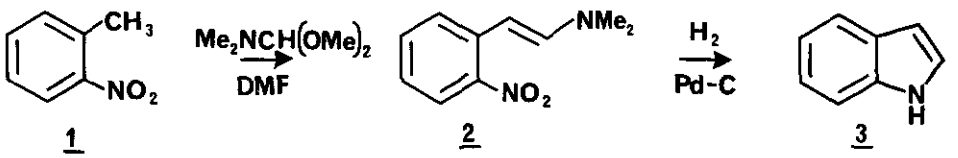
THE LEIMGRUBER-BATCHO INDOLE SYNTHESIS[1]

Robin D. Clark* and David B. Repke
Institute of Organic Chemistry, Syntex Research,
Palo Alto, California 94304 U.S.A.

Abstract - The Leimgruber-Batcho indole synthesis, which involves the reduction of β-dimethylamino-2-nitrostyrenes, is reviewed along with applications and modifications thereof.

INTRODUCTION

Since the first isolation of indole (3) in 1866 by Adolf Baeyer as a result of his studies on the degradation of indigo,[2] the synthesis of this ring system has captured the interest of organic chemists. Indeed, the first synthesis of indole, by reductive cyclization of 2-nitrophenylacetic acid, followed by zinc dust pyrolysis of the intermediate oxindole was reported shortly thereafter by Baeyer in 1869.[3] Subsequently, at least ten major syntheses of the indole ring system have been described. These include the methods of Fischer (1883), Hinsberg (1888), Bischler (1892), Reissert (1897), Pschorr (1910), Weerman (1910), Madelung (1912), Nenitzescu (1930), Heacock (1959), and Leimgruber and Batcho (1971). The details of the first ten of these are admirably covered in a number of reviews.[4-8] A number of important modifications of the earlier syntheses, including the Gassman[9] and Sugasawa[10] syntheses, have been reported. In 1971, Leimgruber and Batcho introduced a new and efficient indole synthesis based on the condensation of o-nitrotoluene (1) with N,N-dimethylformamide dimethyl acetal (DMFDMA) followed by reduction of the resulting trans-β-dimethylamino-2-nitrostyrene (2) (Scheme 1).[11]

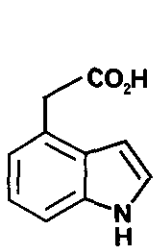


1 2 3

Scheme 1

In subsequent years, this reaction sequence (and modifications thereof) has been utilized for the preparation of many structurally diverse indoles. For example, the Leimgruber-Batcho method has formed the basis for the synthesis of indole-4-acetic acid (4),[12] the dopamine agonists 5 [13] and 6,[14] psilocin analogs 7,[15] a number of dimethyltryptamines such as 8,[16] 9,[17] and 10,[18] the β-blocker pindolol (11),[19] and the natural products 12,[20] chuangxinmycin (13),[21] 6,7-secoagroclavine (14),[22] and chanoclavine I (15)[23] (Table 1).

Table 1



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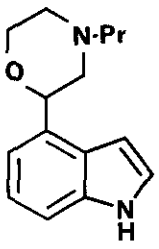

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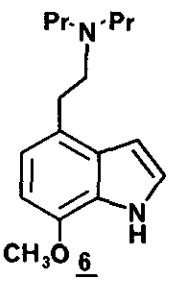

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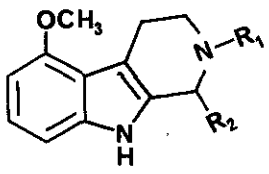

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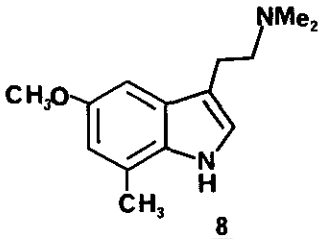

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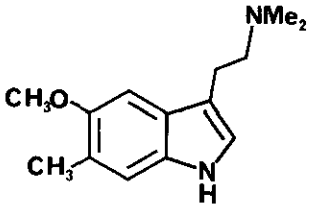

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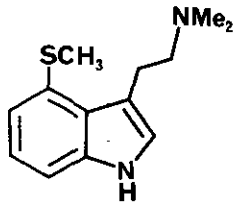

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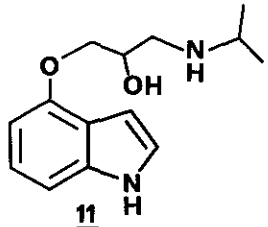

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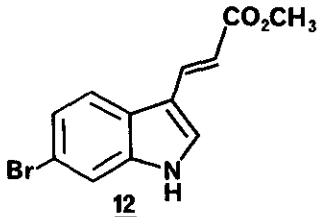

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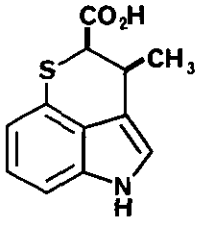

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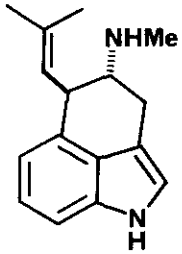

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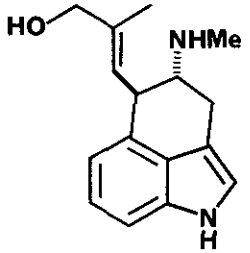

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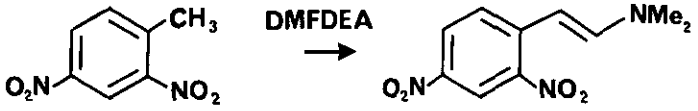
This review will summarize the conditions that have been used for carrying out both the enamine formation and the reduction step, as well as point out side reactions that have been observed. Modifications which have been developed for certain synthetic applications will also be described. The discussion text is organized in the following way:

1. Formation of trans-β-dialkylamino-2-nitrostyrenes
2. Reduction methods
3. Modifications of the general synthesis

Table 6 represents a compilation of 2,3-unsubstituted indoles which have been prepared and the method of enamine formation and reduction. Entry numbers from the Table are used for discussion of examples in the text. Typical experimental procedures have been included in the appropriate sections.

1. FORMATION OF trans-β-DIALKYLAMINO-2-NITROSTYRENES

The original basis for the Leimgruber-Batcho synthesis was Meerwein's observation that 2,4-dinitrotoluene (16) could be condensed with dimethylformamide diethyl acetal (DMFDEA) to give enamine 17.[24]



16 17

It was subsequently reported by Bredereck et al., that 2-nitrotoluene (1) could be converted to 2 by condensation with bis(dimethylamino)-t-butoxymethane.[25] The original Leimgruber-Batcho publications[11] described the use of N,N-dimethylformamide dimethyl and diethyl acetals, N-formylpyrrolidine dimethyl acetal, and N-formylpiperidine dimethyl acetal to carry out this type of transformation.[26] Of these, N,N-dimethylformamide dimethyl acetal (DMFDMA) has found

the widest application. The condensation is generally carried out by heating a DMF solution of the nitrotoluene and DMFDMA at or near reflux. Special procedures for distillation of methanol from the reaction mixture are generally not required and good to excellent yields of enamines are usually obtained. The presence of additional electron—withdrawing groups (e.g. cyano, carbomethoxy, nitro, e.g. 18) ortho to the methyl group greatly facilitates the enamine formation.

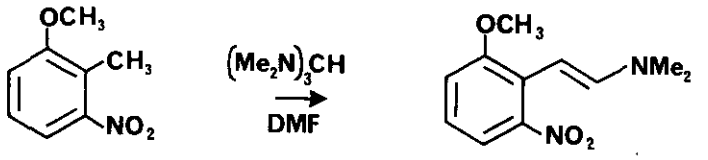
18 19

Conversion of 18 to 6-Carbomethoxy-β-dimethylamino-2-nitrostyrene (19), Table 6, entry 40.[27]

A solution of methyl 2-methyl-3-nitrobenzoate (18) (9.75 g, 0.05 mol) and DMFDMA (17.85 g, 0.15 mol) in 50 ml of DMF was heated at 130°C for 6 h. The DMF was removed under reduced pressure, and the residue was bulb-to-bulb distilled (120-130°C, 0.2 mm) to yield 10.7 g (86%) of 19 as a dark red oil.

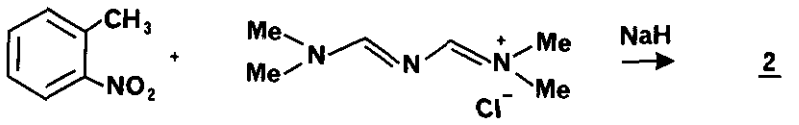
In certain cases, addition of an amine, such as pyrrolidine (entries 19, 23,24, 32,35,53) or triethylamine (entry 30) has been used to facilitate the enamine formation. This can lead to greatly enhanced rates of formation of the enamines, especially when electron-donating substituents are present in the nitrotoluene. For example, the preparation of 2-nitro-6-methoxy-β-dimethylaminostyrene (21) with DMF and DMFDMA requires 48 hours at 150°C. The addition of one molar equivalent of pyrrolidine to this reaction leads to a good yield of the corresponding pyrrolidine enamine in 3 hours (entry 19).[15]

The enamine formation can also be conducted at lower temperatures (100-115°C) with tris(N,N-dimethylamino)methane in DMF:[28]



20 21

Gold's reagent (22) has also been used to prepare enamine 2, although strongly basic conditions are required to effect this transformation:[29]

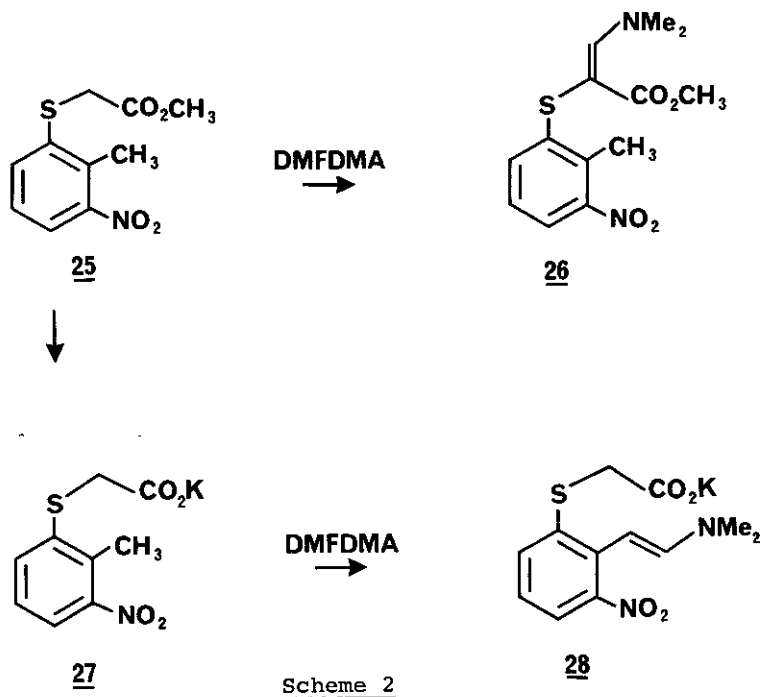


1 22

One limitation of the enamine forming reaction is that active methylene groups other than the methyl adjacent to the nitro group can react with DMFDMA, for example:[30]

23 24

In the synthesis of chuangxinmycin (13), Kozikowski et al. found that enamine formation took place to give 26 rather than the desired adduct (scheme 2).[21] This problem was circumvented by carrying out the condensation on the potassium salt of the acid (27) which achieved the proper regiochemistry.

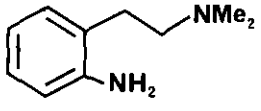


25 26 27 28

Scheme 2

2. REDUCTION METHODS

Leimgruber and Batcho described a number of methods for the reductive cyclization of β-dimethylamino-2-nitrostyrenes to indoles.[11] These included use of hydrogen with palladium on carbon (entry 1) or Raney nickel (entry 6) as catalysts, iron in acetic acid (entry 2), sodium dithionite (entry 3), and ferrous sulfate-ammonia (entry 11). Of these methods, hydrogenation in benzene with palladium on carbon or Raney nickel was described as the method of choice. An examination of Table 6 reveals that these conditions have been successfully employed in the preparation of many substituted indoles. Other solvents which have given good results in the catalytic hydrogenation have included methanol (entry 47), ethanol (entries 15,16,44), tetrahydrofuran (entries 7,18,20,45,50,52), dichloromethane (entry 30), and ethyl acetate (entry 51). A side-reaction in the hydrogenation is reduction of the enamine double bond leading to 2-aminophenylethylamines (e.g. 29). These products are rarely formed in greater than 10% yield and are easily separated from neutral indole products.



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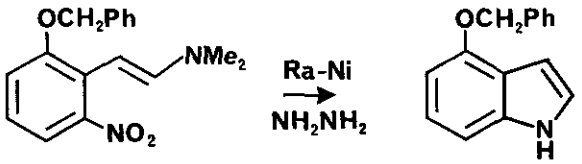
Preparation of Methyl Indole-4-carboxylate (30) (Table 6, entry 40):[27]

A mixture of 7.0 g (28 mmol) of 6-carbomethoxy-β-dimethylamino-2-nitrostyrene (19) in 140 ml of dry benzene containing 1.4 g of 10% palladium on carbon was shaken in a Parr apparatus under a hydrogen atmosphere of 50 psi for 1.5 h. The catalyst was removed by filtration and the benzene solution was washed with 5% HCl and brine, dried ($MgSO_4$), and concentrated. Chromatography of the residue on silica gel with 25% ethyl acetate-hexane afforded 6.9 g (82%) of methyl indole-4-carboxylate (30), mp 63 °C.

Raney nickel-hydrazine reduction affords an attractive alternative to catalytic hydrogenation (entries 19,23,24,53,54), especially in cases where hydrogenolysis (e.g. benzyl groups) poses a potential problem (entry 32).



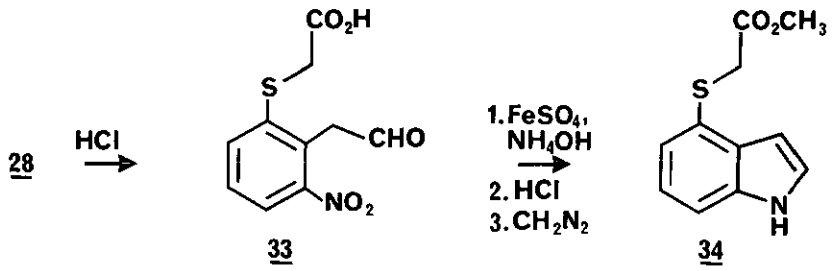
31 32

Preparation of 4-Benzyloxyindole (Table 6, entry 32):[15]

To a solution of 5.0 g (20.6 mmol) of 2-nitro-6-benzyloxytoluene in 35 ml of DMF was added 3.0 ml (22.7 mmol) of DMFDMA and 2.0 ml (24 mmol) of pyrrolidine. The mixture was stirred under a nitrogen atmosphere at 125 °C for 3 h. The solvent was distilled under reduced pressure and the dark red, oily residue (31) was dissolved in 25 ml of tetrahydrofuran and 25 ml of methanol. Raney nickel (5 g) was added and mixture was stirred under nitrogen at 50-60 °C while four 1.0 ml aliquots of 85% hydrazine hydrate were added at 30 min intervals. After 2.5 h total reaction time, the mixture was cooled to room temperature and filtered (Celite). The filtrate was concentrated and the residue was purified by chromatography on silica gel with 30% ether-hexane to afford 3.1 g (68%) of 32, mp 70 °C.

Iron-acetic acid has been used in a number of cases (entries 2,27,35,39,46) and although acceptable yields of indoles have sometimes been realized, the procedure suffers in comparison with the milder and manipulatively easier hydrogenation procedures. The same is also true of the stannous chloride-HCl reduction (entry 43).

In a sequence which combined elements of both the Leimgruber-Batcho and Weermann indole syntheses, enamine 28 was hydrolized to aldehyde 33 which was reduced with ferrous sulfate-ammonia[31] to afford indole 34 (after conversion to the methyl ester) (scheme 3).[21] The ferrous sulfate reduction has been applied to one β-dimethylamino-2-nitrostyrene directly, albeit in low yield (entry 11).

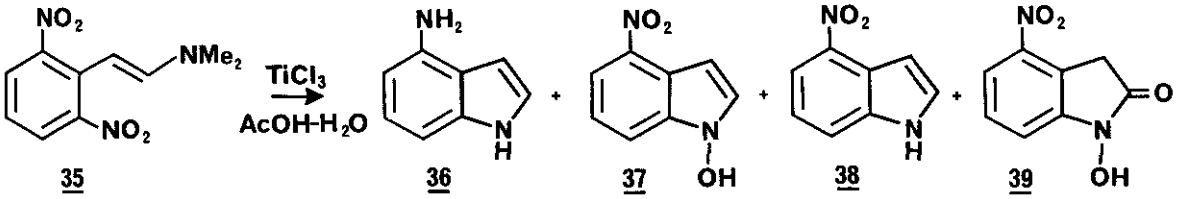


Scheme 3

Somei et al. have demonstrated the utility of titanium (III) chloride as reducing agent in the Leimgruber-Batcho synthesis.[22,32-34] This reagent offers several desirable features: its ability to reduce nitro groups,[35] its acidic nature which promotes hydrolysis of the enamines to phenylacetaldehydes thereby facilitating intramolecular cyclization, and the possibility of controlling the reduction level by regulation of its amount. It was found that methyl indole-4-carboxylate (30) could be prepared in 73% yield by reduction of the enamine (19) with 7 equivalents of titanium (III) chloride in methanol (entry 41). In the reduction of the dinitro-enamine 35, the product distribution was dependent upon the amount of titanium (III) chloride used (Table 2).[32]

With 12 equivalents of reducing agent, a quantity sufficient to reduce both nitro groups, 4-aminoindole (36) was obtained in 83% yield. With 4 equivalents of titanium (III) chloride, the major product was 1-hydroxy-4-nitroindole (37). Under the latter conditions, the predominant reaction pathway is reduction of one nitro group to a hydroxylamine that then cyclizes to the 1-hydroxyindole.

Table 2. Reduction of 2,6-Dinitro-trans-β-dimethylaminostyrene with Titanium (III) Chloride.



35 36 37 38 39

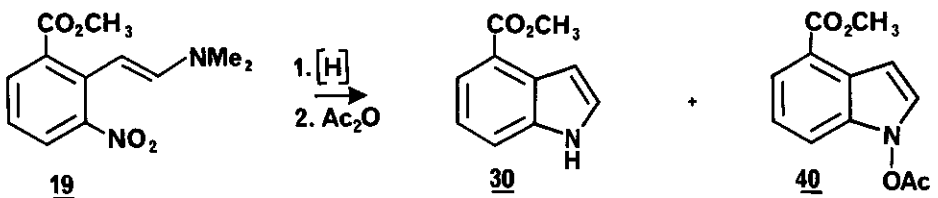
$TiCl_3$ (mol eq)	Yield (%) 36	37	38	39
12	83	0	0	0
8	42	22	6	1
6	6	36	8	8
4	3	57	13	16

Preparation of 4-Aminoindole (36, Table 6 , entry 37):[32]

To a solution of 106 mg (0.4 mmol) of enamine 35 in 6.0 ml of acetic acid-water (2:1, v/v) was added 3.5 ml (12 mol eq) of aqueous $TiCl_3$. The mixture was stirred for 7 min at room temperature. Water was added and the whole was extracted with methanol-dichloromethane (1:9, v/v). The water layer was basified with 30% sodium hydroxide and, after addition of concentrated aqueous ammonia, the mixture was extracted with methanol-dichloromethane (1:9, v/v). The extract was washed with brine, dried (Na_2SO_4), and concentrated to a residue that was purified by preparative TLC on alumina to afford 49 mg (83%) of 36, mp 106-108 °C.

A similar 1-hydroxyindole product (40, after acetylation) was obtained by titanium (III) chloride reduction of enamine 19.[32] The yield of this product was increased considerably with zinc-ammonium chloride reduction (Table 3).

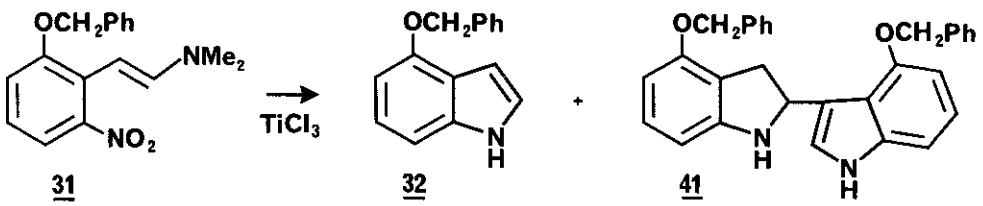
Table 3. Reduction of Enamine 19



19 30 40

Reducing agent	yield %	
$TiCl_3$ (4 mol eq)	12	14
Zn/NH_4Cl	1	40

In the titanium (III) chloride reduction of 31 (scheme 4), a significant quantity (44%) of dimer 41 was formed under the acidic reaction conditions.[32] The formation of this dimer was effectively eliminated by buffering the medium with ammonium acetate and changing the solvent from acetic acid to aqueous methanol. Thus, the yield of 4-benzyloxyindole (32) was increased from 7 to 51% under the buffered conditions.



31 32 41

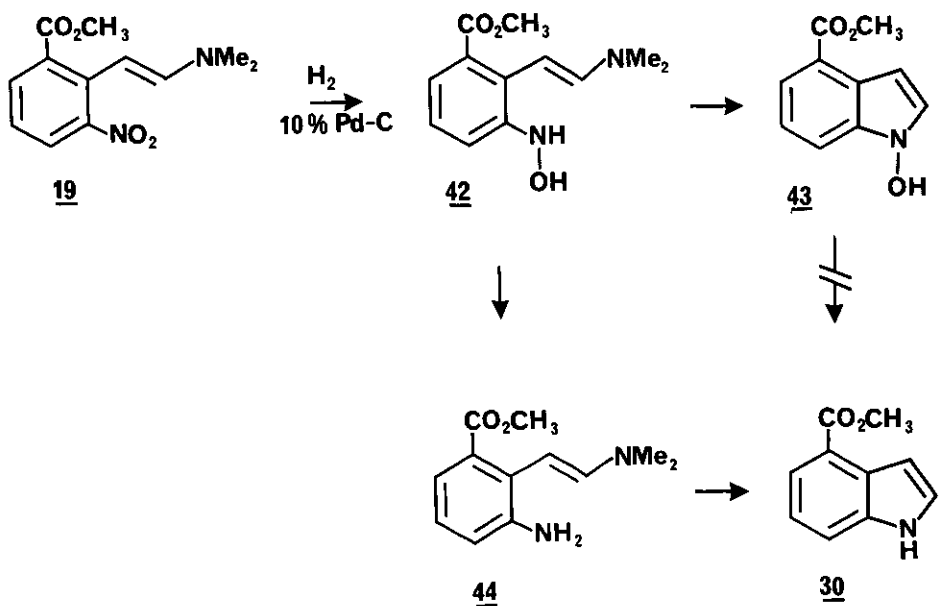
Scheme 4

The observations by Somei et al.[32] that 1-hydroxyindoles substituted in the 4 position with electron withdrawing groups (nitro, carbomethoxy) are relatively stable is significant because the only stable 1-hydroxyindoles that had been previously prepared were substituted in the five-membered ring with electron withdrawing groups or contained a bulky group at the 2 position.[36] It was subsequently observed that substantial quantities of 1-hydroxyindole 43 were formed from hydrogenation of 19 (scheme 5).[30] In this case, it was determined that the critical factor influencing the formation of 43 was the amount of catalyst used (Table 4). Low catalyst loadings favored formation of 43, presumably due to the increased likelyhood of hydroxylamine intermediate 42 cyclizing to 43 prior to reduction to aniline 44. With a large amount of catalyst, virtually no 43 was formed. The 1-hydroxyindole 43 appeared to be stable under the reaction conditions. The formation of such products from catalytic hydrogenation appears to be limited to indoles which are substituted in the 4 position with electron withdrawing groups.[30]

Table 4. Catalytic Hydrogenation of 19[a]

Grams 19	Grams 10%Pd-C	Ratio 19/Catalyst	Solvent(mL)	Yield(%) 43	30
3.6	0.75	4.8	C_6H_6 (140)	<5	81
7.0	1.0	7.0	THF (140)	33	41
50	2.0	25	THF (300)	50	24
80	1.5	53	THF (750)	60	<10

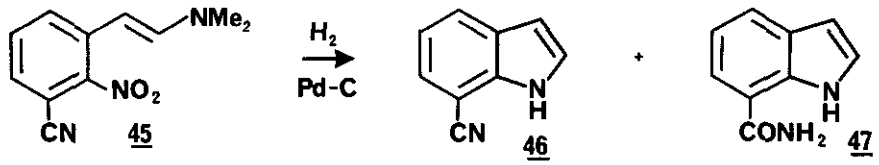
[a]Hydrogenations were carried out on a Parr apparatus at an initial pressure of 50 psi until uptake of hydrogen ceased.



Scheme 5

A side reaction observed in the catalytic hydrogenation of 45 was formation of 7-carboxamidoindole (47) in 44% yield when the reaction was carried out in benzene (scheme 6).[30] This product, which arises from intramolecular addition of the hydroxylamine intermediate to the nitrile, was not, however, observed when the reduction was carried out in tetrahydrofuran (entry 52).

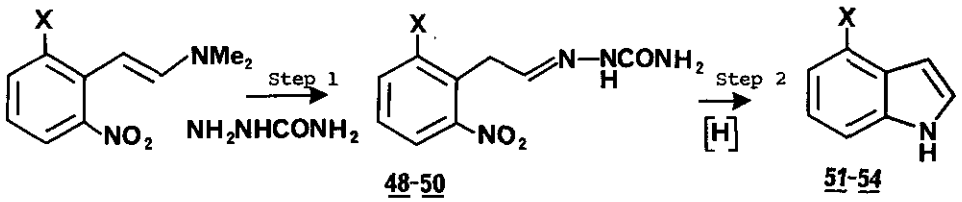
Scheme 6



3. MODIFICATIONS

Kruse reported that, in several instances, superior yields were obtained if the β-dimethylaminostyrene was converted to the phenylacetaldehyde semicarbazone derivative (prepared *in situ* by treatment of the enamine with acidic aqueous semicarbazide) prior to reduction.[28] Thus, indoles 51-54 (table 5) were prepared by catalytic hydrogenation of 48-50. The benzyl group was retained by reduction of 50 with ammoniacal ferrous sulfate.

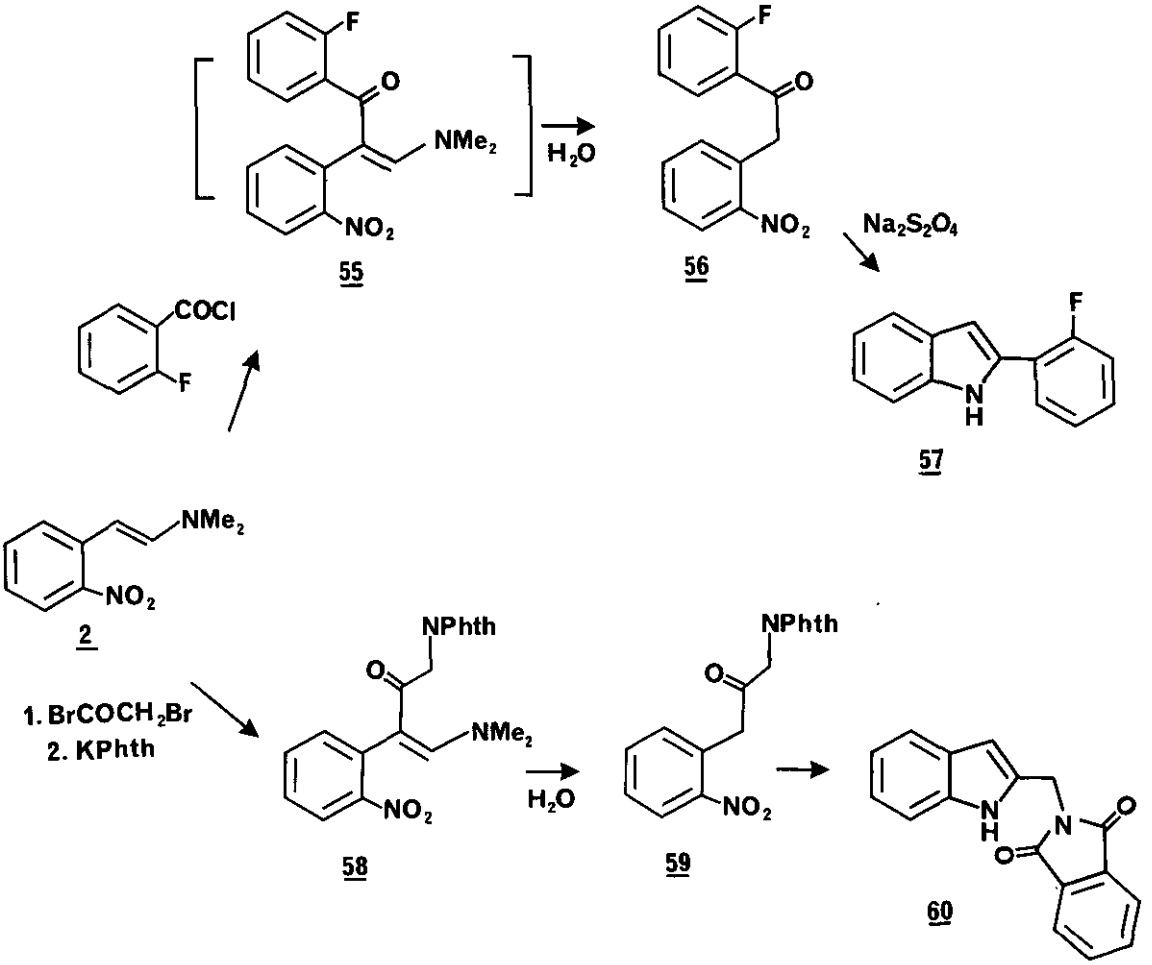
Table 5. Formation and Reduction of Semicarbazones



X	No.	Yield (%) step 1	No.	Yield (%) step 2
CH_3	48	93	51	81
OCH_3	49	82	52	82
OCH_2Ph	50	84	53	71
OH			54	55

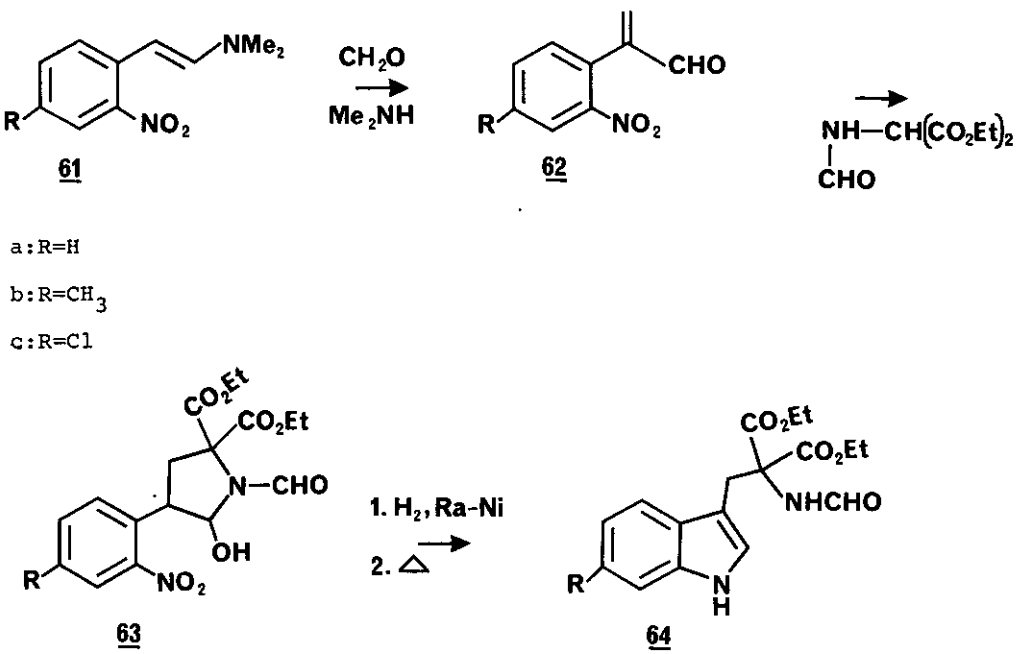
The increase in yield was attributed to the low solubility of the semicarbazones in the reaction medium. This effectively increases the catalyst/substrate ratio and, presumably, lowers the incidence of polymerization reactions.

The β-dimethylamino-2-nitrostyrenes have been used as synthetic intermediates for 2-substituted indoles (scheme 7).[37] Treatment of 2 with o-fluorobenzoyl chloride, followed by in situ hydrolysis and deformylation gave 56. Reduction of 56 with sodium hydrosulfite then furnished 2-(2-fluorophenyl)indole (57). Similarly, bromoacetylation of 2 gave an acylenamine which was converted to phthalimido derivative 58. Hydrolysis and deformylation gave 59 which was reduced (sodium hydrosulfite or hydrogen-Raney nickel) to give 60.



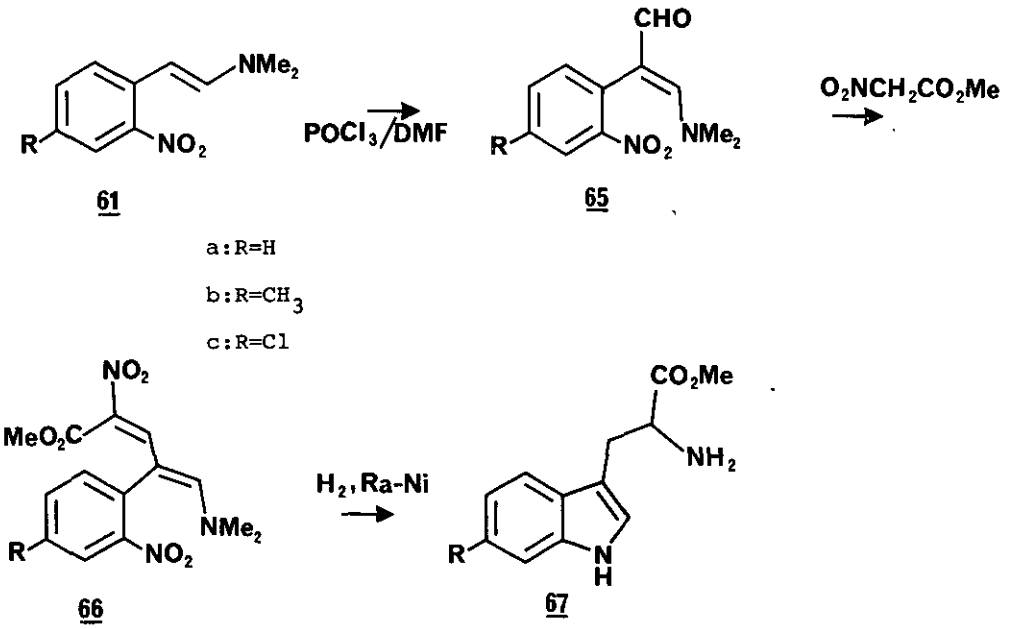
Scheme 7

A new synthesis of tryptophans, based on the intermediacy of β-dimethylamino-2-nitrostyrenes, has also been reported (scheme 8).[38] Mannich reaction of enamines 61abc with formaldehyde and dimethylamine gave the α,β-unsaturated aldehyde (62). Michael addition of diethyl formamidomalonate to 62 gave adducts (63) that were hydrogenated over Raney nickel to furnish tryptophan precursors 64a and 64b. Hydrolysis and decarboxylation then afforded racemic tryptophan and 6-methyltryptophan, respectively. A slight variation of the synthesis gave 6-chlorotryptophan.



Scheme 8

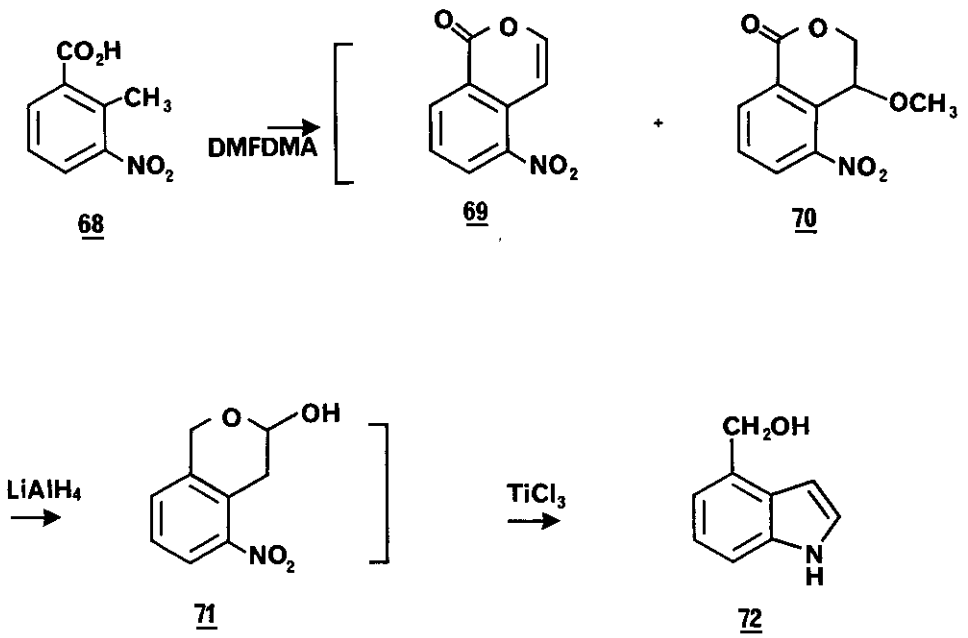
A different approach (scheme 9) also led to racemic tryptophans beginning with the enamines 61abc.[38] Vilsmeier formylation gave the 3-(dimethylamino)acroleins 65 that were condensed with methyl nitroacetate to afford dienes 66. High pressure hydrogenation with Raney nickel accomplished reduction of both nitro groups and one double bond and afforded the tryptophan methyl esters 67abc.



Scheme 9

In a sequence that was, in principle, based on the Leimgruber-Batcho method, a one pot synthesis of 4-hydroxymethylindole (72) was developed (scheme 10).[34] Condensation of 2-methyl-3-nitrobenzoic acid (68) with DMFDMA in DMF gave predominantly 5-nitroisocoumarin (69) and the dihydroisocoumarin 70.

Controlled lithium aluminum hydride reduction of this product mixture gave 71 as the major product which was, without isolation, reduced with titanium (III) chloride to give 72 in 30% overall yield.



68 69 70 71 72

Scheme 10

CONCLUSION

The Leimgruber-Batcho indole synthesis has several advantages over almost all other routes:

1. A wide variety of nuclear substituted indoles can easily be prepared in high yield.
2. The reductive cyclization to the indole can be achieved by relatively mild chemical or catalytic means. Thus, a synthesis can be tailored to produce indoles containing a multitude of functionality.

3. The regiospecificity of the method allows the introduction of substituents at carbons 4,5,6,or 7 without the need for troublesome isomer separation (particularly the 4 and 6 isomers).
4. Indoles unsubstituted in the 2 and/or 3 position are obtained directly. This is especially important when the indole is to be used for further transformations.

The major disadvantage of the Leimgruber-Batcho synthesis is the inaccessibility of multiply substituted 2-nitrotoluenes.

ACKNOWLEDGEMENTS

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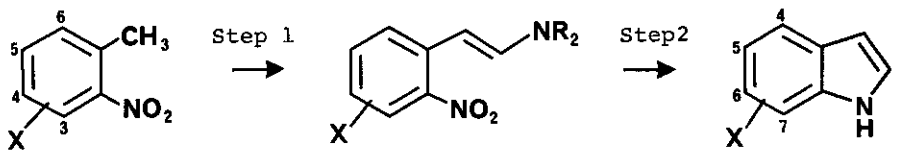
Table 6. Synthesis and Reduction of β-Dialkylamino-2-nitrostyrenes in the Leimgruber-Batcho Indole Synthesis



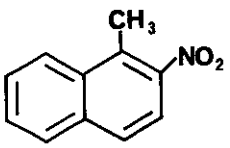
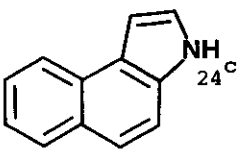
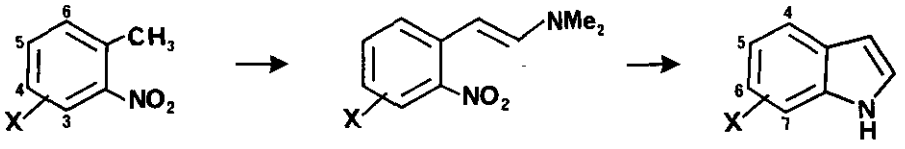
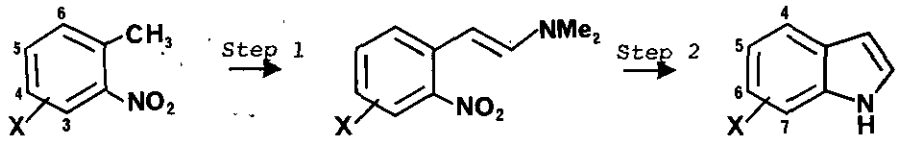
Entry	X	Step 1 Conditions[a]	Yield(%)[b]	Step 2 Conditions	X	Yield(%)	REF
1	3,4,5,6-H	A	97	H_2,10% Pd-C,C_6H_6	4,5,6,7-H	80	11
2	"			Fe,AcoH-EtOH	"	17	11
3	"			$Na_2S_2O_4$,MeOH-H_2O, K_2CO_3	"	18	11
4	"	C	-	H_2,10% Pd-C,C_6H_6	"	82[c]	11
5	"	D	-	H_2,5% Pd-C,C_6H_6	"	70[c]	11
6	6-Me	B	70	H_2,Ra-Ni,C_6H_6	4-Me	57	11
7	"			H_2,10% Pd-C,THF	"	60	30
8	4-Me	A	83	H_2,5% Pd-C,C_6H_6	6-Me	83	38
9	3-Me	B	40	H_2,10% Pd-C,C_6H_6	7-Me	48	11
10	4-(i-pr)	A	84	H_2,10% Pd-C,C_6H_6	6-(i-pr)	51	11
11	4,5-Me	A	58	$Fe(SO_4)$,NH_4OH,H_2O	5,6-Me	3	11
12		B	-	H_2,5% Pd-C,C_6H_6		24[c]	9

Table 6. Synthesis and Reduction of β-Dialkylamino-2-nitrostyrenes in the Leimgruber-Batcho Indole Synthesis (cont'd)



		Step 1		Step 2			
Entry	X	Conditions[a]	Yield(%)[b]	Conditions	X	Yield(%)	REF
13	6-Cl	A	89	H_2,Ra-Ni,C_6H_6	4-Cl	63	11
14	5-Cl	A	88	H_2,Ra-Ni,C_6H_6	5-Cl	78	11
15	4-Cl	A	57	H_2,Ra-Ni,EtOH	6-Cl	52	11
16	4-Br	A	-	H_2,Ra-Ni,EtOH	6-Br	38[c]	20
17	5-F	A	92	H_2,Ra-Ni,C_6H_6	5-F	51	11
18	4-F	A	95	H_2,10% Pd-C,THF	6-F	35	30
19	6-OMe	E	-	N_2H_4,Ra-Ni,THF-MeOH	4-OMe	70[c]	15
20	"			H_2,10% Pd-C,THF	"	70	30
21	5-OMe	B	89	H_2,10% Pd-C,C_6H_6	5-OMe	72	11
22	4-OMe	B	64	H_2,Ra-Ni,C_6H_6	6-OMe	63	11
23	"	E	50	N_2H_4,Ra-Ni,THF-MeOH	"	45	30
24	3-OMe	E	54	N_2H_4,Ra-Ni,THF-MeOH	7-OMe	50	30
25	3-Me,5-OMe	A	54	H_2,10% Pd-C,C_6H_6	7-Me,5-OMe	66	16
26	4,5-OMe	A	-	H_2,10% Pd-C,C_6H_6	5,6-OMe	28[c]	11
27	4-Me,5-OMe	A	-	Fe,AcOH-EtOH	6-Me,5-OMe	15[c]	17

Table 6. Synthesis and Reduction of β-Dialkylamino-2-nitrostyrenes in the Leimgruber-Batcho Indole Synthesis (cont'd)



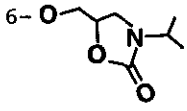
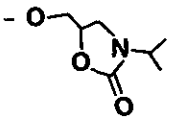
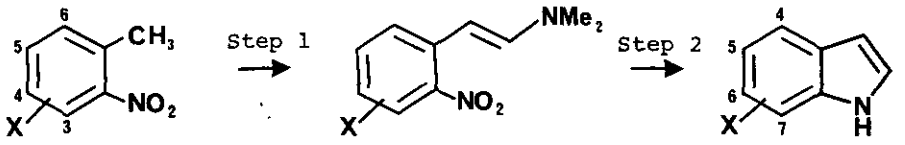
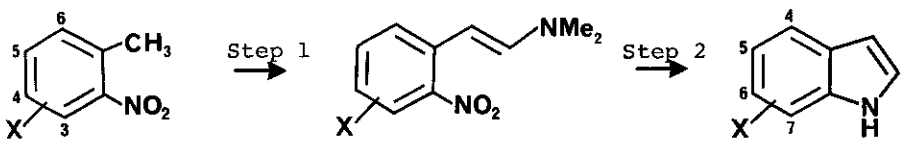
		Step 1		Step 2			
Entry	X	Conditions[a]	Yield(%)[b]	Conditions	X	Yield(%)	REF
28	5,6-OCH_2O	A	-	H_2,10% Pd-C,C_6H_6	4,5-OCH_2O	50[2]	18
29	4,5-OCH_2O	A	72	H_2,Ra-Ni,C_6H_6	5,6-OCH_2O	50	11
30	6- 	F	-	H_2,5% Pd-C, CH_2Cl_2	4- 	70[c]	19
31	6-OCH_2Ph	A	-	$TiCl_3$,NH_4OAc,H_2O-CH_3OH	4-OCH_2Ph	50[c]	32
32	"	E	-	N_2H_4,Ra-Ni,THF-CH_3OH	4-OCH_2Ph	68[c]	15
33	5-OCH_2Ph	A	78	H_2,Ra-Ni,EtOH-DMF	6-OCH_2Ph	45	11
34	4,5-OCH_2Ph	A	86	H_2,Ra-Ni,C_6H_6	5,6-OCH_2Ph	54	11
35	6-SMe	E	-	Fe,AcOH-EtOH	4-SMe	63[c]	18
36	6-NO_2	A	96	H_2,10% Pd-C,C_6H_6	4-NH_2	84	28
37	"	A	90	$TiCl_3$,AcOH-H_2O (12 eq)	"	83	32
37a	"			$TiCl_3$,AcOH-H_2O (4 eq)	4-NO_2	56	32

Table 6. Synthesis and Reduction of β-Dialkylamino-2-nitrostyrenes in the Leimgruber-Batcho Indole Synthesis (cont'd)



		Step 1		Step 2			
Entry	X	Conditions[a]	Yield(%)[b]	Conditions	X	Yield(%)	REF
38	4-NO_2	A	82	H_2,Ra-Ni, EtOH	6-NH_2	23	11
39	6-CO_2Me	A	86	Fe,AcOH-EtOH	4-CO_2Me	63	12
40	"	A	86	H_2,10% Pd-C,C_6H_6	"	82	27
41	"			$TiCl_3$,MeOH	"	73	33
42	6-CO_2H	A	80[d]	H_2,10% Pd-C, C_6H_6	4-CO_2CH_3	82	28
43	6-CO_2Et	B	100	$SnCl_2$,HCl,Et_2O	4-CO_2Et	38	12
44	5-CO_2Et	A	70	H_2,10% Pd-C,EtOH	5-CO_2Et	39	11
45	3-CO_2Me	A	70	H_2,10% Pd-C,THF	7-CO_2Me	61	30
46	6-CN	A	93	Fe,AcOH-EtOH	4-CN	67	12
47	"			H_2,10% Pd-C,MeOH	"	70	30
48	5-CN	A	79	H_2,10% Pd-C,THF	5-CN	44	30
49	4-CN	A	86	H_2,10% Pd-C,C_6H_6	6-CN	65	11
50	"	A	94	H_2,10% Pd-C,THF	"	86	30
51	3-OMe,6-CN	A	78	H_2,10% Pd-C,EtOAc	7-OMe, 4-CN	83	14
52	3-CN	A	91	H_2,10% Pd-C,THF	7-CN	44	30
53	6-CH(OMe)$_2$	E	-	N_2H_4,Ra-Ni,THF-MeOH	4-CHO	33[c]	39

Table 6. Synthesis and Reduction of β-Dialkylamino-2-nitrostyrenes in the Leimgruber-Batcho Indole Synthesis (cont'd)



54	6-$CH_2CH(OMe)_2$	E	-	N_2H_4,Ra-Ni,THF-MeOH	4-$CH_2CH(OMe)_2$	67[c]	39
55	4-CHO	A	55[e]	H_2,Ra-Ni,C_6H_6	6-CHO	26	11
56	"			H_2,10% Pd-C,K_2CO_3, C_6H_6	6-$CH(OMe)_2$	27	11

a A: DMFDMA-DMF. B: N,N-Dimethylformamide diethyl acetal-DMF. D: N-Formylpiperidinyl dimethyl acetal-DMF. E: DMFDMA-DMF-pyrrolidine. F: DMFDMA-DMF-triethylamine. Methods A,B, and F yield the β-dimethylamino-2-nitrostyrene. Methods C and E yield the β-pyrrolidino-2-nitrostyrene. Method D yields the β-piperidino-2-nitrostyrene.

b Per cent yield of isolated β-dialkylamino-2-nitrostyrene. A dash (-) indicates that the crude product was directly reduced to the indole.

c Overall yield from the nitrotoluene.

d The acid was converted to the methyl ester during enamine formation.

e The aldehyde was converted to the dimethyl acetal during enamine formation.

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