



## Substituted diaryldiazomethanes and diazofluorenes: structure, reactivity and stability

Philip J. Davis<sup>a</sup>, Lawrence Harris<sup>a</sup>, Aman Karim<sup>a</sup>, Amber L. Thompson<sup>a</sup>, Martin Gilpin<sup>b</sup>, Mark G. Moloney<sup>a,\*</sup>, Matthew J. Pound<sup>a</sup>, Claire Thompson<sup>a</sup>

<sup>a</sup> Department of Chemistry, Chemistry Research Laboratory, The University of Oxford, 12 Mansfield Road, Oxford OX1 3TA, UK

<sup>b</sup> GlaxoSmithKline Research & Development Ltd, New Frontiers Science Park, Third Avenue, Harlow, Essex CM19 5AW, UK

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### ABSTRACT

The synthesis of several substituted diaryldiazomethanes and diazofluorenes, and an assessment of their structure, reactivity and stability, is reported.

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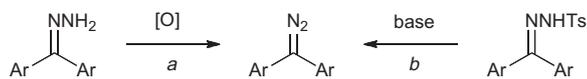
Diaryldiazomethanes are of importance as stable precursors of singlet and triplet carbenes<sup>1–5</sup> and more recently have found application in materials science,<sup>6</sup> particularly for surface modification of diverse materials<sup>7–13</sup> for which their reactivity appears to match more closely that in solid matrices at low temperature, rather than solution or gas phase behaviour.<sup>14,15</sup> Surprisingly, the diaryldiazo group occurs as a key chemical function in the lomaiviticins<sup>16</sup> and the kinamycins,<sup>17,18</sup> natural products known for their antitumor and antibiotic activities. Although not widely used in synthesis, diaryldiazomethanes are best known amongst the synthetic community for their utility for the protection of carboxylic acids,<sup>19</sup> but more recently have been shown to be highly selective reagents for alcohol group protection in carbohydrate substrates.<sup>20</sup> The synthesis of diaryldiazomethanes is well described,<sup>21–23</sup> and may involve either the oxidation of a suitable hydrazone or base elimination of a tosyl hydrazone, although a wholly novel access to these systems was recently reported.<sup>24</sup> Being crystalline or low-melting solids, the stability of diaryldiazomethanes is much greater than that of diazomethane, a known explosive which must only be handled in dilute solution; in fact, it has been reported that diaryldiazomethanes have been used in moderate- to large-scale chemical synthesis over a 20 year period without incident.<sup>20</sup> An investigation of the stability of diphenyldiazomethane has shown that although decomposition starts at any temperature higher than 10 °C, at 25 °C only about 9% had decomposed after 100 h.<sup>25</sup> However, in the melt, it decomposes much more rapidly (13% decomposition after 20 h at 30 °C, and 90% decomposition after 20 h at 50 °C, giving an activation energy of 19.4 kcal/mol). It is reported to be much more stable in the crystalline state, with an activation energy to decomposition of 72.7 kcal/mol, is relatively stable to friction and impact, and has an ignition point of 136–139 °C.<sup>25</sup> Against this background, of interest to us

was an examination of the structure of known substituted diaryl and heteroaryldiazo compounds, along with an assessment of their stability based upon observations of their melting and thermal gravimetric behaviour, in order to ascertain their suitability as reactive intermediates capable of wider application; although widely reported in the literature, such compounds have not always been characterised in detail. It is worth noting that diazirines, kinetically stable but nonetheless valuable precursors for carbene generation, have found important applications, especially in photoaffinity labeling.<sup>26–29</sup>

The standard methods for the preparation of diaryldiazomethanes and diheteroaryldiazomethanes generally use either oxidation of the corresponding hydrazones, or for electron-deficient substrates, base-mediated Bamford-Stevens type elimination of the tosyl hydrazone (Scheme 1, methods *a* and *b*), and we used both to provide access to a range of substituted diarylmethyl and fluorenyl systems. The requisite hydrazones and tosyl hydrazones were preferably prepared and used immediately. The known diazo compounds **1a,b,d,e** were prepared from the corresponding benzophenone hydrazones using method *a*, and compound **1c** by method *b*; in the case of the dimethoxybenzophenone hydrazone, confirmation of the structure was possible by single crystal X-ray analysis at low temperature.<sup>30</sup> Heteroaryl system **2** was accessed by method *a* starting from the corresponding commercially available benzophenone. Diazofluorenes were similarly prepared from the corresponding fluorenones,<sup>31</sup> and this gave access to compounds **3a,b** and **4a,b**. In the case of **3c**, the synthetic route proceeded from diphenic acid by standard methodology to give fluorenone **5** as shown in Scheme 2.<sup>32</sup> Protection, ester reduction and deprotection gave the product ketone **7** in 20% yield over five steps, and this was readily converted into the diazo compound **3c**. The synthesis of the aza-containing diazofluorenes proceeded as shown in Scheme 3, according to literature methodology;<sup>31</sup> similar routes using either benzo[*h*]quinoline **8a** or 9,10-phenanthroline **8b** as the starting

\* Corresponding author.

E-mail address: [mark.moloney@chem.ox.ac.uk](mailto:mark.moloney@chem.ox.ac.uk) (M.G. Moloney).



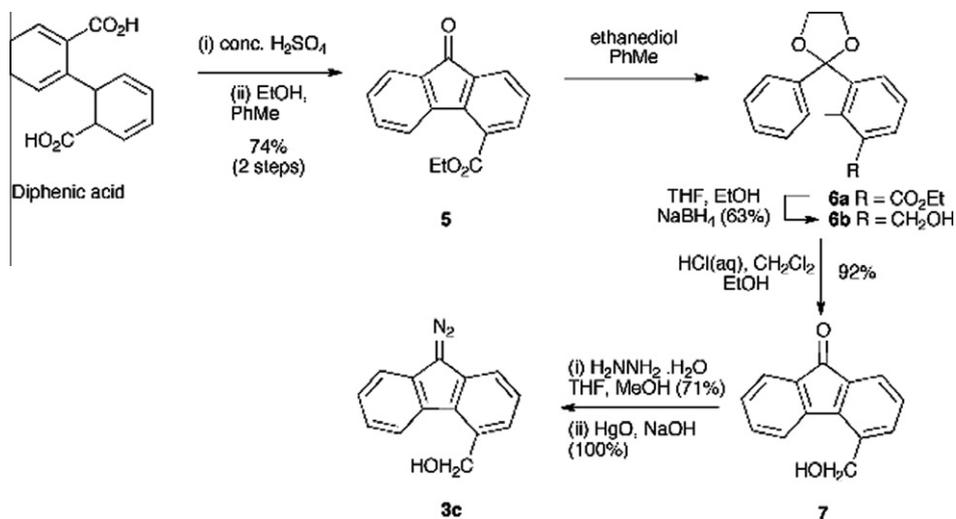
Scheme 1.

materials were applied. Thus, permanganate-mediated oxidation of **8a,b** to give the fluorenones **9a,b**, conversion into the tosyl hydrazones **10a,b** and base-mediated elimination gave the diazo compounds **4a,b** in excellent overall yields; slightly different conditions were required for the latter step as a result of the differing solubilities of **10a,b**. This method proved to be superior to the reported synthesis of 4,5-diaza-9-diazo fluorene (**4b**) by mercury oxidation of the corresponding hydrazone,<sup>6</sup> for which in our hands the yields of both the hydrazone, prepared from the relatively expensive 9,10-phenanthroline, and the final oxidation step, were poor.

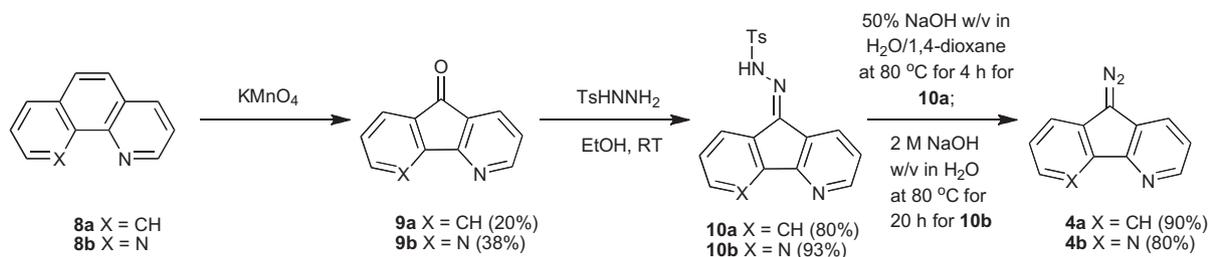
Single crystal X-ray analysis was found to be possible for diazo compounds **1b** and **3c** (Fig. 1); although the X-ray structures of simple diaryldiazo compounds complexed to metals have been reported,<sup>33</sup> similar structural analysis has previously only been reported for sterically congested and therefore more stabilized systems.<sup>3</sup> From these reports, it had been noted in the analysis of diaryldiazo compounds containing electron-withdrawing substituents, that the C=N and N=N bond lengths are in the ranges 1.29(1)–1.32(3) Å and 1.12(3)–1.152(6) Å, respectively,<sup>3</sup> and for compounds **1b** and **3c** the corresponding C=N bond lengths are 1.302(4) Å and 1.305(6)/1.308(6) Å (note that **3c** has two molecules in the asymmetric unit) and N=N bond lengths are 1.129(4) Å and 1.145(5)/1.134(5) Å, respectively. While diazo fluorene **3c** is necessarily planar, there is a high degree of twist in the dimethoxy compound **1b**, evidenced by the large interplanar

angle of the two aromatic rings of 55.7°, and indicating that full cross conjugation in the aromatic system is not possible. Of interest is that the C=N carbon bond angle is 127.8(2)° for the diaryl diazomethane **1b**, but is substantially compressed and only 109.7(4)/108.8(3)° for the fluorenone **3c**.

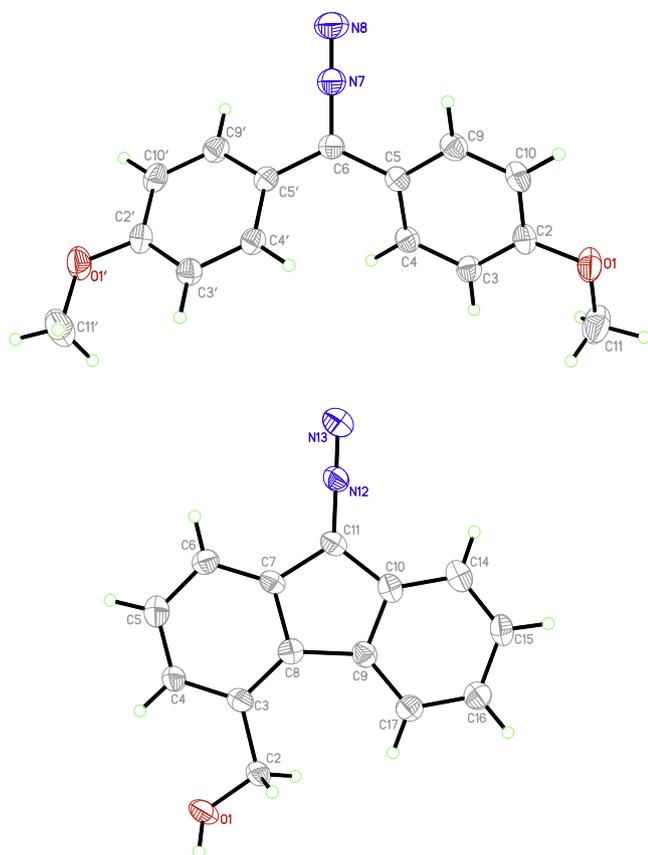
Some physical characterisation data for diazo compounds **1–4** are given in Table 1. All samples are intensely coloured, ranging from red to orange or brown, and most are crystalline high melting materials (although exceptionally **1a** is a low melting oil), stable for indefinite periods when stored neat at low temperature (4 °C or below), but are much less stable at room temperature, and particularly unstable when stored in solution. Decomposition in that case proceeds by reaction with oxygen, to give the parent ketone, or by disproportionation to give the symmetrical azine, as demonstrated by careful carbon NMR spectroscopic analysis. In fact, the reaction of diphenyldiazomethane has been shown to proceed by initial formation of benzophenone oxide  $\text{Ph}_2\text{CO}_2$  ( $\Delta H$  –48 kcal mol<sup>-1</sup>) and is followed by an exothermic disproportionation ( $\Delta H$  –76 kcal mol<sup>-1</sup>) to give benzophenone and oxygen.<sup>34</sup> The principal diazo infra-red absorption of the diaryldiazo compounds **1a,c** and **2** is centred at approximately 2045 ± 4 cm<sup>-1</sup>, although the dimethoxy system **1b** is substantially lower at 2029 cm<sup>-1</sup>. The diazo absorption for the fluorenones **3a–c** and **4a,b** is at the slightly higher value of 2056 ± 5 cm<sup>-1</sup>, although the pyridyl system **4b** is substantially higher at 2076 cm<sup>-1</sup>. Similarly, in the <sup>13</sup>C NMR spectrum, the diazo carbon was typically very weak, generally only observable by HMBC NMR analysis, and the chemical shift was centred around  $\delta_{\text{C}}$  63.0, but relatively unaffected by aryl ring substitution, with the exception of the dipyrindyl systems **4a,b**, which occurred at  $\delta_{\text{C}}$  67.1 and 59.9, respectively. UV–vis spectroscopy indicated a strong absorption in the region 410–550 nm, consistent



Scheme 2.



Scheme 3.



**Figure 1.** Crystal and molecular structures for **1b** (top) and **3c** (bottom) with thermal ellipsoids drawn at 50% probability. Compound **3c** has two molecules in the asymmetric unit, but only one is shown for clarity.

with their observed colour, and strong UV absorptions at 300–400 nm with  $\epsilon > 4.0$  accounting for the ready photolysis of this class of compound. Thermal gravimetric analysis (TGA) of these compounds exhibited a decomposition temperature of 120 °C for the unstable dimethoxydiphenyldiazomethane, but those substituted

with electron-withdrawing groups were stable at higher temperature, and up to 188 °C for the most stable fluorenone **3b**. Decomposition proceeds with a mass decrease corresponding to the loss of half an equivalent of nitrogen in the case of **1a,b**, giving the azine, or the loss of a full equivalent of nitrogen in compounds **2,3a,b** and **4a,b**. In the case of dinitrodiphenyldiazomethane **1c**, additional loss of one nitro group was evident. Of significance were the much higher decomposition temperatures of the diazofluorenones relative to the diaryldiazomethanes, consistent with their higher stability, and the stabilising effect of electron-withdrawing groups. The dimethoxy compound **1b** is relatively unstable in solution at room temperature, decomposing in chloroform to give a mixture containing the starting benzophenone and the corresponding azine, although if kept in a crystalline form at 0 °C, is stable for more extended periods, and of interest is that fluorenyldiazomethanes **3c,b,4a** (but not the diaryldiazomethanes) were all stable to silica chromatography, as has been observed in the literature.<sup>17</sup>

In order to assess the relative reactivity of some of these systems, their thermolysis as a 0.33–0.77 M solution in refluxing ethanol was examined (Scheme 4); the reaction progress was monitored by measuring the concentration of the product diarylmethylethyl ethers by GC, and the extent of reaction as a function of time is shown in Figure 2. Noteworthy is that electron-releasing groups significantly activate the system to reaction, and electron-withdrawing groups have the opposite effect, with **1a,b,d**, and **e** having approximate half lives of 40, 15, 100 and 60 min, respectively. By contrast, the dinitro compound **1c** is indefinitely stable at room temperature, although it suffers from poor solubility in organic solvents, and was unreactive with ethanol under thermal conditions alone. However, it has been reported by Just that diazo compound **1c** is reactive with alcohols in the presence of a Lewis acid.<sup>36</sup> This relative reactivity was reflected in the isolated yields of product, obtained under thermolytic and photolytic conditions (Table 2), of compounds **1a,b,d**, and **e** on reaction with ethanol; the end-point of the reaction was indicated conveniently by loss of colouration of the starting diazo material. These results are in keeping with an earlier report by Schechter which examined the electronic effects in the unimolecular decomposition of substituted diphenyldiazomethanes in water 1,2-dimethoxyethane to give benzhydryl products,<sup>42,43</sup> and with the fact that the enthalpy of

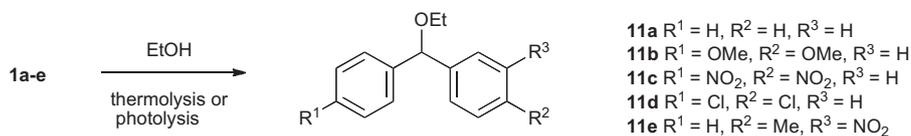
**Table 1**  
Physical characteristics and decomposition data for diazo compounds

Diazo compound	Mp (°C)	Reference	IR diazo function (cm <sup>-1</sup> )	NMR Diazo carbon ( $\delta_c$ )	Colour	UV-vis $\delta_{\max}/\text{cm}^{-1}$ (log $\epsilon$ )	TGA	
							T/°C (mass loss %)	Fragment loss
<b>1a</b>	27	35	2042	62.4 <sup>c</sup>	Violet	290 (4.3) 524 (2.0)	130 (7)	-0.5 N <sub>2</sub>
<b>1b</b>	90–92	35	2029	60.7	Violet	290 (4.5) 547 (1.9)	120 (5)	-0.5 N <sub>2</sub>
<b>1c</b>	135	36	2047	64.2 <sup>c</sup>	Orange	401 (4.4) 412 (2.0)	160 (25)	-N <sub>2</sub> , -NO <sub>2</sub>
<b>2</b>	50–52	37	2049	62.7	Red	303 (4.3) 497 (2.3)	125 (14)	-N <sub>2</sub>
<b>3a</b>	98–99	38	2057	63.2 <sup>c</sup>	Orange	— 457 (2.8)	165 (15)	-N <sub>2</sub>
<b>3b</b>	179–180 <sup>a</sup>	39,40	2061	63.1	Orange	244 (4.7) 471 (1.5)	188 (16)	-N <sub>2</sub>
<b>3c</b>	140–141	—	2051	63.4	Orange	243 (4.7) 487 (1.5)	170 (12)	-N <sub>2</sub>
<b>4a</b>	70	41	2059	67.1	Orange/ brown	302 (4.4) 438 (2.2)	165 (25)	-N <sub>2</sub>
<b>4b</b>	120 <sup>b</sup>	41,6	2076	59.9	Brown	311 (4.4) 413 (1.8)	165 (23)	-N <sub>2</sub>

<sup>a</sup> Softens.

<sup>b</sup> Decomposes.

<sup>c</sup> Literature values.<sup>42</sup>



Scheme 4.

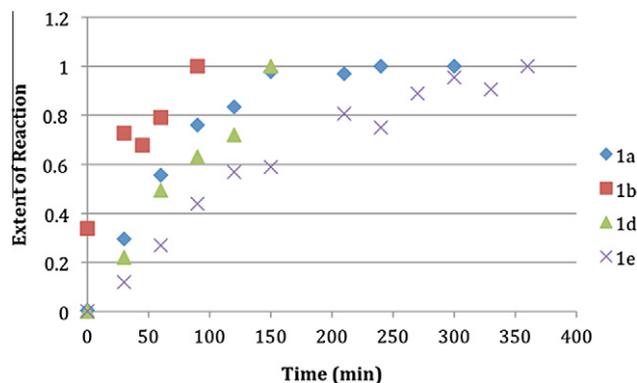


Figure 2. Time course of reactions according to Scheme 4.

**Table 2**  
Reaction times and yields according to Scheme 4

Compound	Product	Reaction time (h) (Yield %)	
		Photolysis	Thermolysis
<b>1a</b>	<b>11a</b>	72 (81)	4 (75)
<b>1b</b>	<b>11b</b>	24 (90)	1.5 (60)
<b>1d</b>	<b>11d</b>	48 (73)	3 (78)
<b>1e</b>	<b>11e</b>	72 (94)	5 (81)

reaction of diphenyldiazomethane with ethanol has been measured to be  $-53.6 \text{ kcal mol}^{-1}$ .<sup>34</sup>

These data indicate that substituted diaryldiazomethanes and diazofluorenes, which are readily available, stable and storable solids, have decomposition temperatures dependent on substitution pattern, and not less than 120 °C amongst the examples studied; they are reactive with alcohols at elevated temperature in the absence of catalysts. Notable is the stability of systems containing free hydroxy **3c** and pyridyl **4a,b** groups, and of diazofluorenes generally (**3** and **4**).

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### Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.01.116.

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