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AN EXPEDIENT SYNTHESIS OF SUBSTITUTED INDOLES

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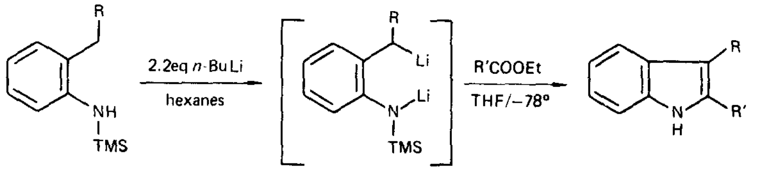
Summary: Condensation of carboxylic acid esters with organodilithium reagents derived from N-trimethylsilyl-o-toluidine or N-trimethylsilyl-o-ethyl aniline affords substituted indoles.

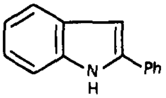
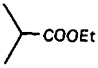
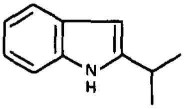
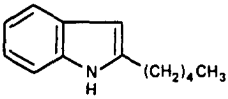
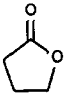
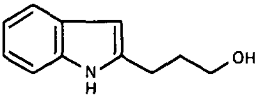
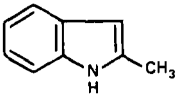
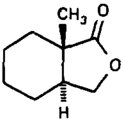
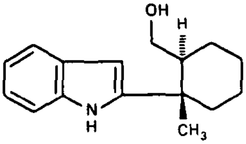
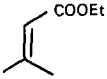
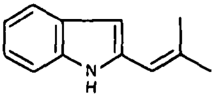
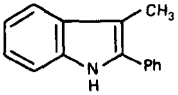
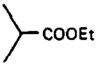
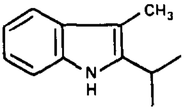
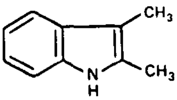
The indole ring system, one of the most prevalent structural subunits in natural products chemistry,[3] has captured the interest of organic chemists since indole was first isolated in 1866 by Adolf von Baeyer.[4] Significant in this regard are the number of synthetic methods that have been developed for the construction of this important functional group.[5] In connection with a program directed towards the synthesis of tremorgenic indole diterpenoid alkaloids,[6] we have developed a new, expedient procedure (eq. 1) for the regiospecific synthesis of mono and disubstituted indoles. The method is predicated on an earlier observation by Corriu,[7] in which silylated allylic amines were exploited for the synthesis of heterocyclic compounds.



(1)

While N,N-dialkyl amines are poor activators for metallation reactions,[8] [e.g., N,N-dimethyl-o-toluidine undergoes only 25% benzylic lithiation (nBuLi, ether-hexane, 20h)],[9] treatment of N-trimethylsilyl-o-toluidine[10] in hexane at reflux for 6 h with 2.2 equivalents of n-butyllithium affords a deep red solution containing an orange-red precipitate. Quenching studies with D_2O at 0°C followed by acid hydrolysis gave o-toluidine (>95% yield) with >95% deuterium[11] incorporation at the benzylic position. Inverse addition of this organodilithium reagent to a solution of ethyl benzoate in THF cooled to -78°C, followed by quenching with ice-water afforded 2-phenyl indole in 65% yield (Table 1, entry 1).[12] We envision this transformation to take place via a 3-stage

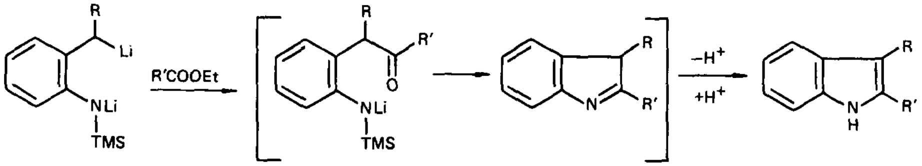
TABLE 1: Synthesis of Indoles

Entry	*Electrophile*	*Indole*[11]	*Method of Addition*[a]	*Yield*	*m.p.*
1.	PhCOOEt		A B	65%	182-184° (lit. 185-187°)[15]
2.			A	62%	72.5-73° (lit. 73-74°)[16]
3.	$CH_3(CH_2)_4COOEt$		A	62%	44-44.5° (lit. 47-48°)[17]
4.			A B	61% 59%	54.5-55.5° (lit. 53-55°)[18]
5.	CH_3COOEt		A	60%	59-59.5° (lit. 56-57°)[19]
6.			A	59%	152.5-154°[20]
7.			B	38%	103-105° (lit. 102-103°)[21]
8.	PhCOOEt		B	50%	91.5-92.5° (lit. 89-90°)[22]
9.			B	45%	liquid [23]
10.	CH_3COOEt		B	32%	103-105° (lit. 106°)[23]

a) Method A - the preformed organodimetallic reagent in hexanes 0.2 mmol/mL) is cooled to −78° C, and the ester dissolved in THF is added in one operation at this temperature.

Method B - the preformed organodimetallic reagent is added via cannula to the ester in THF at −78° C.

process involving initial C–C bond formation between the electrophilic reagent and the benzylic carbon of the organodilithium species (eq. 2). Subsequent intramolecular heteroatom Peterson olefination[13] results in the formation of the indolenine, which in turn tautomerizes to the indole.



(2)

The examples listed in Table 1 document the versatility of this indole synthesis.[14a,b] In particular, the selective metallation of N-trimethylsilyl-o-toluidine and its ready preparation from commercially available o-toluidine make this indole synthesis both expedient and economical. Futhermore, it is possible to convert o-toluidine directly to 2-substituted indoles in a one-pot reaction, precluding isolation of the silylated amine. The overall yield however is somewhat diminished (ca. 40% for 2-phenylindole). As indicated in Table 1 the method of addition of the organodilithium species to the electrophile has little effect on the overall yield of the process.

We have extended the method to the preparation of 2,3-disubstituted indoles employing o-ethyl-N-trimethylsilyl aniline.[10] In this case, formation of the organodilithium species required use of the n-butyllithium-TMEDA complex.[9] Addition of this dianion to a -78° solution of ethyl benzoate in THF afforded 3-methyl-2-phenylindole in 50% yield. Other representative 2,3-dialkylindoles which have been prepared by this method are shown in Table 1. In general, the method is best for esters which are least likely to undergo facile enolization. Unsaturated esters that show a propensity to undergo polymerization afford only modest yields (see entry 7).

In summary, we have developed a new, expedient and highly versatile method for the preparation of mono and disubstituted indoles. Studies to extend the generality, as well as exploit this method in the synthesis of architecturally complex natural products, will be reported in due course.

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2. American Cancer Society Postdoctoral Fellow 1983-1985.
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10. Prepared by the treatment of o-toluidine with n-butyllithium at -78°C, followed by addition of trimethylsilyl chloride, warming to room temperature, and distillation (bp 74-75°/0.1mm). o-Ethyl-N-trimethylsilyl aniline was prepared by the same method (bp 88-89°/0.1 mm).
11. Deuterium incorporation was determined by repeated integration of NMR signals at 250 MHz.
12. All products gave satisfactory spectral data in comparison with known literature values.
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14. (a) A typical procedure follows: To a mixture of 200 mg (1.12 mmole) of N-trimethylsilyl-o-toluidine in 10 mL of dry commercial hexanes was added dropwise 980 μL (2.2 equiv.) of a 2.5 M solution of n-butyllithium in hexanes. The resultant yellow solution was brought to reflux, maintained at this temperature for 6 h and then allowed to cool to room temperature. The dianion was then added via cannula to a precooled (-78°C) solution of 176 mg (1.17 mmol) of ethyl benzoate in 4 mL of THF. The reaction mixture was warmed to room temperature and then partitioned between 10 mL each of ether and ice-water. The aqueous layer was extracted four times with 10 mL of ether, the combined organic portions washed with 10 mL of brine, dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography [5% ethyl acetate-hexanes (v/v)] gave 140 mg (65% yield) of 2-phenyl indole (mp 182-184°, lit.^{15} 182-184°), identical (IR, ^{1}H NMR, and UV) to an authentic sample purchased from the Aldrich Chemical Co., Milwaukee, Wisconsin. (b) Interestingly, condensation of the above dianion with ethyl formate in THF at -78°C afforded indole in only 11% yield. Use of DMF as the electrophile gave indole in 42% yield, as well as a 20% yield of N-trimethylsilyl indole.
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20. ^{1}H NMR ($CDCl_3$): 1.33 (s, 3H), 1.04-2.25 (m, 10H), 3.24 (dd, J = 10.7 and 7.8 Hz, 1H), 3.48 (dd, J = 10.7 and 4.5 Hz, 1H), 6.30 (d, J = 2.1 Hz, 1H), 7.01-7.53 (m, 4H), 8.23 (br s, 1H): IR ($CHCl_3$): 3470 (m), 3330 (m), 2930 (s), 1460 (s), 1280 (s) and 1020 (m) cm^{-1}.
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