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Regioselective *ortho* alkylation of nitro indole, carbazole, benzothiophene and benzofuran

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ABSTRACT

Substituted indoles, carbazoles, benzothiophenes and benzofurans are important motifs in the pharmaceutical industry. Herein we report a novel, regioselective method to introduce alkyl substituents into position *ortho* of nitro groups by the addition of a Grignard reagent followed by subsequent oxidation with DDQ.

Heterocyclic motifs such as indoles, benzothiophenes and benzofurans have long been of significant interest in the pharmaceutical industry. Drugs such as the PDE5 (phosphodiesterase type 5) inhibitor Tadalafil[1] and the SERM (selective oestrogen receptor modulator) Raloxifene[2] are representative examples which illustrate the importance of these heterocycles (Fig. 1).

As part of a drug discovery programme[3] we were interested in synthesising carbazoles containing specific alkyl groups (e.g., methyl) **1a** and **1b** and as such we decided to approach this via *ortho*-alkylation of the requisite nitrocarbazole. The *ortho* alkylation reaction is known in the literature,[4–6] however during this work unexpected regioselectivity was discovered when performing the methylation step on 9-isopropyl-3-nitrocarbazole **1** (Scheme 1) from which compound **1a** was exclusively isolated (confirmed by ^{1}H NMR and NOE studies). To the best of our knowledge there are no examples of this observed regioselectivity in heterocyclic systems. As it was believed to be a synthetically useful reaction for organic chemists, we sought to determine the scope of such selective alkylation reactions.

To rationalise the observed regioselectivity the likely transition states resulting from Grignard addition at either the 2- or 4-position (**1d** and **1c**, respectively) were considered. It was postulated that the observed selectivity arose due to the reaction progressing via favourable structure **1c**. Formation of **1d** would be disfavoured

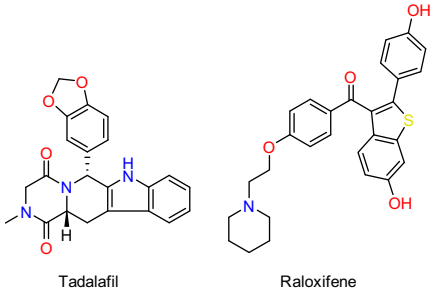
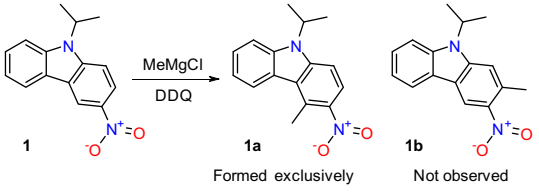


Figure 1. Structures of Tadalafil and Raloxifene.



Scheme 1. Initial observed selectivity in a Grignard addition reaction with carbazole **1**. Reagents and conditions: **1** (3.9 mmol), MeMgCl (5.9 mmol), THF (40 mL), −15 °C, 1 h, then DDQ (6.69 mmol), −10 °C to RT, 16 h, 68%, **1a** formed exclusively.[9]

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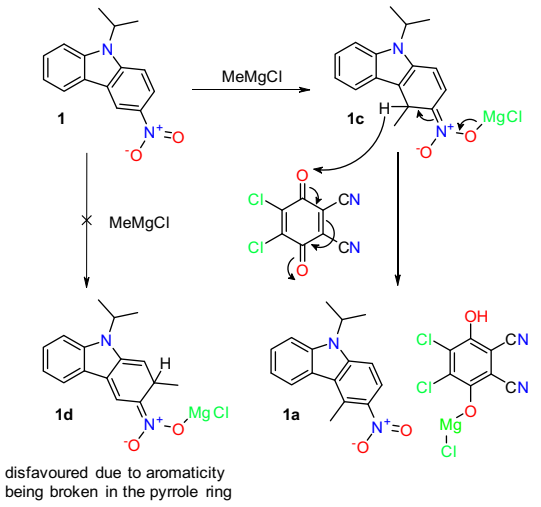
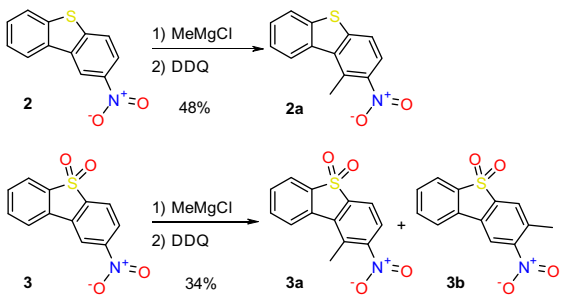


Scheme 2. Proposed reaction pathway and unfavourable reaction intermediate.



Scheme 3. Grignard additions to benzothiophene and benzothiophene dioxide. Reagents and conditions: **2** or **3** (3.9 mmol), MeMgCl (5.9 mmol), THF (40 mL), −15 °C, 1 h, then DDQ (6.69 mmol), −10 °C to RT, 16 h. **2a**, 48% and **3a** and **3b**, 34%.

as this would require breaking the aromaticity of the carbazole pyrrole ring. It was believed that the energy barrier to disrupting the aromaticity was significant enough to give rise to the observed selectivity. The reaction is completed by the addition of DDQ (4,5-dichloro-3,6-dioxocyclohexa-1,4-diene-1,2-dicarbonitrile) which furnishes the desired product. It is well known in the literature that DDQ can be used to oxidise semi-saturated rings to aromatic systems.[7,8] The proposed mechanism involves hydride transfer to the quinone oxygen followed by transfer of magnesium to the phenolate ion (Scheme 2).

This hypothesis was further supported by observations made with the corresponding benzothiophene **2** and benzothiophene dioxide **3**. In the case of fully aromatic benzothiophene, complete regioselectivity was observed to exclusively give methyl compound **2a**. However, with benzothiophene dioxide a 2:1 mixture of **3a** and **3b** was obtained (Scheme 3). Because in the case of **3** the central ring is not aromatic, it was rationalised that the relative energy barriers of the transition states leading to **3a** and **3b** were similar, therefore giving rise to a mixture of products.

These observations prompted us to investigate the synthetic utility of this regioselective reaction with additional heterocycles (Table 1). In the case of indoles with no substitution on nitrogen, it was necessary to use tosyl protected derivatives to avoid deprotonation by the Grignard reagent (Table 1). It should be noted that the yields of these reactions are as yet unoptimised.

Following our initial observations with carbazole **1**, analogous carbazoles **4** and **5** were investigated, and were noted to proceed with similar selectivity to give methyl analogues **4a** and **5a**. A similar outcome was observed when nitroindoles were used as substrates. In the cases of 5-nitro indole **7** and 6-nitro indole **6**, the reaction proceeded with the expected selectivity, however when 4-nitro indole **10** and 7-nitro indole **11** were employed, an inseparable mixture of isomers was obtained. This was due to competing alkylation occurring at the *para* position. Because this competing reaction does not break the aromaticity of the heterocyclic ring it is therefore still energetically favourable (see Scheme 4).

Additionally, we were interested to see if this methodology could be extended to other heterocyclic systems. In the case of benzofuran **8** and benzothiophene **9**, the reaction proceeded with the expected selectivity to give the corresponding *ortho* methyl compounds **8a** and **9a**.

Other Grignard reagents could also be employed in this reaction. When carbazole **1** was treated with ethyl magnesium chloride ethyl substituted carbazole **1e** was the only product isolated. When the same carbazole was treated with isopropyl magnesium chloride, the analogous isopropyl carbazole **1f** was formed exclusively. Unfortunately, when carbazole **1** was treated with phenyl magnesium chloride the corresponding phenyl carbazole **1g** was not observed, presumably due to the lower nucleophilicity of the phenyl Grignard reagent.

In summary, we have described a highly regioselective methodology for the alkylation of a variety of nitro containing aromatic heterocycles. Given the highly versatile nature of the nitro functional group we believe this methodology to be of synthetic value and allows the expedient synthesis of a wide variety of non-com-

Table 1

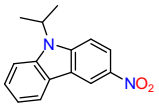
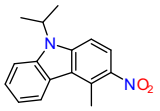
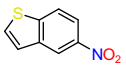
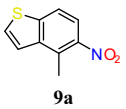
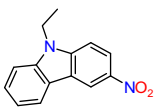
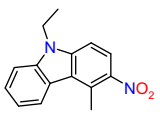
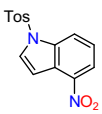
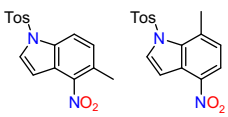
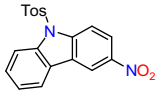
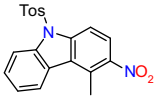
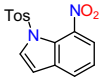
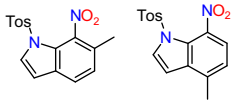
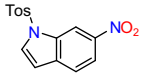
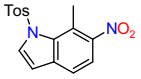
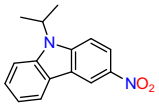
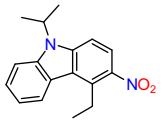
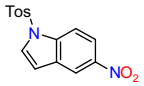
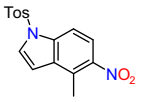
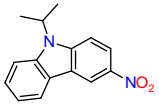
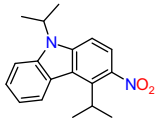
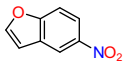
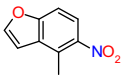
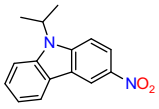
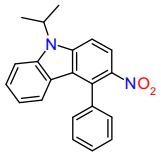
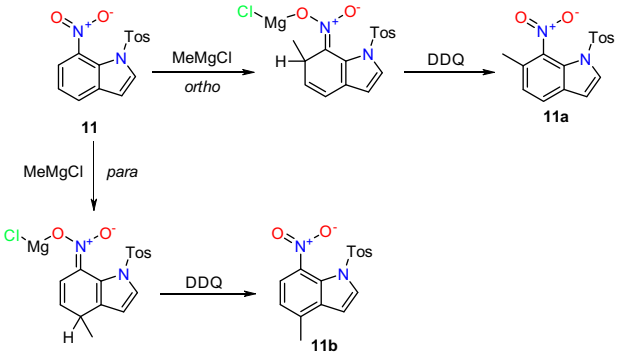
Substrate	Product	Yield[a] (%)	Substrate	Product	Yield[a] (%)
 **1**	 **1a**	68	 **9**	 **9a**	39
 **4**	 **4a**	55	 **10**	 **10a:10b** (1:1 mixture)	74

Table 1 (*continued*)

Substrate	Product	Yield[a] (%)	Substrate	Product	Yield[a] (%)
 **5**	 **5a**	69	 **11**	 **11a:11b** (1:1 mixture)	33
 **6**	 **6a**	33	 **1**	 **1e**	65
 **7**	 **7a**	71	 **1**	 **1f**	55
 **8**	 **8a**	48	 **1**	 **1g**	0



Scheme 4. *ortho*/*para* alkylations observed with 7-nitroindole **11**.

mercial or highly expensive substituted heterocycles from readily available starting materials.

Acknowledgement

We would like to thank Howard Beeley, Paul Davey, Peter Barton and David Whittaker for analytical support.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.11.036.

References and notes

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9. Representative procedure for the Grignard alkylation reaction. Preparation of 9-isopropyl-4-methyl-3-nitro-9*H*-carbazole (**1a**). Methylmagnesium chloride (1.97 mL, 5.90 mmol) was added dropwise to a stirred solution of 9-isopropyl-3-nitro-9*H*-carbazole (1 g, 3.93 mmol) in THF (40 mL) at −15 °C. The resulting solution was stirred at −15 °C for 1 h. DDQ (1.518 g, 6.69 mmol) was then added keeping the temperature below −10 °C and then the reaction mixture was allowed to warm temperature and stirred for 16 h. Dichloromethane (100 mL) was then added and the mixture washed with water (100 mL). The organic layer was passed through a phase separating cartridge and concentrated in vacuo to give a brown solid. The crude product was purified by flash silica chromatography, gradient 0–30% dichloromethane in heptane. Pure fractions were evaporated to dryness to afford 9-isopropyl-4-methyl-3-nitro-9*H*-carbazole (0.722 g, 68%) as a yellow solid.; ^{1}H NMR (400 MHz, DMSO) 1.65 (d, *J* = 7.0 Hz, 6H), 3.02 (s, 3H), 5.24 (p, *J* = 7.0 Hz, 1H), 7.33 (t, *J* = 7.6 Hz, 1H), 7.49–7.64 (m, 1H), 7.76 (d, *J* = 9.1 Hz, 1H), 7.87 (d, *J* = 8.4 Hz, 1H), 8.05 (d, *J* = 9.1 Hz, 1H), 8.34 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR (176 MHz, DMSO, 30 °C) 16.49, 20.17, 46.50, 108.24, 111.24, 120.06, 121.29, 122.13, 123.04, 123.10, 126.26, 129.64, 140.07, 140.62, 141.81. HRMS (ESI): MH^{+}, found 269.12836, $C_{16}H_{16}O_2N_2$ requires 269.12845.