

Synthesis of highly substituted diphenylacetamides and diphenylsulfonamides by the Goldberg coupling reaction

M. Manuela M. Raposo^{a*}, Alexandra M.B. Pereira^a, Ana M.F. Oliveira-Campos^a, and Patrick V.R. Shannon^b

^aDepartamento de Química, Universidade do Minho, 4700 – 320 Braga, Portugal

^bDepartment of Chemistry, University of Wales, College of Cardiff, P.O. Box 912, Cardiff CF1 3TB, Wales, UK

J. Chem. Research (S),
2000, 156–158
J. Chem. Research (M),
2000, 0528–0558

We report the synthesis and characterisation of multisubstituted diphenylacetamides, diphenylsulfonamides and diphenylamines (and some observations on cyclisation of the last).

In a preliminary paper on the Goldberg coupling reaction of aryl halides with amides, the effect of a variety of substituents in the reactants was investigated and it was shown that the yields are markedly susceptible to the presence of electron withdrawing groups in both reactants.¹

The effect of substituent methyl groups on the reaction yield was not investigated but this could be important if the products such as **1** or **2** were to be used for the synthesis of 1,4-dimethylcarbazoles **3** (Scheme 1) as precursors of ellipticines. Until now, carbazoles have been fruitful precursors of ellipticines.²

Apart from possible effects on the yields of the coupled products **1–2**, the 2,5-dimethyl groups could sterically inhibit the cyclisation to carbazoles **3**. It is known that, without 2,5-dimethyl substitution, the cyclisation of diphenylamines with palladium (II) acetate can give good yields of carbazoles.³ However, to date this route has led to the synthesis, in poor yield, of only two ellipticines **4**⁴ and **5**.⁵

Miller and Moock⁴ obtained ellipticine **4** by cyclisation of 5,8-dimethyl-6-phenylaminoisoquinoline with palladium (II) acetate. In our hands, the diphenylamine **20g** was cyclised to the carbazole **3c** and this was then converted to ellipticine **5**.

We now report the synthesis of a series of multisubstituted diphenylacetamides **1** and diphenylsulfonamides **2** which embody 2,5-dimethyl substituents, thus extending our earlier work.¹

The diphenylacetamides (**1a–f**) were prepared by Goldberg coupling, as shown in the Table 1. The different effect of substituents in the coupling components on the yields obtained is noteworthy (16–81%).

The ¹H NMR spectra of all the diphenylacetamides in CDCl₃ at 25°C showed broad overlapping signals due to hindered rotation which were resolved when the spectra were run in DMSO-d₆ at 80°C.

Since the diphenylacetamides **1** were potential precursors of the carbazoles **3** we first attempted the alkaline hydrolysis of the former to diphenylamines (**20a–f**), [KOH/(EtOH/H₂O)].

As expected the diphenylacetamides **1d** and **1e** with electron-withdrawing groups *para* and three vacant *ortho* positions to the amide readily hydrolysed to give high yields of diphenylamines (**20d**, 84%) and (**20e**, 85%).

With only two vacant *ortho* positions, however, *i.e.* **1a** and **1b** yields were much lower (**20a**, 28%) and (**20b**, 20%).

For diphenylacetamide **1c** with only two vacant *ortho* positions and without an electron withdrawing group in the *para* position, the hydrolysis was even slower, and after 22 h 15 min. only traces (3%) of the amine **20c** and much more of unchanged diphenylacetamide **1c** (40%) was recovered. Under forcing conditions (NaOH/ethylene glycol) only the product (**20f**, 19%) was obtained with improved yield,

Table 1 The yields for diphenylacetamides (**1a–f**) prepared from Goldberg coupling

Acetamide	Bromide	Product	Yield (%)
14	11	1a	68
13	11	1b	44
10	15	1b	57
12	11	1c	81
16	6	1d	32
16	15	1e	29
12	17	1f	31
18	19	1f	16

together with the by product (**21**, 24%) but no improvement was found for hydrolysis of **1c**.

We also examined the reactivity of sulfonamides in the Goldberg reaction. The yields of coupling of aryl halides to diphenylsulfonamides were generally lower (2–44%) (Table 2) than those obtained for analogous reactions with the acetamides. For example the yield of product **2c** from the bromo compound **11** and sulfonamide **22** was significantly lower (44%) than the yield of the diphenylacetamide **1c** (81%) (Table 1), also obtained from bromocompound **11**.

Attempts to convert the diphenylamines **20d** and **20e** into the corresponding carbazoles **3a** and **3b** using palladium (II) acetate gave only very low yields of the desired products.

Thus the amine **20d** gave 10% of the carbazole **3a** together with 11% of the by-product **29**; M⁺ 308.1156 (C₁₈H₁₆N₂O₃). The NMR spectrum of **29** showed only one singlet at δ 2.74 due to the 4-Me group and three 1 H singlets at δ 7.98, 8.39 and 8.84, assignable to the 2-H and to the methylene protons whilst the aromatic proton of ring A (8-H) gave the expected singlet at δ 7.27.

When the cyclisation of amine **20e** was attempted, we isolated only 2% of the bromocarbazole **3b** with the alternative oxidation product **30** in a yield of 4%. The ¹H NMR spectrum

Table 2 The yields for diphenylsulfonamides (**2a–f**) prepared from Goldberg coupling

Sulfonamide	Bromide	Product	Yield (%)
27	11	2a	16
9	6	2a	14
26	11	2b	26
9	15	2b	17
22	11	2c	44
27	25	2d	17 ^a
23	6	2d	31 ^b
23	15	2e	2 ^c
26	25	2e	35
27	17	2f	8 ^d

^a By-product **28** (8%) was also obtained.

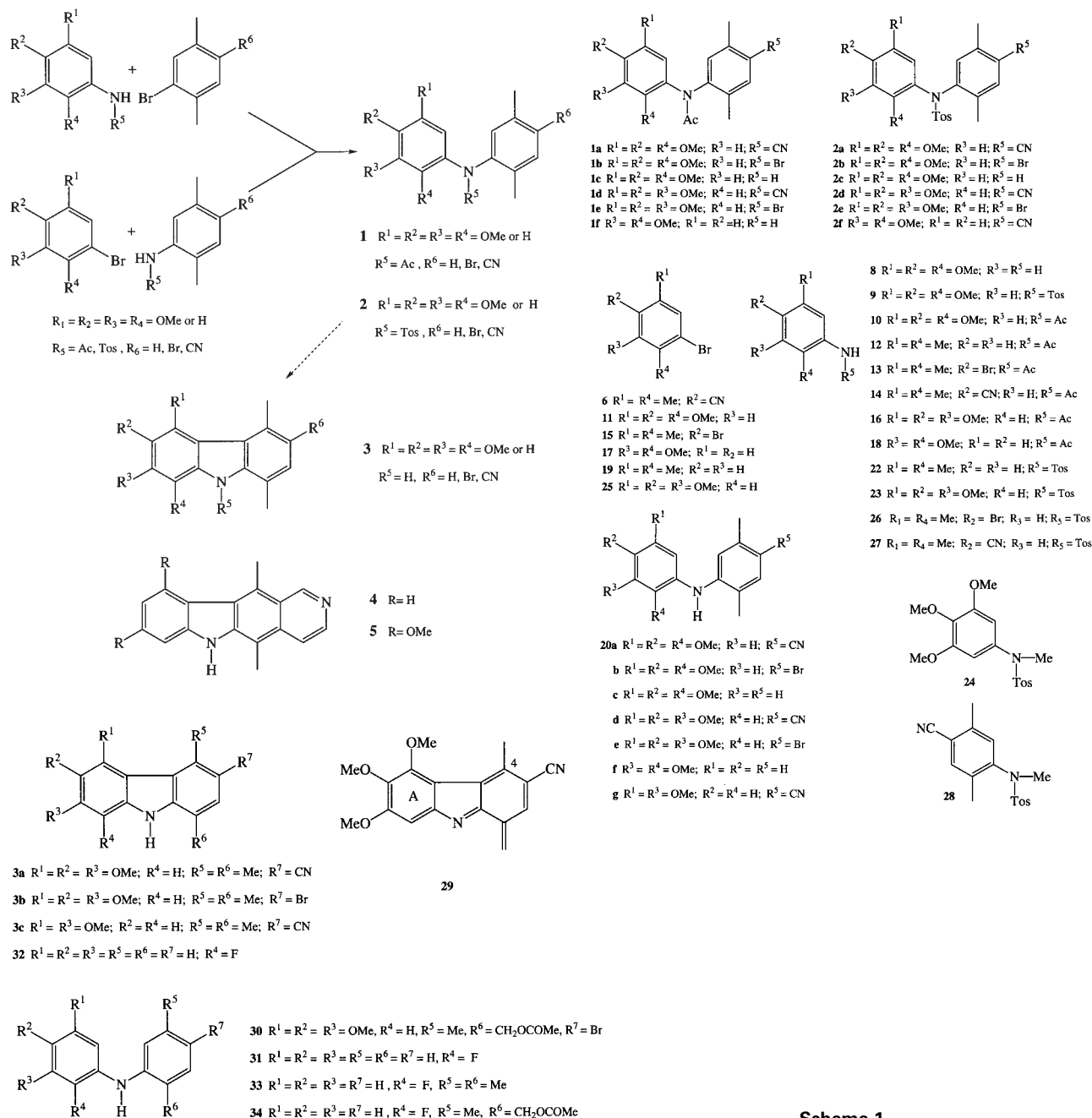
^b The coupling gave only the by-product **24** instead of the sulfonamide **2d**

^c By-product **24** (1%) was also obtained.

^d By-product **28** (9%) was also obtained.

* To receive any correspondence.

E-mail: mfox@ci.uminho.pt



Scheme 1

of **30** showed a singlet at δ 5.08, due to the CH_2OAc group.

It is significant that under similar conditions we were able to cyclise the 2-fluorodiphenylamine¹⁸ **31**, lacking 2,5-dimethyl substitution, to the 1-fluorocarbazole **32**¹⁹ in 66% yield. But when the cyclisation of the fluorodiphenylamine **33**²⁰ with 2,5-dimethyl substitution was tried, instead of the required carbazole we obtained only the product of oxidation **34** (19%).

This work shows that the Goldberg coupling of aryl bromides gives significantly better yields for diphenylacetamides than for the corresponding sulfonamides. Hydrolysis of the diphenylacetamides to diphenylamines is difficult to achieve if there are two or less vacant positions *ortho* to the amide group. This may often be the case for diphenylamides with 2,5-dimethyl substitution.

The palladium acetate cyclisation of diphenylamines to carbazoles seems also to be susceptible to steric hindrance. When

the diphenylamines are highly substituted a low yield or none of the carbazoles may be obtained. By-products resulting from oxidation of carbazole, such as **29** or from acetoxylation of diphenylamines, such as **34**, may be formed.

The general route via Goldberg coupling, hydrolysis and cyclisation by palladium acetate or light has led to some carbazole intermediates used in ellipticines synthesis.^{5,21,22} However, due to the limitations described in this paper, the sequence cannot be considered as generally useful to obtain new derivatives of ellipticines.

Acknowledgements: We thank FCT, ICCTI and CRUP (Portugal) and the British Council for financial support.

Techniques used: ¹H-NMR spectroscopy, mass spectrometry, elemental analysis.

References: 22.

Schemes: 18.

Tables: 4.

Received 27 December 1999; accepted 6 March 2000
Paper 99/118

References cited in this synopsis

- 1 P.M. Dharmasena, A.M.F. Oliveira-Campos, M.M.M. Raposo and P.V.R. Shannon, *J. Chem. Research*, 1994, (S) 296, (M), 1601.
- 2 M.J.E. Hewlins, A.M.F. Oliveira-Campos and P.V.R. Shannon, *Synthesis*, 1984, **4**, 289.
- 3 B. Åkermark, L. Ebersson, E. Jonsson and E. Pettersson; *J. Org. Chem.*, 1975, **40** (9), 1365.
- 4 R.B. Miller and T. Moock; *Tetrahedron Lett*; 1980, **21**, 3319.
- 5 L. Chunchatprasert, P. Dharmasena, A.M.F. Oliveira-Campos, M.J.R.P. Queiroz, M.M.M. Raposo and P.V.R. Shannon, *J. Chem. Research*, 1996, (S) 84, (M), 630.
- 18 A. Roe and W.F. Little, *J. Org. Chem*; 1955, **20**, 1577.
- 19 F.L. Allen and H. Suschitzky, *J.Chem.Soc.*, 1953, 3845.
- 20 P.W. Groundwater, D. Hughes, M.B. Hursthouse and R. Lewis, *J. Chem. Soc. Perkin Trans. 1*, 1996, **7**, 669.
- 21 R.J. Hall, J. Marchant, P. Dharmasena, A.M.F. Oliveira-Campos, M.J.R.P. Queiroz, M.M.M. Raposo and P.V.R. Shannon, *J.Chem.Soc. Perkin Trans. 1*, 1993, 1879.
- 22 A.M.F. Oliveira-Campos, M.J.R.P. Queiroz, M.M.M. Raposo and P.V.R. Shannon, *Tetrahedron Lett.*, 1995, **36** (1), 133.