Tetrahedron Letters,Vol.30,No.16,pp 2129-2132,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

THE REACTION OF VINYL GRIGNARD REAGENTS WITH 2-SUBSTITUTED NITROARENES: A NEW APPROACH TO THE SYNTHESIS OF 7-SUBSTITUTED INDOLES

Giuseppe Bartoli*, Gianni Palmieri
Dipartimento Scienze Chimiche, via S.Agostino 1, 62032 Camerino (Mc), Italy
Marcella Bosco, Renato Dalpozzo
Dipartimento Chimica Organica, viale Risorgimento 4, 40136 Bologna, Italy

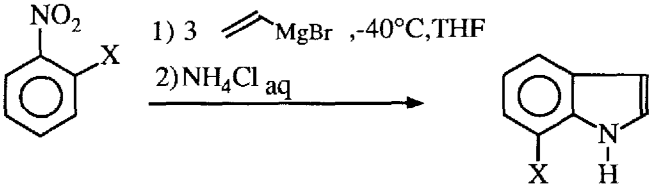
The reaction of three moles of vinylmagnesium bromide with one mole of nitroarene leads to the formation of indoles after aqueous work up of the mixture. Good yields are obtained with ortho-*substituted nitroarenes.*

Because of the potent biological activity exhibited by various indole derivatives, the methods of construction of this heterocyclic system have been object of considerable attention. The best known and classic among them are the Fischer, Bischler, Madelung, Reissert, Nenitzescu and Gassman procedures.[1] Other interesting methods are based on nucleophilic[2] and free radical addition,[3] intramolecular amidoalkylations,[4] intramolecular cyclisation of *ortho* aminostyrenes[5] or *via* organometallic intermediates.[6] However, notwithstanding the availability of a wide variety of approaches, modifications of previous methodologies[7] and new syntheses[8] continue to appear in the literature, in order to improve the efficiency of the reaction and to start from easily available materials.

In this communication we report a completely new approach to the synthesis of 7-substituted indoles.

In a typical procedure, vinylmagnesium bromide (15 mmol) was quickly added to a stirred THF solution (10 mL/mmol) of 2-nitrotoluene (5 mmol) cooled at -40 °C, under nitrogen. The reaction mixture was stirred for 20 minutes and then poured into saturated aqueous ammonium chloride, extracted with ether and dried over anhydrous sodium sulphate. After chromatographic purification 7-methylindole was obtained in 67% yield (scheme 1). The reaction proceeds in good yields with other 2-substituted nitrobenzenes (see table). Starting from 2-chloro and 2-bromonitrobenzene, about 30% of 2-oxoindole was also recovered. Nevertheless, the chromatographic separation of the two products can be easily performed.

SCHEME 1



It is surprising that satisfactory yields are only obtained when the *ortho* position is substituted. In fact 4-chloro- and 4-bromonitrobenzene led to the corresponding indoles in very low yields (17 and 12% respectively), the 4-substituted aniline being the major product. This limitation also applies to nitroaromatic bicyclic systems: while 1-nitronaphthalene, 5-nitroacenaphthene and 5-nitroquinoline gave the corresponding indoles in satisfactory yields (see table), only 17% of benzindole was recovered from the 2-nitronaphthalene system.

Carrying out the reaction of styrylmagnesium bromide with 2-chloronitrobenzene, one mole of phenylacetaldehyde and one mole of styrene were produced per mole of indole according to the stoichiometry reported in scheme 2.[9] However, no conclusive proposal can be put forward about the reaction mechanism, since, even using a deficiency of Grignard reagent no intermediates were isolated, very likely because of their polymerisation. This reactivity is quite different from the normal reactivity of Grignard reagents with nitroarenes. In fact it was reported that the alkyl[10] and the allyl[11] reagents react with nitroarenes in a 1:1 ratio essentially leading to conjugate or 1,2 addition respectively. Furthermore arylmagnesium halides react in a 2:1 ratio with the formation of diarylhydroxylamines *via* reductive addition.[12] We speculate that the present reaction might be similar to the latter one and that the indole may be formed by cyclization of a vinylarylhydroxylamine intermediate promoted by the third mole of Grignard reagent.

In conclusion, a reaction which employs cheap reactants and mild conditions is now available to synthesize 7-substituted indoles. Since in our opinion this approach to the construction of the indole nucleus is open to very interesting developments, studies on the reaction mechanism are in progress in order to understand why the reaction proceeds well only with *ortho* substituted nitroarenes.

Acknowledgments: Authors wish to thanks the Italian MPI for financial support. Dr. E. Mezzina is also acknowledged.

References and notes

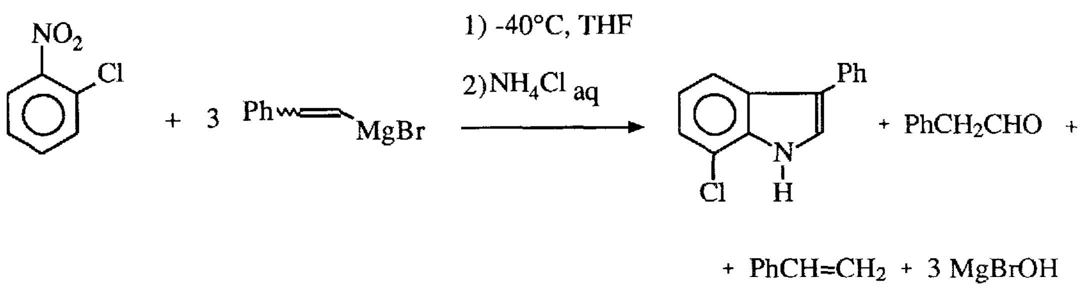
1. (a) Houlihan, W.J., Ed., *Indoles*, Wiley-Interscience; New York, 1972, Part 1. (b) Sundberg, R.J., *Chemistry of Indoles*, Academic Press; New York, 1970. (c) Newkome, G.R.; Paudler, W.W., *Contemporary Heterocyclic Chemistry*, Wiley-Interscience; New York, 1982, ch 5.1. (d) Gassman, P.G.; van Bergen, T.J.; Gilbert,

Table - Results of the Reaction of Vinylmagnesium Bromide with Nitroarenes in THF at -40 °C.

Substrate	Product	Yield (%)	mp (°C)^a	Notes
2-Methylnitrobenzene	7-Methylindole	67	80-82 (81-83)	b
2-Bromonitrobenzene	7-Bromoindole	62	43-44 (42-43)	c,d
2-Fluoronitrobenzene	7-Fluoroindole	42	61-63 (61-62)	e
2-Chloronitrobenzene	7-Chloroindole	63	57-58 (57-58)	f,g
2-Trimethylsilyloxynitrobenzene	7-Trimethylsilyloxyindole	41	oil	h
3-Chloronitrobenzene	4- and 6-Chloroindole	19	oil and 88-90 (bp 129/4 mm and 89-91)	b,i
4-Bromonitrobenzene	5-Bromoindole	12	91-92 (90-92)	b,j
4-Chloronitrobenzene	5-Chloroindole	17	69-70 (68-70)	b,k
1-Nitronaphthalene	Benzo[g]indole	54	182-183 (180-181)	l
5-Nitroacenaphthene	5,6-Dihydroindeno-[1,7-fg]indole	59	96-97	m
2-Nitronaphthalene	Benzo[e]indole	17	oil (bp 144/0.5 mm)	l,n
5-Nitroquinoline	Pyrrolo[2,3-f]quinoline	42	222-224	o

(a). literature values in parentheses. (b). recognized by comparison with an authentic sample. (c). Leggetter, B.E.; Brown, R.K.; *Can. J. Chem.*, **1960**, *38*, 1467. (d). 30% of 2-oxoindole, recognized by comparison with an authentic sample, was also recovered. (e). Allen, F.L.; Brunton, J.C.; Suschitzky, H.; *J. Chem. Soc.*, **1955**, 1283. (f). 33% of 2-oxoindole, recognized by comparison with an authentic sample, was also recovered. (g). Rydon, H.N.; Tweddle, J.C.; *J. Chem. Soc.*; **1955**, 3499. (h). ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 0.41 (s, 9H, Me_3Si); 6.57-6.60 (m, 1H, H-3); 6.69 (d, 1H, H-4); 7.03 (t, 1H, H-5, $J_{4,5}=J_{5,6}=$ 7.8 Hz); 7.16-7.19 (m, 1H, H-2); 7.36 (d, 1H, H-6); 8.32 (bs, 1H, NH). m/z: 205 (M+), 190, 174, 159, 130, 116, 89, 73, 45. (i). 32% of 3-chloroaniline, recognized by comparison with an authentic sample, was also recovered. (j). 42% of 4-bromoaniline, recognized by comparison with an authentic sample, was also recovered. (k). 35% of 4-chloroaniline, recognized by comparison with an authentic sample, was also recovered. (l). Rydon, H.N.; Siddappa, S.; *J. Chem. Soc.*, **1951**, 2462. (m). ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 3.20-3.60 (m, 4H, CH_2CH_2); 6.63-6.68 (m, 1H, H-3); 7.24-7.34 (m, 2H, H-3 and H-7); 7.27 (s, 1H, H-4); 7.48 (t, 1H, H-8, $J_{7,8}=J_{8,9}=7.5$ Hz); 7.70 (d, 1H, H-9); 8.80 (bs, 1H, NH). m/z: 193 (M+), 192, 165, 163, 139, 96, 82, 63, 50. (n). 15% of 2-naphthylamine, recognized by comparison with an authentic sample, was also recovered. (o). ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 6.67 (d, 1H, H-3, $J_{2,3}=$ 3.0 Hz); 7.40-7.65 (m, 3H); 7.95 (d, 1H, J= 8.8 Hz); 8.67-8.73 (m, 2H). m/z: 168 (M+), 140, 114, 84, 70, 63, 50

SCHEME 2



D.P.; Cue, B.W. Jr, *J. Am. Chem. Soc.*, **1974**, *96*, 5495. (e) Gassman, P.G.; Gruetzmacher, G.I.; van Bergen, T.J.; *J. Am. Chem. Soc.*, **1974**, *96*, 5512.

2. (a) Germain, C.; Bourdais, J.; *J. Heterocycl. Chem.*, **1976**, *13*, 209. (b) Fleming, I.; Woolias, M.; *J. Chem. Soc. Perkin Trans 1*, **1979**, 827 and 829. (c) Ito, Y.; Kobayashi, K.; Saegusa, T.; *J. Am. Chem. Soc.*, **1977**, *99*, 3522. (d) Ito, Y.; Kobayashi, K.; Saegusa, T.; *J. Org. Chem.*, **1979**, *44*, 2030.
3. Ueno, Y.; Chino, K.; Okawara, M.; *Tetrahedron Lett* ., **1982**, *23*, 2575.
4. (a) Ben-Ishai, D.; *J. Chem. Soc. Chem. Comm.*, **1980**, 687. (b) Ben-Ishai, D.; Peled, N.; Sataty, I.; *Tetrahedron Lett* ., **1980**, *21*, 569. (c) Nordlander, J.E.; Catalane, D.B.; Kotian, K.D.; Stevens, R.M.; Haky, J.E.; *J. Org. Chem.*, **1981**, *46*, 778.
5. Hengartner, U.; Batcho, A.D.; Blount, J.F.; Leimgruber, W.; Larscheid, M.E.; Scott, J.W.; *J. Org. Chem.*, **1979**, *44*, 3748.
6. (a) Wender, P.A.; White, A.W.; *Tetrahedron*, **1983**, *39*, 3767. (b) Castro, C.E.; Gaughan, E.J.; Owsley, D.C.; *J. Org. Chem.*, **1966**, *31*, 4071. (c) Hegedus, L.S.; Allen, G.F.; Olsen, D.J.; *J. Am. Chem. Soc.*, **1980**, *102*, 3583. (d) Mori, M.; Ban, Y.; *Tetrahedron Lett.*, **1979**, *20*, 1133. (e) Ames, D.E.; Ribeiro, O.; *J. Chem. Soc. Perkin Trans 1*, **1976**, 1073. (f) Kraus, G.A.; Frazier, K.; *Tetrahedron Lett.*, **1978**, *19*, 3195. (g) Sakamoto, T.; Kondo, Y.; Yamanaka, K.; *Heterocycles*, **1984**, *22*, 1347. (h) Larock, R.C.; Liu, C.-L.; Lau, H.H.; Varapath, S.; *Tetrahedron Lett.*, **1984**, *24*, 4459.
7. (a) For a modification of the Fischer indolisation see: Baccolini, G.; Todesco, P.E.; *J. Chem. Soc. Chem. Comm.*, **1981**, 563; Baccolini, G.; Dalpozzo, R.; Todesco, P.E.; *J. Chem. Soc. Perkin Trans 1*, **1988**, 971.
   (b) For modifications of the Madelung indolisation see: Houlihan, W.J.; Parrino, V.A.; Uike, Y.; *J. Org. Chem.*, **1981**, *46*, 4511. Le Corre, M.; Hercouet, A.; Le Stane, Y.; Le Baron, H.; *Tetrahedron*, **1985**, *41*, 5513. Bergman J., Sand P., Tilstam U.,*Tetrahedron Lett.*, **1983**, *24*, 3665. Bartoli, G.; Bosco, M.; Dalpozzo, R.; Todesco, P.E.; *J. Chem. Soc. Chem. Comm.*, **1988**, 807.
   (c) For a modification of the Reissert indolisation see: RajanBabu, T.V.; Chenard, B.L.; Patti, M.A.; *J. Org. Chem.*, **1986**, *51*, 1704.
8. (a) Crotti, C.; Cenini, S.; Rindone, B.; Tollari, B.; Tollari, S.; Demartin, F.; *J. Chem. Soc. Chem. Comm.*, **1986**, 784. (b) Tsuji, T.; Huh, K.-T.; Watanabe, Y.; *J. Org. Chem.*, **1987**, *52*, 1673.
9. 7-Chloro-3-phenylindole was recovered in 44% yield. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 7.00-7.59 (m, 8H); 7.77 (d, 1H, J=7.8 Hz); 8.36 (bs, 1H, NH). m/z: 227-229 (M+), 190, 165, 139, 114, 96, 82, 63.
10. Bartoli, G.; *Acc. Chem. Res.*, **1984**, *17*, 109.
11. Bartoli, G.; Bosco, M.; Dalpozzo, R.; Marcantoni E.; *Tetrahedron Lett.*, **1988**, 2251.
12. (a) Bartoli, G.; Bosco, M.; Cantagalli, G.; Dalpozzo, R.; Ciminale, F.; *J. Chem. Soc. Perkin Trans. II*, **1985**, 773. (b) Buck, P.; Kobrik, G.; *Tetrahedron Lett.*, **1967**, 1563. (c) Yost, Y.; Gutmann, H.R.; Muscoplat, C.C.; *J. Chem. Soc. C*, **1971**, 2119.

(Received in UK 27 February 1989)