Available online at www.sciencedirect.com

SCIENCE DIRECT®

Tetrahedron Letters 46 (2005) 6983–6985

Tetrahedron Letters

Unusual dimerization of *N*-protected bromomethylindoles using phenylmagnesium chloride

Arasambattu K. Mohanakrishnan,* Neelamegam Ramesh and Chandran Prakash

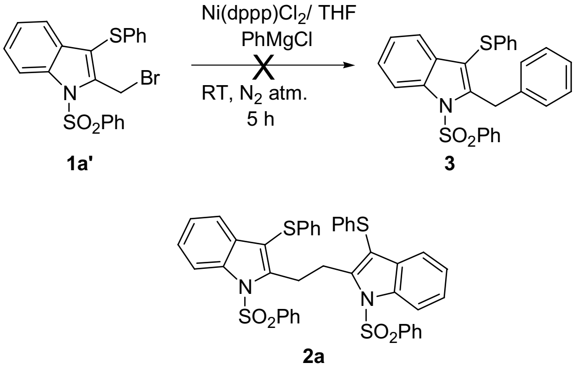
Department of Organic Chemistry, University of Madras, Guindy Campus, Chennai 600 025, Tamil Nadu, India

Received 17 June 2005; revised 8 August 2005; accepted 17 August 2005

Abstract—A novel dimerization of *N*-protected bromomethylindoles involving an exchange reaction with phenylmagnesium chloride is reported.

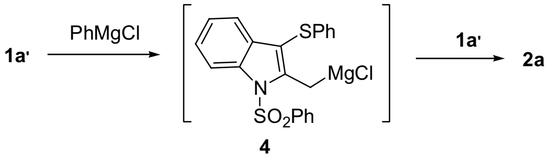
In continuation of our interest on the synthesis of carbazole-based alkaloids,[1] we wanted to develop a viable procedure for the arylation of *N*-protected bromomethylindoles[2] as the existing procedure is applicable only to electron rich arenes.[3] Numerous developments have been achieved recently using transition metal mediated carbon–carbon bond formation.[4] Nevertheless, these developments are yet to be adapted to the indole system. In continuation of our efforts to explore the synthetic utility of *N*-protected bromomethyl indoles using transition metal complexes as catalysts,[5] the Ni(II)-mediated coupling reaction of bromo compound **1a′** was carried out with phenylmagnesium chloride. However, the reaction failed to produce the expected benzylindole **3** (Scheme 1). Careful analysis of the ^{1}H NMR and ^{13}C NMR spectra confirmed the product as dimer **2a** in 50% yield. Recently, Qian and Negishi observed[6] a similar dimerization during the Pd-mediated coupling of benzyl bromide with phenylethynylzinc bromide. Repetition of the coupling reaction using freshly prepared 4-methoxyphenylmagnesium bromide also afforded the self-dimerization product **2a** in 52% yield.

In order to gain an insight into the mechanism of the dimerization, the coupling reaction of bromo compound **1a′** was carried out in the presence of Ni(II)/Pd(0) without the addition of the Grignard reagent. However, the reaction did not afford the dimerization product **2a**, only the starting bromo compound **1a′** was recovered.



Scheme 1.

Next, the bromo compound **1a′** was reacted with phenylmagnesium chloride in the absence of the Ni(II)/Pd(0) complex at 0–10 °C under a nitrogen atmosphere for 5 h to afford the dimerized product **2a** in 60% yield. Obviously, the reaction of bromo compound **1a′** with PhMgCl led to the formation of indolylmethyl Grignard **4** via Grignard exchange (Scheme 2), which reacts with more bromomethylindole **1a′** to form the dimer **2a**.



Scheme 2.

Keywords: Bromomethylindoles; Phenylmagnesium chloride; Dimerization.

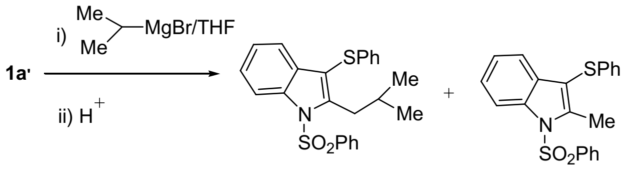
---

* Corresponding author. Tel.: +91 44 24451108; fax: +91 44 22352494; e-mail: mohan_67@hotmail.com

0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.08.068

It is also clear that the self-dimerization of bromo compound **1a**′ is not catalyzed by Ni or Pd.

In order to verify the proposed Grignard exchange, bromo compound **1a**′ was reacted with isopropylmagnesium bromide at room temperature. Acidic workup of the reaction mixture followed by mass spectral analysis indicated the formation of isopropylmethyl indole **5** [M$^+$, 421 (10%)] and 1-phenylsulfonyl-3-phenylthio-2-methylindole **6** [M$^+$, 379 (15%)], Scheme 3. The formation of **5** can be visualized through nucleophilic attack and compound **6** can be formed only through Grignard exchange. The formation of the latter compound confirmed that bromomethylindole **1a**′ underwent Grignard exchange.

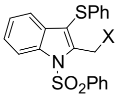
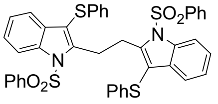
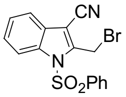
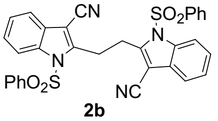
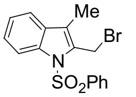
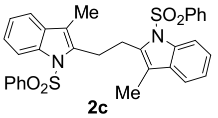
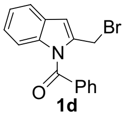
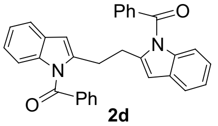
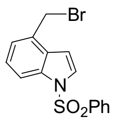
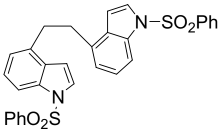
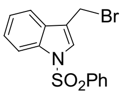
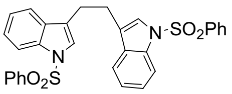
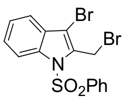
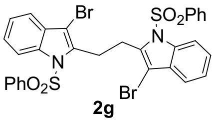
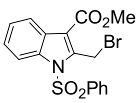
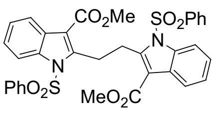


5 **6**

Scheme 3.

At this point it is worthwhile mentioning that the attempted formation of Grignard **4** from bromo compound **1a**′ in the presence of Mg in dry THF under reflux was found to be unsuccessful. Even though aryl Grignards have been generated via exchange reactions

Table 1. Dimerization of *N*-protected bromomethyl indoles using PhMgCl

Entry	bromo/chloroindole[8]	Conditions	Dimerized product[9]	Yield[a] (%)/mp
1	 **1a'** X = Br **1a"** X = Cl	1.2 equiv PhMgCl, rt, 3 h 1.2 equiv MeOC$_6$H$_4$MgBr, rt, 5 h 1.2 equiv PhMgCl, rt, 5 h	 **2a**	60 (220 °C) 52 48
2	 **1b**	1.2 equiv PhMgCl, rt, 8 h	 **2b**	20 (230 °C)
3	 **1c**' X = Br **1c"** X = Cl	1.2 equiv PhMgCl, rt, 5 h 1.2 equiv PhMgCl, rt, 7 h	 **2c**	48 (268 °C) 43
4	 **1d**	1.2 equiv PhMgCl, rt, 5 h	 **2d**	42 (liquid)
5	 **1e**	1.2 equiv PhMgCl, rt, 10 h	 **2e**	40 (230 °C)
6	 **1f**	1.2 equiv PhMgCl, rt, 5 h	 **2f**	58 (148 °C)
7	 **1g**	1.2 equiv PhMgCl, rt, 10 h	 **2g**	71 (208 °C)
8	 **1h**	1.2 equiv PhMgCl, rt, 6 h	 **2h**	48 (148 °C)

---

[a] Isolated yield after column chromatography.

between aryl iodides and phenylmagnesium chloride,[7] to our knowledge, this is the first time Grignard exchange has been observed with benzylic, or more specifically, an indolylmethyl system.

The unusual dimerization reaction was then tested with a variety of bromomethylindoles **1a–h** and the results are described in Table 1. The dimerization was found to be facile irrespective of the position of the bromomethyl unit. The rate and yield of the dimerization were found to be somewhat decreased with the corresponding *N*-protected chloromethylindoles (entries 1 and 3). The presence of a cyano group at the 3-position significantly lowers the yield of the dimerization process (entry 2). In contrast, the presence of a methyl ester at the indole-3-position allowed the dimerization to proceed smoothly to afford the product **2h** in 48% yield (entry 8).

In conclusion, we have observed an unusual Grignard exchange reaction of *N*-protected bromomethylindoles with aryl and isopropylmagnesium bromides. Using the observed Grignard exchange phenomena, a novel dimerization of *N*-protected bromomethyl indoles was achieved in reasonable yields. Investigations are underway to utilize the Grignard exchange technique to synthesize various indole analogs.

Acknowledgements

We thank UGC, New Delhi (F.12-140/2001 SR-1), for the financial support. Financial support to the Department by DST-FIST is also acknowledged.

References and notes

1. (a) Mohanakrishnan, A. K.; Srinivasan, P. C. *J. Org. Chem.* **1995**, *60*, 1939–1946; (b) Mohanakrishnan, A. K.; Balamurugan, R. *Tetrahedron Lett.* **2005**, *37*, 2659–2662.
2. (a) Nagarathnam, D.; Vedachalam, M.; Srinivasan, P. C. *Synthesis* **1983**, 156–157; (b) Nagarathnam, D. *Synthesis* **1992**, 743–745; (c) Nagarathnam, D. *J. Heterocycl. Chem.* **1992**, *29*, 953–958.
3. (a) Rajeswaran, W. G.; Srinivasan, P. C. *Synthesis* **1992**, 835–836; (b) Rajeswaran, W. G.; Srinivasan, P. C. *Indian J. Heterocycl. Chem.* **1992**, *2*, 89–91.
4. (a) Chowdhury, S.; Georghiou, P. E. *Tetrahedron Lett.* **1999**, *40*, 7599–7603; (b) Langle, S.; Abarbri, M.; Duchene, A. *Tetrahedron Lett.* **2003**, *44*, 9255–9258; (c) Nobre, S. M.; Monteiro, A. L. *Tetrahedron Lett.* **2004**, *45*, 8225–8228; (d) Bandgar, B. P.; Bettigeri, S. V.; Phopase, J. *Tetrahedron Lett.* **2004**, *45*, 6959–6962; (e) Chang, C.; Huang, Y.; Hong, F. *Tetrahedron* **2005**, *61*, 3835–3837; (f) Kuwano, R.; Yokogi, M. *Org. Lett.* **2005**, *7*, 945–947.
5. Mohanakrishnan, A. K.; Ramesh, N. *Tetrahedron Lett.* **2005**, *46*, 4577–4579.
6. Qian, H.; Negishi, E. *Tetrahedron Lett.* **2005**, *46*, 2927–2930.
7. For generation of aryl Grignards using phenylmagnesium chloride, see: (a) Collibee, S. E.; Yu, J. *Tetrahedron Lett.* **2005**, *46*, 4453–4455; (b) Sapountzis, I.; Dube, H.; Lewis, R.; Gommermann, N.; Knochel, P. *J. Org. Chem.* **2005**, *70*, 2445–2454.
8. The required bromo/chloro compounds (**1a**–**h**) were prepared via bromination/chlorination of the corresponding methylindoles using NBS/NCS in the presence of a catalytic amount of benzoyl peroxide in CCl_4 at reflux.
9. All the dimeric indole derivatives **2a**–**h** gave satisfactory spectral and analytical data.
   *Typical experimental procedure for **2a***: 1-Phenylsulfonyl-3-phenylthio-2-bromomethylindole **1a′** (0.5 g, 1.09 mmol) dissolved in dry THF (10 mL) was stirred at 0-10 °C under a nitrogen atmosphere. To this, phenylmagnesium chloride (0.65 mL, 2 M in THF) was added slowly. The reaction mixture was slowly raised to room temperature and stirred for 5 h. Then it was quenched with saturated ammonium chloride solution (10 mL), extracted with ethyl acetate (2 × 20 mL) and the extracts were combined and dried (Na_2SO_4). Removal of the solvent followed by column chromatographic purification (silica gel, hexane–EtOAc; 9:1) afforded **2a** as a colourless solid (0.42 g, 52%); mp 220 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.77 (s, 4H), 6.65–6.68 (m, 4H), 6.92–6.94 (m, 6H), 7.16 (t, $J = 7.8$ Hz, 2H), 7.24 (t, $J = 7.3$ Hz, 2H), 7.27–7.32 (m, 2H), 7.37 (t, $J = 16.1$ Hz, 4H), 7.51–7.53 (m, 2H), 7.73 (d, $J = 7.3$ Hz, 4H), 8.22 (d, $J = 8.3$ Hz, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 28.1, 113.7, 115.6, 120.3, 124.4, 125.2, 125.4, 126.3, 126.5, 128.7, 129.5, 130.9, 134.1, 136.6, 137.3, 138.8, 144.6. Anal. Calcd for $C_{42}H_{32}N_2O_4S_4$: C, 66.64; H, 4.26; N, 3.70; S, 16.94. Found: C, 66.30; H, 4.40; N, 3.92; S, 16.81. Data for **2b**: mp 230 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.27 (s, 4H), 7.37 (t, $J = 7.1$ Hz, 2H), 7.42–7.44 (m, 2H), 7.49 (t, $J = 8.1$ Hz, 4H), 7.55 (d, $J = 7.8$ Hz, 2H), 7.61 (t, $J = 7.4$ Hz, 2H), 7.86 (d, $J = 7.8$ Hz, 4H), 8.25 (d, $J = 8.8$ Hz, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 28.9, 96.5, 112.9, 115.1, 119.5, 125.1, 126.5 (2C), 127.1, 129.8, 134.8, 135.9, 137.6, 146.7. Anal. Calcd for $C_{32}H_{22}N_4O_4S_2$: C, 65.07; H, 3.75; N, 9.49; S, 10.86. Found: C, 65.31; H, 3.91; N, 9.35; S, 10.67.
   Data for **2g**: mp 208 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.65 (s, 4H), 7.25–7.43 (m, 10H), 7.51–7.53 (m, 2H), 7.77 (d, $J = 7.3$ Hz, 4H), 8.22 (d, $J = 8.3$ Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 28.2, 104.8, 115.6, 120.3, 124.9, 126.3, 127.9, 129.4, 129.9, 130.1, 134.7, 136.7, 139.1. Anal. Calcd for $C_{30}H_{22}Br_2N_2O_4S_2$: C, 51.59; H, 3.17; N, 4.01; S, 9.18. Found: C, 51.51; H, 3.41; N, 4.16; S. 8.98.