

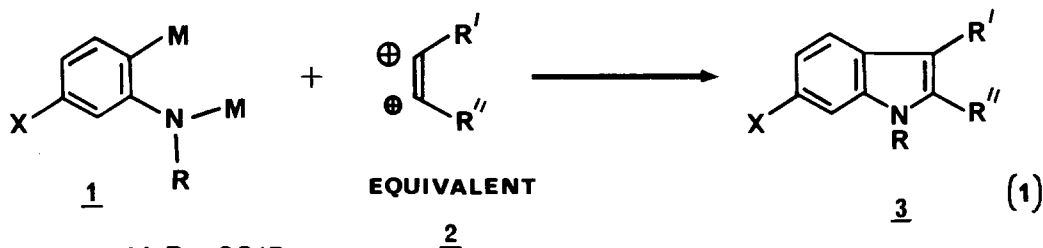
METHODOLOGY FOR INDOLE SYNTHESIS

Paul A. Wender^{1*} and Alan W. White

Department of Chemistry, Harvard University, Cambridge, MA 02138

Abstract: An efficient synthesis of indole derivatives in one operation by reaction of organodilithium reagents with vicinal dication equivalents is described.

The indole ring system is one of the medicinally important expressions² of the more general ortho-alkylaniline problem in organic synthesis. A methodology for indole synthesis³ (eq 1), which was developed in connection with our continuing studies on organodimetallic reagents⁴ and designed to deliver the target system in one operation with complete regiocontrol, is described herein.

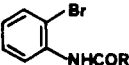

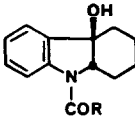
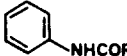
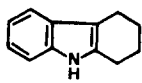
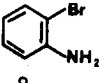

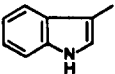

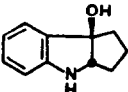
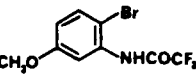
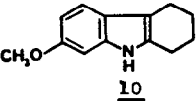


- a) X = H, M = Li, R = COtBu
b) X = OCH₃, M = Li, R = COCF₃
c) X = H, M = Li, R = COCF₃

The organodimetallic reagents required in this strategy were readily prepared from 2-bromoaniline derivatives via bromine-lithium exchange, a process which allows for efficient, site-specific lithiation. Thus, reaction of 2'-bromo-2,2-dimethylpropionanilide (4a) with methylolithium at -78°C followed by addition of t-butyllithium provided the organodilithium derivative 1a⁵ in a minimum of 89% as determined by the efficiency of its reaction with benzaldehyde.⁶ When 2-chlorocyclohexanone (5), a differentiated biselectrophile equivalent (cf 2), was used in place of benzaldehyde and the reaction was subsequently quenched with saturated NH₄Cl, the indole precursor 6a was obtained in 92% yield (Table I, entry 2).⁷ The formation of both of the bonds required for the indole system is consistent with the intermediacy of a cis-chloroalkoxide.⁸ The effect of variations in the nitrogen protecting group and reaction temperature on this process are shown in entries 1-4 in Table I.

As required for synthetic versatility, either an N-protected or unprotected indole can be formed from intermediate 6a. Thus, its dehydration induced by a trace of CF₃CO₂H in CH₂Cl₂ at room temperature provided the N-protected product, 9-(2',2'-dimethylpropionyl)-1,2,

TABLE 1

ENTRY/ANILINE DERIVATIVE	PREPARATION OF ^a ORGANODIMETALLIC	BISELECTROPHILE/ ^b WORK-UP	PRODUCTS (YIELD)	
1)  <u>4a</u> (R=tBu)	A	 (-78 ⁰ C) / B <u>5</u>	 <u>6a</u> (77%)	 <u>7a</u> (13%)
2) <u>4a</u>	A	<u>5</u> (-10 ⁰ C) / B	<u>6a</u> (92%)	<u>7a</u> (7%)
3) <u>4b</u> (R=OtBu)	A	<u>5</u> (-10 ⁰ C) / B	<u>6b</u> (67%)	<u>7b</u> (24%)
4) <u>4c</u> (R=CF ₃)	A	<u>5</u> (-10 ⁰ C) / B	<u>6c</u> (58%) <u>8</u> (18%)	<u>7c</u> (15%)
5) <u>4a</u>	A	<u>5</u> (-10 ⁰ C); KOtBu; H ₂ O / C	 <u>8</u> (77%)	
6) <u>4c</u>	A	<u>5</u> (-30 ⁰ C); 10% KOH/MeOH / C	<u>8</u> (75%)	
7)  <u>9</u>	2CH ₃ Li, r.t.; tBuCOCl, -78 ⁰ C; 2tBuLi, -78 ⁰ C	<u>5</u> (10 ⁰ C); KOtBu; H ₂ O / C	<u>8</u> (74%)	
8) <u>4c</u>	A	 (-78 C); HOAc; Et ₃ N(xs); ^c 10% KOH/ MeOH / C	 (52%) <u>7c</u> (45%)	
9) <u>4c</u>	A	 (-30 C); 10% KOH/MeOH / C	 <u>8</u> (67%) ^d	
10)  <u>10</u>	A	<u>5</u> (-30 ⁰ C); 10% KOH/MeOH / C	 <u>10</u> (69%)	

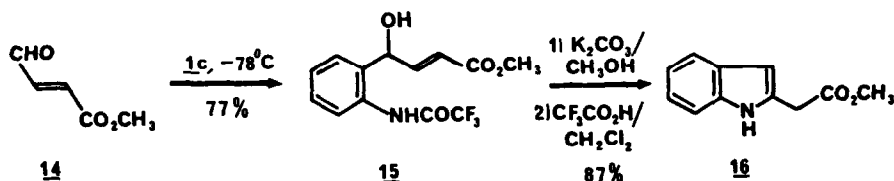
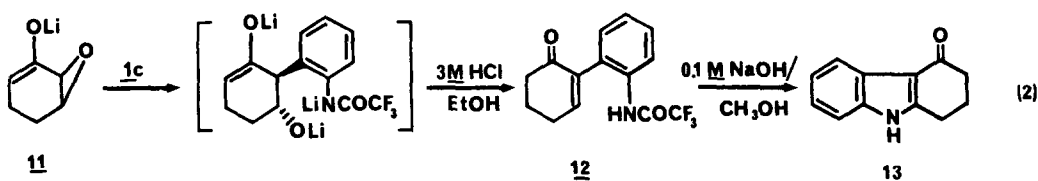
a) Method A - CH₃Li; 2tBuLib) Method B - saturated NH₄Cl; Method C - 5% HClc) If the chloroalkoxide is not quenched at -78⁰C, the predominant pathway for reaction is apparently epoxide formation.

d) This aminoalcohol can be quantitatively dehydrated to the corresponding indole with trifluoroacetic acid in methylene chloride.

3,4-tetrahydrocarbazole, in 94% yield. Alternatively, hydrolysis of 6a according to Gassman's anhydrous hydroxide procedure⁹ gave, after standard extractive workup (5% HCl)¹⁰ tetrahydrocarbazole 8 in 93% yield. Importantly, tetrahydrocarbazole 8 was obtained directly from 4a in 77% yield when the addition of chlorocyclohexanone was followed by the addition of KOtBu and H₂O (entry 5). Similarly, when the dilithium derivative of 4c was reacted with 2-chlorocyclohexanone and 10% KOH/MeOH was added to the resulting mixture, 8 was obtained directly in 75% yield (entry 6). Finally, commercially available 2-bromoaniline (9) can be converted to tetrahydrocarbazole 8 in 74% yield, in one operation (entry 7). For this purpose, 9 was first treated with methyl lithium (2 equiv.) and pivaloyl chloride (1 equiv.) and the resulting intermediate submitted to halogen-lithium exchange with t-butyllithium. The dianion 1a produced in this way was then used directly in the aforementioned condensation/hydrolysis sequence.

The regiocontrol provided by this methodology is reflected in its application to the preparation of 7-methoxy-1,2,3,4-tetrahydrocarbazole 10 (entry 10). In this case, the exchange process provided the 2-lithio-5-methoxy anilide intermediate 1b whereas deprotonation of the corresponding 3-methoxy anilide would be expected to give the 2-lithio-3-methoxy anilide. Variations in the chloroketone substrate do not change the regiochemistry of the addition of 1; however, some reagent induced enolization generally occurs depending on substrate substitution and reaction temperature.

Biselectrophile equivalents other than α -chlorocarbonyl compounds can also be used for the production of indoles. The enolate of cyclohexenone epoxide (11),¹¹ for example, served well in this connection (eq 2). Thus, treatment of this enolate with dianion 1c provided after acidic workup 12 in 59% yield. Treatment of this compound with 0.1N NaOH/MeOH at room



temperature for 12h gave 13 in greater than 60% yield. Ene-diones also serve effectively as another type of biselectrophile. For example, reaction of dianion 1c with 14 gave the expected alcohol 15 in 77% yield. Hydrolysis of 15 followed by dehydration afforded the methyl ester of indole-2-acetic acid (16). Further studies are in progress.

Acknowledgement. This work was supported by a grant from the National Science Foundation (CHE-7821463).

References and Notes

1. Fellow of the Alfred P. Sloan Foundation, 1979-1981; Camille and Henry Dreyfus Teacher-Scholar Award Recipient, 1980-1985.
2. R.T. Brown, J.A. Joule, and P.G. Sammes, in "Comprehensive Organic Chemistry", D.H.R. Barton and W.D. Ollis, eds., Vol. 4, Pergamon Press, Oxford, 1979 p. 411; J.P. Kutney in "Total Synthesis of Natural Products", J. ApSimon, ed., Vol. 3, Wiley-Interscience, New York, 1977; L.R. Smith in "Heterocyclic Compounds", W.J. Houlihan, ed., Vol. 25, Wiley-Interscience, New York, 1972, p.65.
3. For recent indole syntheses, see R. Odle, B. Blevins, M. Ratcliff, and L.S. Hegedus, J. Org. Chem. 45, 2709 (1980); R.R. Bard and J.F. Bunnett, J. Org. Chem. 45, 1546 (1980); L.S. Hegedus, G.F. Allen, and D.J. Olsen, J. Amer. Chem. Soc. 102, 3583 (1980); R. Beugelmans and G. Roussi, J. Chem. Soc. Chem. Commun. 950 (1979); T. Sugawara, M. Adachi and K. Sasakura, J. Org. Chem. 44, 578 (1979); and Ref. 2.
4. P.A. Wender and S.L. Eck, Tetrahedron Letters, 1245 (1977).
5. For an alternative preparation of 5 and a related dilithium reagent, see W. Fuhrer and H.W. Gschwend, J. Org. Chem. 44, 1133 (1979); J.M. Muchowski and M.C. Venuti, J. Org. Chem. 45, 4798 (1980).
6. All new compounds reported were homogeneous by TLC and gave satisfactory IR, NMR, MS and exact mass or combustion analysis.
7. 4a (1.00 mmole) was dissolved in 20 mL of THF and cooled to -78°C. CH₃Li (1.00 mmole) was added, and the resulting clear solution was stirred for 10 min. *t*-BuLi (2.00 mmole) was then added over 5 min. After 1h at -78°C, the yellow solution was warmed slowly (20 min) to -10°C. 2-chlorocyclohexanone (1.20 mmole) was added (neat) over 10 min, and the now colorless solution was stirred for 30 min at -10°C and 30 min at r.t. After a standard workup with saturated NH₄Cl, the majority of the product could be crystallized from crude reaction mixture with 25% Et₂O/hexanes. The remainder can be obtained by silica gel chromatography. IR (KBr) 3350, 1620, 1585 cm⁻¹; NMR (CDCl₃) 1.40 (s, 9H), 0.75-2.65 (m, 9H), 4.30-4.55 (m, 1H), 7.00-7.50 (m, 3H), 8.05-8.30 (m, 1H); mp 115.5-116.5°C (d).
8. For other examples of lithium and Grignard reagent additions to cyclic α-chloro-ketones, see A.J. Sisti and A.C. Vitale, J. Org. Chem. 37, 4090 (1972); A.S. Hussey and R.R. Herr, J. Org. Chem. 24, 843 (1959); A. Marcou, W. Chodkiewicz, and P. Cadiot, Bull. Soc. Chim. France, 2429 (1967).
9. P.G. Gassman and W.N. Schenk, J. Org. Chem. 42, 918 (1977); P.G. Gassman, P.K.G. Hodgson, and R.J. Balchunis, J. Am. Chem. Soc. 98, 1275 (1976).
10. TLC indicates that the hydroxyamide 6a is hydrolyzed to the corresponding amino alcohol which dehydrates on workup.
11. A study of the reaction of this and other epoxyenolates with organometallics has been submitted for publication.

(Received in USA 5 January 1981)