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A NEW APPROACH TO THE SYNTHESIS OF 2-SUBSTITUTED INDOLES: REACTION OF DIMETALLATED *ORTHO*-TRIMETHYLSILYLMETHYLANILIDES WITH ESTERS

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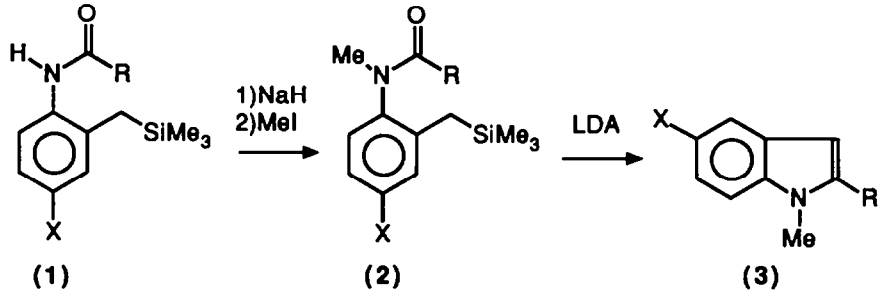
The reaction of 2-trimethylsilylmethylanilides and esters in basic medium provides a new general method for the synthesis of indoles. The advantages of this method are the mild reaction conditions (-10-0 °C), the ready availability of the starting materials and the use of a non-nucleophilic base (lithium 2,2,6,6-tetramethylpiperidide) to promote cyclisation.

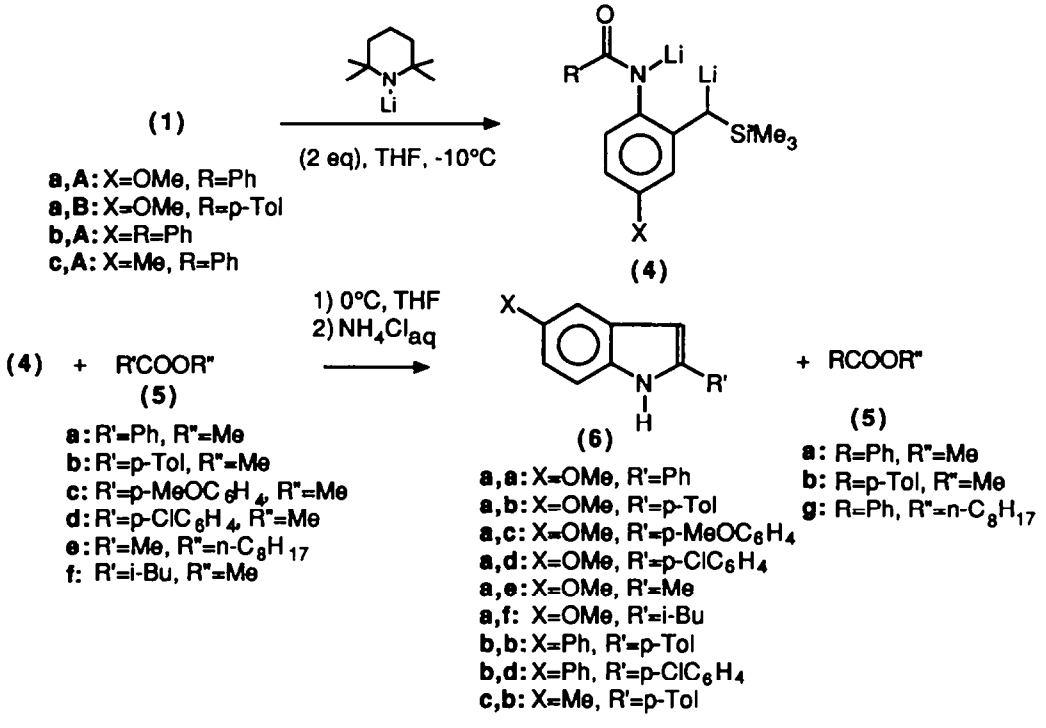
The construction of the indole ring system, one of the most prevalent subunits in natural product chemistry, has captured the interest of organic chemists for over a century[1]. The cyclisation of *ortho*-alkylanilides in strong basic medium (Madelung reaction)[2] represents one of the most common approaches to this problem. However, the drastic experimental conditions (200-400 °C), made the original method incompatible with a large variety of organic functions. Recently, interesting modifications allowed the reaction to be carried out in milder conditions, but all these suffer from some drawbacks. For example, the Houlihan method[3], in which the benzylic carbanion is formed by butyllithium, cannot be applied to the synthesis of indoles with electrophilic substituents. Furthermore, when the amides carry hydrogen atoms on the α-position of the carbonylic function, the metallation of this position deactivates the cyclisation. The Bergman synthesis is restricted to the preparation of nitro substituted indoles[4]. The cyclisation of *ortho*-acylaminobenzyltriphenylphosphonium salts appears more widely applicable[5], notwithstanding the laborious three-stage procedure required for the preparation of the starting material.

In a recent communication[6], we reported that *ortho*-trimethylsilylmethylanilides (**1**) can be almost quantitatively converted into indoles *via* an intramolecular Peterson olefination by treatment with equimolecular amounts of lithium diisopropylamide (LDA) in tetrahydrofuran (THF) (Scheme 1). The advantageous aspects of this method are the ready availability of the starting anilines, from reductive chemoselective alkylation of nitroarenes[7], and the very mild reaction conditions which allow the survival of a lot of organic functions. Unfortunately, this method can be applied only to the synthesis of *N*-methyl substituted indoles (**3**) and the removal of the methyl protective group can often be a difficult process.

SCHEME 1



SCHEME 2



We report now a new approach to the synthesis of *N*-unsubstituted indoles starting from (**1**).

When a THF solution of 4-methoxy-2-trimethylsilylmethylbenzanilide (**1a,A**) is treated with 2.5 equivalents of lithium 2,2,6,6-tetramethylpiperidide at -10 °C, the dilithiated compound (**4a,A**) is very likely formed. The lithiation goes to completion in a few minutes. In fact, upon quenching with AcOD/D_2O after 30 minutes, compound (**1a,A**) is recovered in 96% yield containing more than 97% deuterium incorporation at the benzylic function. The addition of methyl *p*-toluate (**5b**) to (**4a,A**), followed by quenching with a saturated solution of ammonium chloride, gives 5-methoxy-2-(*p*-tolyl)indole (**6a,b**) and

methyl benzoate (**5a**) (Scheme 2). In analogous manner, the reaction of (**1a,B**) and (**5a**) leads to 5-methoxy-2-phenylindole (**6a,a**) and methyl *p*-toluate (**5b**). These findings indicate that the indole incorporates in the 2-position the framework present in the parent ester, while the final ester carries the acyl group of the starting amide.

The reaction very likely proceeds *via* a preliminary addition of the benzylic carbanion to the ester and form ketone (**7**), which undergoes an intramolecular cyclisation to (**8**), followed by Peterson olefination to give *N*-benzoylindole (**9**). The lithium methoxide formed in the first stage is very likely able to give a nucleophilic displacement of the benzoyl group leading to the metallated indole (**10**) (Scheme 3)[8]. The attack of the lithium salt (**4**) on the starting ester (**5**) very likely occurs much faster than subsequent steps, therefore the final ester is slowly formed in the reaction medium and it cannot compete with the starting one (**5**). However, a 2:1 excess of starting ester generally allows this competition to be avoided.

The reaction shows a general character: 2-unsubstituted, 2-alkyl and 2-arylindoles can be obtained in good to moderate yields.

Carrying out the reaction of (**4a**) with ethyl formate (**5h**) or ethyl carbonate (**5i**), the indoles (**11a,h** and **11a,i**, respectively) substituted in the 3-position with the benzoyl group were recovered as major products (Scheme 4). Indole lithium salts (**10**) are reported to afford products from attack at carbon in the 3-position[9] in the reaction with esters in aprotic medium. The presence in the 2-position of electron-donating substituents (such as alkoxy groups) or the absence in this position of bulky frameworks (as in the 2-unsubstituted indole **11a,h**) very likely favours the attack at the 3-position. Owing to the greater electrophilic reactivity of ethyl benzoate than of ethyl carbonate, the latter does not compete with the former in the reaction with (**10a,i**) even if a large excess (2:1) of (**5i**) is employed. In contrast, in the reaction with ethyl formate under the same conditions, some 5-methoxyindole-3-carbaldehyde is recovered. However, the use of only a moderate excess (1.5:1) of (**5h**) allows the 3-formyl derivative formation to be drastically reduced.

The use of a non-nucleophilic base such as the lithium 2,2,6,6-tetramethylpiperidide is essential to ensure good yields. In fact, poor yields or no reaction are obtained with the more usually employed LDA. In addition a large amount of trans-amination product is observed.

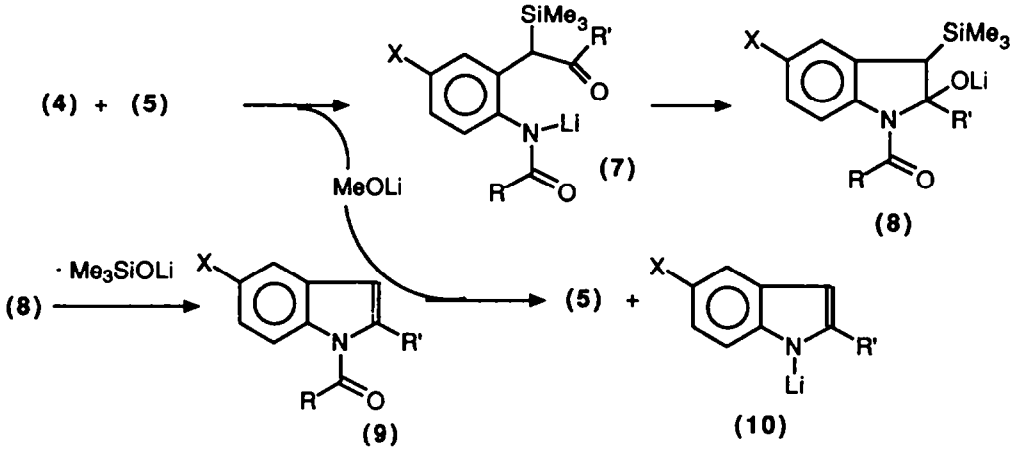
In conclusion, a new general method for construction of the indole nucleus is now available. The advantages of this method are the mild reaction conditions, the ready availability of the starting materials[7] and the use of a non-nucleophilic, less strong base than butyllithium[3].

Experimental

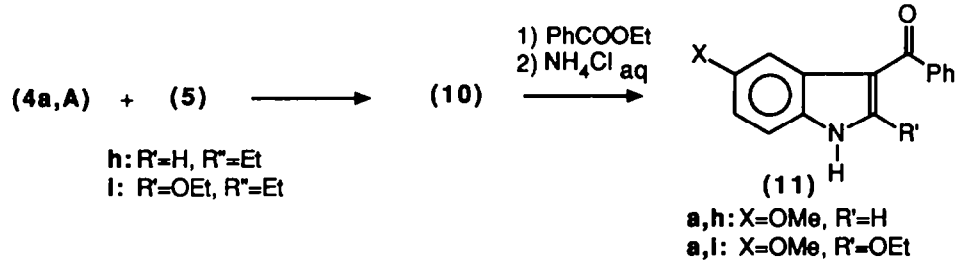
^{1}H-NMR spectra were recorded with a Varian VXR 300 instrument. Chemical shifts are given in p.p.m. from Me_4Si in $CDCl_3$ solutions. Mass spectra were recorded by a VG 7070 spectrometer. IR spectra were recorded with a Perkin-Elmer 257 spectrophotometer. VPC Analyses were performed on a Carlo Erba Fractovap 4160 HRGC instrument using OV1 capillary column. Melting points are uncorrected and were determined with a Büchi apparatus. THF was dried by refluxing over sodium wire until the blue colour of

benzophenone ketyl persisted and then distilling it into a dry receiver under nitrogen atmosphere. The *ortho*-trimethylsilylmethylanilines were synthesized as previously described[7]. Amides (1) were prepared by reaction of the crude amines (5 mmol) with acyl chloride (5.2 mmol) in the presence of triethylamine (5.5 mmol) in ethereal solution, followed by purification on a silica gel column[10].

SCHEME 3



SCHEME 4



Synthesis of indoles by reaction of *ortho*-trimethylsilylmethylanilides (1) and esters (5) in the presence of lithium 2,2,6,6-tetramethylpiperidide.

A THF solution (2 mL) of 2,2,6,6-tetramethylpiperidine (3 mmol) was charged in a dropping funnel under nitrogen atmosphere and treated with BuLi (3 mmol) at -10 °C. After 5 minutes, the yellow solution of the piperidide was added dropwise to a THF solution (3 mL) of the amide (1) (1.2 mmol) at -10 °C under magnetic stirring and nitrogen atmosphere. Then a THF solution (2 mL) of ester (5, 2.4 mmol) was combined within 10 minutes to the mixture warmed at 0 °C. After 20 minutes, the reaction was quenched with saturated ammonium chloride, extracted with dichloromethane, dried over anhydrous sodium sulphate and evaporated under reduced pressure. The residue was submitted to a chromatographic separation on a silica gel column by elution with a 9/1 mixture of hexane:ethyl acetate. In the reaction between (**1a,A**) and (**5h**) 8% of 5-methoxyindole-3-carbaldehyde was recovered and identified by comparison with a commercial specimen

(Aldrich). Using a 1.5:1 excess of (**5h**) the carbaldehyde was detected only in traces. Yields and physical data follows:

6a,a: 71% from **1aA**. 69% from **1aB**. 168-9 °C (lit[11] 168). IR (CCl_4) ν_{NH} 3420 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 3.86 (s, 3H); 6.77 (bs, 1H, H-3); 6.87 (dd, 1H, H-6); 7.10 (d, 1H, $J_{4,6}$=2.46 Hz, H-4); 7.28 (d, 1H, $J_{6,7}$=8.78 Hz, H-7); 7.31-7.67 (m, 5H); 8.25 (bs, 1H).

6a,b: 74%. mp. 188-9 °C. IR (CCl_4) ν_{NH} 3420 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 2.41 (s, 3H); 3.88 (s, 3H); 6.72 (bs, 1H, H-3); 6.86 (dd, 1H, H-6); 7.10 (d, 1H, $J_{4,6}$=2.44 Hz, H-4); 7.22-7.26 (m, 2H); 7.27 (d, 1H, $J_{6,7}$=8.73 Hz, H-7); 7.52-7.56 (m, 2H); 8.25 (bs, 1H). Anal calcd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90%. Found C, 81.00; H, 6.35; N, 5.90%.

6a,c: 68%. mp. 219-20 °C(lit[11] 214). IR (CCl_4) ν_{NH} 3440 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 3.86 (s, 3H); 3.87 (s, 3H); 6.65 (bs, 1H, H-3); 6.83 (dd, 1H, H-6); 6.97 (d, 2H, J=8.85 Hz); 7.07 (d, 1H, $J_{4,6}$=2.44 Hz, H-4); 7.26 (d, 1H, $J_{6,7}$=8.65 Hz, H-7); 7.57 (d, 2H); 8.19 (bs, 1H).

6a,d: 61%. mp. 192-3 °C. IR (CCl_4) ν_{NH} 3380 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 3.87 (s, 3H); 6.73 (bs, 1H, H-3); 6.87 (dd, 1H, H-6); 7.08 (d, 1H, $J_{4,6}$=2.42 Hz, H-4); 7.28 (d, 1H, $J_{6,7}$=8.87 Hz, H-7); 7.39 (d, 2H, J=8.46 Hz); 7.56 (d, 2H); 8.25 (bs, 1H). Anal calcd for $C_{15}H_{12}NOCl$: C, 69.91; H, 4.69; N, 5.43%. Found C,69.90; H, 4.70; N, 5.45%.

6a,e: 58%. mp. 89-90 °C (lit[12] 89-90). IR (CCl_4) ν_{NH} 3400 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 2.40 (s, 3H); 3.85 (s, 3H); 6.15 (bs, 1H, H-3); 6.79 (dd, 1H, H-6); 7.03 (d, 1H, $J_{4,6}$=2.60 Hz, H-4); 7.15 (d, 1H, $J_{6,7}$=8.69 Hz, H-7); 7.75 (bs, 1H).

6a,f: 54%. oil. IR (CCl_4) ν_{NH} 3400 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 0.99 (d, 6H, J=6.60 Hz); 1.98 (m, 1H); 2.60 (d, 2H, J=7.17); 3.86 (s, 3H); 6.19 (bs, 1H, H-3); 6.79 (dd, 1H, H-6); 7.05 (d, 1H, $J_{4,6}$=2.49 Hz, H-4); 7.19 (d, 1H, $J_{6,7}$=8.79 Hz, H-7); 7.77 (bs, 1H). Anal calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89%. Found C, 76.85; H, 8.45; N, 6.85%.

6b,b: 59%. mp. 210-12 °C. IR (CCl_4) ν_{NH} 3420 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 2.40 (s, 3H); 6.83 (bs, 1H, H-3); 7.20-7.85 (m, 12H); 8.38 (bs, 1H). Anal calcd for $C_{21}H_{17}N$: C, 89.01; H, 6.05; N, 4.94%. Found C, 89.00; H, 6.05; N, 4.95%.

6b,d: 58%. mp. 235-6 °C. IR (CCl_4) ν_{NH} 3420 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 6.84 (bs, 1H, H-3); 7.30-8.25 (m, 12H); 8.45 (bs, 1H). Anal calcd for $C_{20}H_{14}NCl$: C, 79.07; H, 4.65; N, 4.61%. Found C, 79.05; H, 4.65; N, 4.65%.

6c,b: 52%. mp. 230-32 °C (lit[13]. 230). IR (CCl_4) ν_{NH} 3420 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 2.40 (s, 3H); 2.46 (s, 3H); 6.71 (bs, 1H, H-3); 7.01 (dd, 1H, H-6); 7.22-7.27 (m, 2H); 7.28 (d, 1H, $J_{6,7}$=8.49 Hz, H-7); 7.53-7.57 (m, 2H); 7.67 (d, 1H, $J_{4,6}$=1.78 Hz, H-4); 8.20 (bs, 1H).

11a,h: 56%. mp. 169-70 °C. IR (CCl_4) ν_{NH} 3300, ν_{CO} 1620 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 3.87 (s, 3H); 7.04-7.10 (m, 3H); 7.40 (d, 1H, $J_{6,7}$=8.78 Hz, H-7); 7.50-8.20 (m, 5H); 9.40 (bs, 1H). Anal calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57%. Found C, 76.45; H, 5.20; N, 5.60%.

11a,i: 55% oil. IR (CCl_4) ν_{NH} 3300, ν_{CO} 1670 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 1.30 (t, 3H, J=7.23 Hz); 3.91 (s, 3H); 4.30 (q, 2H); 6.92 (dd, 1H, H-6); 7.28 (d, 1H, $J_{6,7}$=8.82 Hz, H-7); 7.42-7.47 (m, 3H); 7.61-7.67 (m, 2H); 7.75 (d, 1H,$J_{4,6}$=2.55 Hz, H-4); 8.45 (bs, 1H). Anal calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74%. Found C, 73.15; H, 5.85; N, 4.75%.

Deuterium labelling experiments

Thirty minutes after mixing lithium 2,2,6,6-tetramethylpiperidide and (**1a,A**) under the conditions described above, a 5% solution of AcOD in deuterium oxide was added dropwise. The mixture was extracted with dichloromethane, washed in 5% aqueous $NaHCO_3$, dried over anhydrous sodium sulphate and evaporated under reduced pressure.

The amide (**1a,A**) was recovered in 96% yield with a deuterium incorporation greater than 97%. ^{1}H-NMR ($CDCl_3$) δ 2.05 (s, 1H). ^{13}C-NMR ($CDCl_3$) δ 22.61 (t, J_{C-D}=11.75 Hz); 314.1563 (M^+ $C_{18}H_{22}DNO_2Si$ requires 314.1561).

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