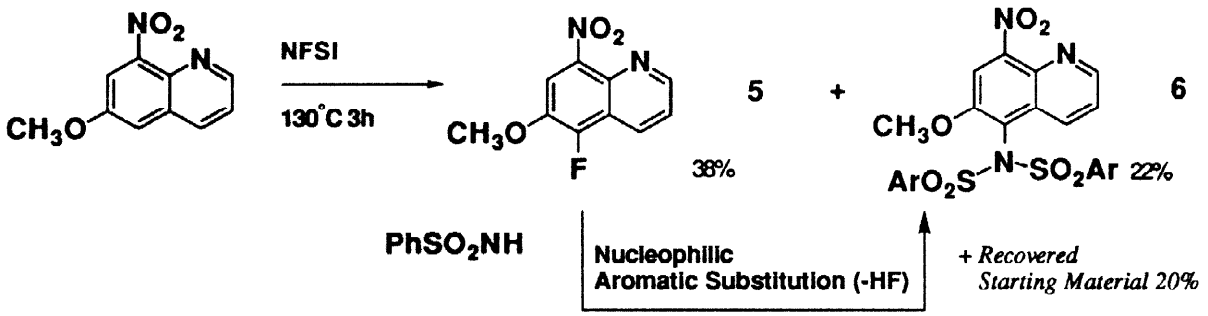


Scheme 2. Retrosynthetic Analysis of 5-Fluoropamaquine and attempted synthesis of 5-Fluoro-6-methoxy-8-nitroquinoline via the Skraup reaction

Results and Discussion

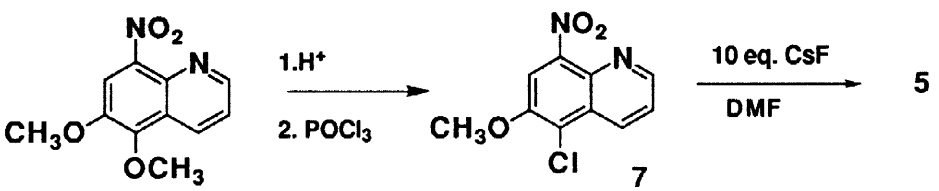
In this study, comparison of three approaches to the synthesis of the required intermediate 5-fluoro-6-methoxy-8-nitroquinoline **5** is made. It was envisaged that **5** would be readily accessible by electrophilic substitution of 6-methoxy-8-nitroquinoline with an appropriate fluorinating agent such as NFSI[13] or NFPT.[14,15] Reaction of 6-methoxy-8-nitroquinoline with NFPT in refluxing 1,1,2-trichloroethane resulted in the formation of polymeric tars with no evidence for product formation. However, treatment with 5 equivalents of NFSI at 130°C resulted in the formation of **5** in 38% yield (Scheme 3).

In addition to the required fluoroquinoline, the sulfonimide **6** (20%) was obtained. This product is proposed to have arisen by nucleophilic aromatic substitution of **5** with the side product dibenzene sulfonimide. In an independent experiment, **5** was transformed in high yield to the corresponding by product **6** in 70% yield.[16] Thus, it was apparent that formation of **5** was compromised by this unwanted side reaction and an alternative preparation was undertaken.



Scheme 3. Electrophilic fluorination of 6-Methoxy-8-Nitroquinoline with NFSI

Nucleophilic aromatic substitution of activated halogenobenzenes with alkali metal fluorides is an important route to fluorinated aromatics.[17] In particular, it has been shown that the chlorine atom in 4-chloronitrobenzene can be replaced routinely by fluorine by treatment with an alkali metal fluoride in refluxing solvents such as dimethylformamide (DMF), or dimethylsulfoxide (DMSO).[18] By analogy, the chlorine atom at the 5-position of 5-chloro-6-methoxy-8-nitroquinoline **7**[19] is activated and might be expected to undergo replacement by treatment with a suitable source of nucleophilic fluorine. The requisite chloroquinoline **7** was synthesised in two steps from 5,6-dimethoxy-8-nitroquinoline[20] and it was found that treatment with 10 equiv. cesium fluoride in DMF at 110°C led to a 33% conversion to the required fluoroquinoline (Scheme 4). Major drawbacks in this route were purification of the product and difficulties in scaling up the reaction to obtain suitable quantities for conversion into the required target molecule.



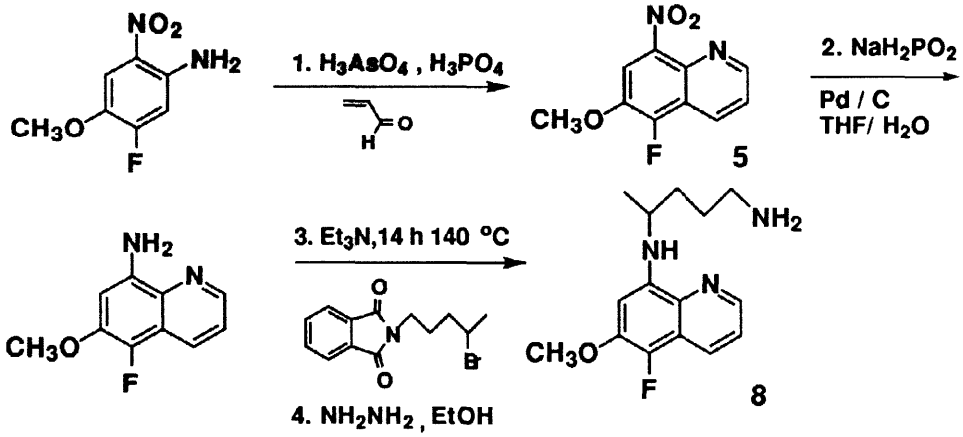
Scheme 4. Halex reaction of 5-Chloro-6-Methoxy-8-Nitroquinoline with Cesium Fluoride

Finally the Skraup reaction of 5-fluoro-4-methoxy-2-nitroaniline was reinvestigated. The conditions employed by Elderfield involved heating the reaction mixture at high temperatures in 98% sulfuric acid as described.[12] We decided to modify these conditions by employing the procedure of Yale and Bernstein[21] whereby 80% phosphoric acid, acrolein and arsenic acid are employed with a shorter reaction time and a lower temperature. Using these conditions a yield of 30% was obtained following purification by flash column chromatography.

This represents a significant improvement over the earlier procedure where only 5% of product was obtained following optimisation of reaction conditions. The major advantage of this method is that the reaction can be scaled up to multigram quantities.

The reaction sequence was completed as shown in Scheme 5. Reduction of the nitro group was performed in quantitative yield by using sodium hypophosphite with 10% palladium as catalyst. The amine was then

alkylated with 2-bromo-5-phthalidimidopentane to give phthaloyl protected primaquine in excellent yield. The synthesis was completed by removal of the phthalimide protecting group with hydrazine hydrate. The final product **8** was recrystallised from aqueous ethanol/phosphoric acid as the monophosphate.



Scheme 5. Synthesis of 5-Fluoroprimaquine

EXPERIMENTAL

General. ^{1}H NMR were recorded on a Bruker ACE 200 spectrometer operating at 200MHz. CDCl3 was used as the solvent. I.R. spectra are for nujol mulls. Mass spectra were recorded under electron impact at 70 meV on a VG Micromass 7070E instrument. Microanalyses were performed in the microanalytical laboratory at Liverpool University. Melting points were recorded on a Reichert hot stage apparatus and are uncorrected. Flash column chromatography was performed using Merck 9385 silica as the stationary phase.

5-Fluoro-6-methoxy-8-nitroquinoline (5)

(Preparation via Electrophilic Fluorination). 6-Methoxy-8-nitroquinoline (0.50 g, 2.45 mmol) and N-fluorobenzenesulfonimide (NFSI) (3.85 g, 0.012 mol) were heated at 130°C for 3 h. The reaction mixture was allowed to cool and was dissolved in 100 ml of dichloromethane. The mixture was washed with sodium thiosulfate (10 % solution, 100 ml), saturated sodium bicarbonate solution and then with water (3 x 75 ml). The organic layer was separated and dried ($MgSO_4$). Column chromatography using dichloromethane / petrol gave the required product as a yellow solid (0.20 g, 38 %), m.p. 155°C (lit.,[12] m.p. 156 °C); ^{1}H NMR, δ 9.02 (1H, dd, J_{H-H} = 3.85 Hz and 1.65 Hz, ArH), 8.45 (1H, dd, J_{H-H} = 8.80 Hz and 1.65 Hz, Ar-H), 8.04 (1H, d, J_{H-F} = 9.00 Hz, Ar-H), 7.57 (1H, dd, J_{H-H} = 8.80 Hz and 3.85 Hz, Ar-H), 4.11 (3H, s, -OCH_3); MS *m/z* 222 (M+, 100 %), 192 (56 %), 133 (33 %), 121 (28 %); HRMS *m/z* 222.04420, ($C_{10}H_7FN_2O_3$ requires 222.04412).

The other major product, a yellow solid, obtained from the column was identified as the dibenzene sulfonimide product **6** (0.107 g, 22 %) ^{1}H NMR, δ 8.91 (1H, dd, J_{H-H} = 4.12 Hz and 1.64 Hz, ArH), 7.5-8.0 (12H, m, 2 x C_6H_5, Ar-H), 7.35 (1H, dd, J_{H-H} = 8.52 Hz and 4.12 Hz, 3.60 (3H, s, OCH_3); MS *m/z* 499 (M^+, 100 %), 358 (46 %), 232 (28 %), 187 (41 %)

5,6-Dimethoxy-8-nitroquinoline

This compound was prepared by the modified Skraup reaction of 3,4-dimethoxy-6-nitroaniline as described by Elderfield.[20] The yield obtained was 70 %. ^{1}H NMR, δ 9.00 (1H, dd, J_{H-H} = 3.85 Hz and 1.65 Hz, ArH), 8.55 (1H, dd, J_{H-H} = 8.25 Hz and 1.65 Hz, Ar-H), 8.03 (1H, s, Ar-H), 7.51 (1H, dd, J_{H-H} = 8.25 Hz and J_{H-H} = 3.85 Hz, Ar-H), 4.13 (3H, s, -OCH_3), 4.07 (3H, s, -OCH_3); MS *m/z* 234 (M^+, 100 %), 204 (40 %), 102 (40 %); HRMS *m/z* 234.06420, ($C_{11}H_{10}N_2O_4$ requires 234.06406).

5-Chloro-6-methoxy-8-nitroquinoline (7)

This compound was prepared by acid-catalysed hydrolysis of 5,6-dimethoxy-8-nitroquinoline and treatment of the resultant 5-hydroxy-6-methoxy compound with phosphorus oxychloride as described by Fuson.[19] m.p. 204-205 °C (lit. m.p. 204 °C); ^{1}H NMR, δ 9.05 (1H, dd, J_{H-H} = 3.85 Hz and 1.10 Hz, ArH), 8.65 (1H, dd, J_{H-H} = 8.25 Hz and 1.65 Hz, Ar-H), 7.90 (1H, s, Ar-H), 7.62 (1H, dd, J_{H-H} = 8.25 Hz and J_{H-H} = 1.65 Hz, Ar-H), 4.07 (3H, s, OCH_3); MS *m/z* 238 (M^+, 100 %), 208 (44 %), 180 (32 %); HRMS *m/z* 238.01406, ($C_{11}H_{10}N_2O_4$ requires 238.01451).

3-Fluoro-4-methoxy-6-nitroaniline

3-Fluoro-4-methoxy-6-nitroacetanilide was prepared by nitration of 3-fluoro-4-methoxyacetanilide using the conditions of Fuson.[19] ^{1}H NMR, δ 8.70 (1H, d, J_{H-F} = 9.00 Hz, ArH), 7.85 (1H, d, J_{H-F} = 4.00 Hz, Ar-H), 3.95 (3H, s, OCH_3), 2.25 (3H, s, $NHCOCH_3$); MS *m/z* 228 (M^+, 20 %), 208 (44 %), 186 (100 %); HRMS *m/z* 228.05426, ($C_{11}H_{10}N_2O_4$ requires 228.05463). The amide function was hydrolysed using the conditions of Fuson[19] to give the amine which was used without further purification

5-Fluoro-6-methoxy-8-nitroquinoline (3)

Phosphoric acid (36 ml, 0.36 mol) and arsenic acid (14.00 g) were placed in a three necked flask. The temperature was brought to 100°C by external heating and 3-fluoro-4-methoxy-6-nitroaniline (7.00 g, 0.037 mol) was added. Acrolein (5 ml, 0.089 mol) was then added to keep the temperature at 100°C ± 2°C . The reaction was kept at 100°C for 25 min and was then poured onto water. The resulting solution was basified with ammonia solution and the dark brown solid filtered off. Chromatography on basic alumina using dichloromethane gave the pure product as a yellow solid (2.50 g, 30 %). The spectral data were identical to those obtained from the sample prepared by electrophilic fluorination.

4-Bromo-1-Phthalimidopentane (10)

This compound was prepared according to the procedure of Elderfield[20]; ^{1}H NMR, δ 7.84 (4H, m), 4.20 (1H, m), 3.76 (2H, m), 2.40 - 1.62 (7H, m,); IR (neat) 2920, 1770, 1710 and 705 cm-1; MS *m/z* 297 / 295 (M^+, 3 % / 3 %), 216 (46 %) 215 (13 %) 161 (15 %), 160 (100 %), 148 (14 %)

5-Fluoro-6-methoxy-8-aminoquinoline (8)

5-Fluoro-6-methoxy-8-nitroquinoline (1.00 g, 4.5 mmol) was dissolved in THF (10 ml) in a two necked flask and a solution of sodium hypophosphite (3.00 g, 34 mmol) in water (4 ml) was added followed by 10% Pd/C catalyst (0.70 g) in THF (3 ml). The mixture was stirred vigorously at room temperature under nitrogen for 10 min and then was filtered and washed with chloroform (5 ml). Sodium hydroxide solution (2M, 25 ml) was added to the filtrate and the mixture extracted with chloroform (3 x 30 ml). The combined chloroform extracts were washed with water (2 x 25 ml), dried ($MgSO_4$) and the solvent removed by rotary evaporation to give the pure amine (0.82, 96 % yield). The products of two reduction steps were combined and used without purification in the alkylation step.

5-Fluorophthaloyl Protected Primaquine

A mixture of 5-fluoro-6-methoxy-8-aminoquinoline (1.92 g, 10 mmol) and 1-phthalimido-4-bromopentane (3.9 g, 13 mmol) was heated to 150°C under argon with stirring in a three neck, round bottom flask fitted with a reflux condenser and dropping funnel. Triethylamine (1.75 ml, 13 mmol) was added in portions down the condenser over 1.5 h. After an additional 1.5 h at 150°C, 1-phthalimido-4-bromo-pentane (5.1 g, 17 mmol) was added followed by triethylamine (1.7 ml, 8.5 mmol) dropwise down the condenser over 1 h. Stirring under argon was continued for a further 2 h at 150°C then 1-phthalimido-4-bromopentane (0.95 g, 3.25 mmol) was added followed by triethylamine (0.5 ml, 3.6 mmol) dropwise down the condenser over 1h. Stirring was continued at 150°C for 2h until all the amine had reacted (tlc). The mixture was allowed to cool, diluted with acetone (50 ml) and filtered to remove triethylamine hydrobromide. Rotary evaporation of the filtrate gave a red-black oil. The residue was dissolved in chloroform (250 ml) and washed with water (3 x 75 ml). The chloroform extracts were dried ($MgSO_4$) and the solvent removed under reduced pressure. The product (yellow oil) was isolated using column chromatography (petroleum ether / dichloromethane 1:1 and then dichloromethane) (2.84 g, 70 %); ^{1}H NMR, δ 8.56 (1H, dd, $J_{H\text{-}H}$ = 4.40 Hz and 1.65 Hz, ArH), 8.19 (1H, dd, $J_{H\text{-}H}$ = 8.25 Hz and 1.65 Hz, Ar-H), 7.60-7.80 (5H, m, Ar-H (Phth), 7.36 (1H, dd, $J_{H\text{-}H}$ = 8.25 Hz and 4.40 Hz, Ar-H), 7.2 (1H, d, J = 2.74 Hz, Ar-H), 6.35 (1H, d, $J_{H\text{-}F}$ = 7.7 Hz), 4.02 (3H, s, OCH_3), 3.73 (2H, m, $C\underline{H}_2NPhth$), 1.40-1.90 (5H, m, $\underline{CHCH}_2\underline{CH}_2N$), 1.3 (3H, d, $J_{H\text{-}H}$ = 7 Hz, $C\underline{H}_3$-CH) ; IR (neat)

3390, 1770, 1710 and 718 cm-1; MS *m/z* 407 (M^+, 14 %), 219 (100 %), 204 (18 %) 160(23 %); HRMS *m/z* 407.16452, $C_{23}H_{22}FN_3O_3$ requires 407.16452).

5-Fluoroprimaquine (1a)

5-Fluoroprimaquine was prepared by hydrazinolysis of the 5-fluorophthaloyl primaquine by a modification of the procedure used by Elderfield.[20] 5-Fluorophthaloyl primaquine (2.44 g, 6 mmol) was dissolved in ethanol (50 ml) in a 100 ml two necked fitted with a reflux condenser. Hydrazine hydrate (1.0 g, 20 mmol) was added and the mixture refluxed with stirring for 6 h under nitrogen. The mixture was filtered to remove phthaloyl hydrazide (1.0 g, 100 %). The ethanol was removed by rotary evaporation and 30 % potassium hydroxide added to the residue. The mixture was extracted with warm ether (3 x 50 ml) and the combined ether extracts washed with water and then dried ($MgSO_4$). A solution of 90% orthophosphoric acid, (0.6 ml) in ethanol (10 ml), was added to a solution of the product in ether to give the product as an orange oil. The oil was crystallised from aqueous ethanol to give the monophosphate as a yellow solid (1.34 g, 60 %); ^{1}H NMR , δ 8.58 (1H, dd, J_{H-H} = 4.40 Hz and 1.65 Hz, ArH), 8.23 (1H, dd, J_{H-H} = 8.25 Hz and 1.65 Hz, Ar-H), 7.37 (1H, dd, J_{H-H} = 8.25 Hz and 4.40 Hz, Ar-H), 6.38 (1H, d, J_{H-F} = 7.70 Hz, Ar-H), 4.02 (3H, s, $-OCH_3$), 3.73 (2H, m, $C\underline{H}_2NH_2$), 1.40-1.90 (5H, m, $\underline{CH}_2\underline{CH}_2N$, $\underline{CH}NH$), 1.33 (3H, d, J_{H-H} = 7 Hz, $C\underline{H}_3$-CH); IR (neat) 1590 and 810, cm-1; MS *m/z* 277 (M^+, 14 %), 219 (100 %), 204 (23 %); HRMS *m/z* 277.15947, ($C_{15}H_{20}FN_3O$ requires 277.15903).

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16. The nitro compound **5**, (1 equivalent), was heated with dibenzenesulfonimide (1 equivalent), at 120°C for half an hour. The reaction mixture was allowed to cool and was then chromatographed on silica gel (dichloromethane/petrol, 1:1) to give the substitution **6** product in 70% yield.
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