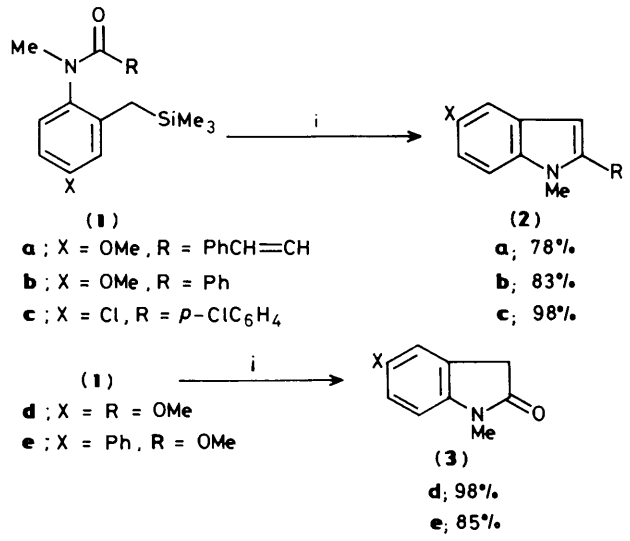
Intramolecular Peterson Olefination of *ortho*-Trimethylsilylmethyl Anilides: a New Synthesis of *N*-Methylindoles

Giuseppe Bartoli,[a]* Marcella Bosco,[b] Renato Dalpozzo,[b] and Paolo E. Todesco[b]

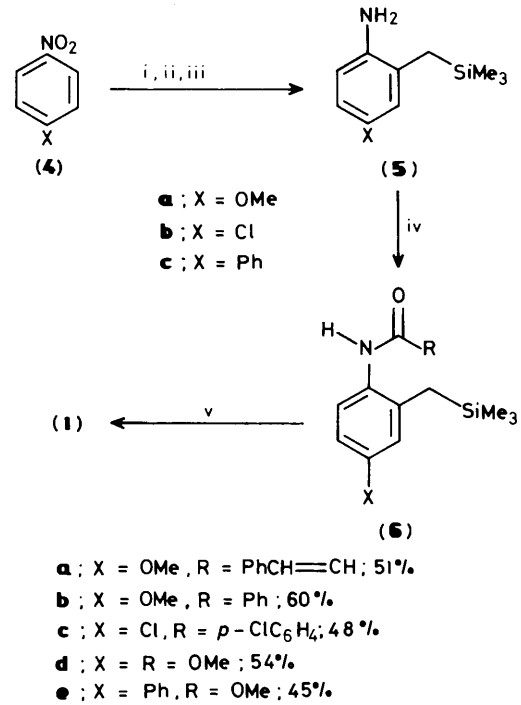
[a] *Dipartimento Scienze Chimiche, Università, via S. Agostino 1, I-62032 Camerino (MC), Italy*
[b] *Dipartimento di Chimica Organica, Università, viale Risorgimento 4, I-40136 Bologna, Italy*

A modified Madelung synthesis of indoles by cyclisation of *ortho*-trimethylsilylmethyl anilides under mild conditions is reported.

In recent years, the Madelung synthesis of indoles[1] by cyclisation of *ortho*-alkyl anilides under basic conditions at high temperatures (200—400 °C) has undergone various constructive modifications to obviate its restricted applicability, but all these suffer from some drawbacks. For example, the use of butyl-lithium as cyclisation-promoting base[2] allows the reaction to be carried out at room temperature, so making the method compatible with the presence of halogeno and alkoxy substituents in the benzene ring. However, this procedure fails in the synthesis of 2-alkenylindoles and/or related systems which do not survive the presence of such a nucleophilic base. The recently proposed[3] cyclisation of *ortho*-acylaminobenzyltriphenylphosphonium salts appears widely applicable only if the starting material can be made readily



Scheme 1. *Reagents and conditions*: i, LDA, THF, −20 °C, 20 min.



Scheme 2. *Reagents and conditions*: i, Me_3SiCH_2MgCl, THF, 0 °C; ii, $LiAlH_4$, Pd/C, room temp.; iii, aq. NH_4Cl; iv, RCOCl, Et_3N; v, NaH, MeI.

available. Finally, the Bergman synthesis[4] is restricted to the preparation of indoles carrying a strongly electron-withdrawing substituent (such as nitro) on the benzene ring.

We report a new highly efficient indole synthesis based on lithium di-isopropylamide-promoted cyclisation of *ortho*-(trimethylsilylmethyl) *N*-methylanilides (**1a—e**) (Scheme 1). The very mild conditions allow this method to be applied to the synthesis of 2-alkenyl- and chloro- or methoxy-substituted indoles (**2a—c**). Moreover, our procedure can be extended to an easy synthesis of 2-oxoindoles (**3d** and **e**) from the corresponding methylcarbamates.

A typical procedure is as follows: lithium di-isopropylamide (LDA) in tetrahydrofuran (THF) (2 equiv.) was added dropwise at −20 °C to a solution of the amide (**1**) in the same solvent. The mixture was allowed to warm to room temperature (20 min), then treated with dilute HCl (3%) and extracted with ether. The organic layer was dried and evaporated to give the desired indole in high to almost quantitative yield.†

The most advantageous aspect of our method is the ready availability of starting materials. The key intermediates for the synthesis of the amides (**1a—e**) [the anilines (**5a** and **c**)] can be efficiently prepared in good yield according to a recently reported general and highly chemoselective one-pot method of reductive alkylation of nitroarenes.[5] The reaction steps from the nitro derivative (**4**) to the amides (**1**) (Scheme 2) can be carried out without purification of the intermediates (**5**) and (**6**).‡ Yields of the amides (**1a—e**) reported in Scheme 2 were calculated with respect to the starting nitroarenes (**4**) and refer to pure isolated products.§

Furthermore, this method offers the same advantages as the Peterson olefination with respect to the Wittig procedure, in that the siloxane by-products are easily removed by evaporation.

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References

1 R. K. Brown in 'Indoles,' ed. W. J. Houlihan, Wiley-Interscience, New York, 1972, part 1; R. L. Augustine, A. J. Gustavsen, S. F. Wanat, I. C. Pattison, K. S. Hougton, and G. Koletar, *J. Org. Chem.*, 1973, **38**, 3004; W. E. Noland and C. Reich, *ibid.*, 1967, **32**, 828; L. Marion and W. R. Ashford, *Can. J. Res.*, 1945, **23**, 26.
2 W. J. Houlihan, V. A. Parrino, and Y. Uike, *J. Org. Chem.*, 1981, **46**, 4511.
3 M. Le Corre, A. Hercouet, and H. Le Baron, *J. Chem. Soc., Chem. Commun.*, 1981, 14.
4 J. Bergman, P. Sand, and U. Tilstam, *Tetrahedron Lett.*, 1983, **24**, 3665.
5 G. Bartoli, M. Bosco, R. Dalpozzo, and M. Petrini, *Tetrahedron*, 1987, **43**, 4221.
6 A. H. Beckett, R. W. Daisley, and J. Walker, *Tetrahedron*, 1968, **24**, 6093.

† *Selected data:* Yields refer to pure isolated products. (**2a**), m.p. 165—166 °C; ^{1}H n.m.r. ($CDCl_3$) δ 4.00 (s, 3H, NMe), 4.07 (s, 3H, OMe), and 7.07—8.13 (m, 11H, arom. and CH=CH); *m/z* 263 (M^+), 248, 220, 204, 152, 115, and 91. (**2b**), m.p. 124—125 °C; ^{1}H n.m.r. ($CDCl_3$) δ 3.67 (s, 3H, NMe), 3.87 (s, 3H, OMe), and 6.30—7.63 (m, 9H, arom.); *m/z* 237 (M^+), 222, 194, 165, 119, and 76. (**2c**), m.p. 125—127 °C; ^{1}H n.m.r. ($CDCl_3$) δ 3.77 (s, 3H, NMe), and 6.47—7.87 (m, 8H, arom.); *m/z* 275, 277, 279 (M^+), 239, 204, 102, and 63. (**3d**), m.p. 97—99 °C (lit.,[6] 98 °C). (**3e**), m.p. 168—170 °C; ^{1}H n.m.r. ($CDCl_3$) δ 3.33 (s, 3H, OMe), 3.67 (s, 2H, CH_2), and 6.90—7.80 (m, 8H, arom.); *m/z* 223 (M^+), 194, 152, 97, and 77.

‡ The reaction steps from (**4**) to (**1**) were followed by g.l.c.–mass spectrometric analysis. The anilines (**5**) and the amides (**6**) were identified from the mass spectra of the crude products: (**5a**) *m/z* 209 (M^+); (**5b**) 213—215 (M^+); (**5c**) 255 (M^+); (**6a**) 338 (M^+); (**6b**) 313 (M^+); (**6c**) 351/353/355 (M^+); (**6d**) 281 (M^+); (**6e**) 313 (M^+).

§ *Selected data* for (**1**): (**1a**), oil; ^{1}H n.m.r. ($CDCl_3$) δ −0.10 (s, 9H, $SiMe_3$), 1.80 (s, 2H, CH_2), 3.00 (s, 3H, NMe), 3.60 (s, 3H, OMe), 6.00 (d, 1H, CH=, *J* 16.0 Hz), 6.33—7.23 (m, 8H, arom.), and 7.43 (d, 1H, CH=); *m/z* 353 (M^+), 348, 277, 262, 192, 131, 103, and 73. (**1b**), oil; ^{1}H n.m.r. ($CDCl_3$) δ 0.10 (s, 9H, $SiMe_3$), 1.67—2.27 (AB, 2H, CH_2), 3.43 (s, 3H, NMe), 3.83 (s, 3H, OMe), and 6.50—7.40 (m, 8H, arom); *m/z* 327 (M^+), 312, 250, 238, 134, 105, and 73. (**1c**), oil; ^{1}H n.m.r. ($CDCl_3$) δ 0.00 (s, 9H, $SiMe_3$), 1.47—2.10 (AB, 2H, CH_2), 3.17 (s, 3H, NMe), and 6.70—7.27 (m, 7H, arom.); *m/z* 364, 366, 368 ($M^+ - 1$), 254, 139, 111, and 73. (**1d**), oil; ^{1}H n.m.r. ($CDCl_3$) δ 0.00 (s, 9H, $SiMe_3$), 2.00 (s, 2H, CH_2), 3.17 (s, 3H, NMe), 3.63 (s, 3H, CO_2Me), 3.77 (s, 3H, OMe), and 6.47—7.20 (m, 3H, arom.); *m/z* 281 (M^+), 250, 177, 162 and 73. (**1e**), m.p. 91—93 °C; ^{1}H n.m.r. ($CDCl_3$) δ 0.00 (s, 9H, $SiMe_3$), 2.00 (s, 2H, CH_2), 3.13 (s, 3H, NMe), 3.60 (s, 3H, CO_2Me), and 7.10—7.73 (m, 8H, arom.); *m/z* 327 (M^+), 312, 296, 223, 194, 89, and 73.